

# Guidance for State Medical Cannabis Testing Programs



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## **Acknowledgments**

### **Kenneth Aldous, PhD**

Director, Division of Environmental Health Sciences  
Wadsworth Center, NYS Department of Health  
and Associate Professor, School of Public Health  
State University at Albany

### **Jeremy Applen**

Co-founder  
Canopy Systems

### **Zhihua (Tina) Fan, PhD**

Research Scientist/Program Manager  
Chemical Terrorism, Biomonitoring and Food Testing  
New Jersey Department of Health  
Public Health Infrastructure, Laboratories & Emergency Preparedness.  
Public Health & Environmental Laboratories

### **Mary A. Fox, PhD MPH**

Assistant Professor, Health Policy and Management  
Acting Director, Risk Sciences and Public Policy Institute  
Johns Hopkins Bloomberg School of Public Health

### **Shawn Kassner**

Senior Scientist  
Neptune and Company, Inc.

### **Megan Weil Latshaw, PhD MHS**

Director, Environmental Health Programs  
Association of Public Health Laboratories

### **Marc A. Nascarella, PhD**

Chief Toxicologist  
Director, Environmental Toxicology  
Massachusetts Department of Public Health

### **Gary Starr, MD**

FOCUS Standards

### **Shannon Swantek**

ORELAP Compliance Specialist  
Oregon Public Health Lab

### **David Verbrugge**

Manager, Analytical Toxicology  
State of Alaska Public Health Lab

## Introduction

As part of the nation's public health infrastructure, **state and federal agencies establish programs to protect population health**. There are a wide variety of programs in place in different agencies that test, monitor and evaluate whether human exposures from the use of air, water or consumer products (including food and drugs) present potential risks to health.

On the basis of these testing and evaluation programs, agencies have authority to protect our health by **taking action to ensure that air, water, and consumer products are of good quality**. Protecting resources and consumer products may take many forms, e.g., preventing contamination (pollution prevention, regulating production processes), reducing or preventing exposure (recalling contaminated products) or restricting uses such that health protective conditions are met and maintained. In the case of drugs, including cannabis, public health agencies have concerns for the quality, therapeutic benefit, and the balance between therapeutic benefit and possible side-effects.

Medical cannabis has been approved for use in a number of states but remains outside federal control. As has been reported, **the absence of federal guidance when it comes to cannabis testing has led states to develop their own approaches**. Since 2014, the Association of Public Health Laboratories (APHL) has convened a monthly community of practice call so that member laboratories could share questions, advice, lessons learned and resources. During these calls, a theme emerged where every new participant asked the same questions as others who came before. In order to collect the knowledge being shared, APHL created this guidance document.

The main audience for this document is **laboratorians who are being asked to develop new cannabis testing programs**. It can also be used to assess existing programs. Other audiences may include state legislators and their staff, state health officials, and those working in the cannabis industry.

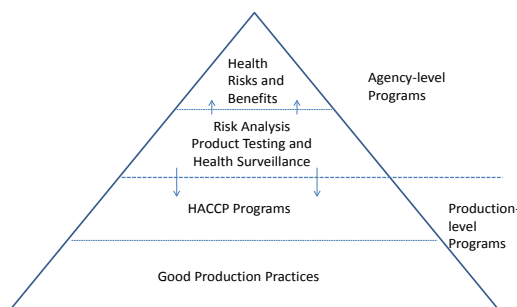
Since the guidance was developed by a workgroup, it is heavily weighted toward those states that participated in its writing. If you would like to add your perspective or suggest edits, please email [eh@aphl.org](mailto:eh@aphl.org). Given the rapid changes in this field, APHL views this as a living document.

## Risk Assessment

There are various approaches to the assessment and management of hazards that can be applied to cannabis programs. Drawing upon the variety of tools and methods applied in product evaluation and protection programs for other types of products such as food or drugs,<sup>1</sup> the product protection pyramid identifies activities implemented by public health agencies and by producers/product handlers to evaluate and ensure product quality. At the base of the pyramid, growers and processors implement good practices (maintaining growing facilities, appropriate use of insecticides, etc).

A Hazard Analysis and Critical Control Point (HACCP) program is a management system designed to ensure product quality from production to consumption. HACCP programs are developed to be specific to each type of process, along the production, distribution and consumption continuum. Public health

### Product Protection Pyramid



Adapted from Gorris 2005

<sup>1</sup> Gorris 2005. Food safety objective: An integral part of food chain management. Food Control 16: 801–809.

agencies conduct product testing and health surveillance programs; the resulting data can be used for risk analysis to understand the potential health risks and benefits of cannabis products. Results of risk analysis inform HACCP and good production practices.

There are three types of data collected, evaluated and combined in a risk assessment:

- Sources/Hazards (contaminants, pesticides, microbes or active ingredients)
- Health effects/consequences/adverse events associated with each hazard
- Exposure which involves sampling of products to determine concentrations of ingredients/contaminants and human exposure through use of the target product. Exposure scenarios reflect known uses of the product and include a range of scenarios from low to high exposure depending on difference uses. They can also include human biomonitoring data—looking for the analyte or its metabolite in human specimens, such as blood lead testing.<sup>2</sup>

Using the estimation of risks, based on the exposure-hazard-health effect sets, public health can better characterize risk and develop health protective approaches to managing it. Practitioners may use screening approaches—risk ranking to identify the highest risk products, risk-driving hazards or risk-driving processes—to inform product warnings and further sampling.

In order to develop a standard, practitioners must develop criteria for “acceptable risk” and identify exposure-use scenarios that fall within or outside the acceptable risk criteria. Based on that standard, it is possible to establish mechanisms for removal of products or to limit usage so that human exposures remain below the acceptable risk criterion.

## Types of Product

As with most programs in the United States, every state takes a different approach. For example as of January 2016, New Jersey’s Public Health & Environmental Laboratories only test cannabis plant material. Just across the Hudson, however, New York’s Public Health Laboratory will not be testing any plant material, only cannabis extracts. In addition, the New York Department of Health will provide an oversight role for commercial cannabis laboratories that are licensed by the federal Drug Enforcement Administration (DEA) and approved for testing cannabis products. On the other hand, New Jersey state government does all testing in-house for the medical cannabis program.

This section provides an overview the various types of products available across the country, as well as some testing considerations.

### Pill/Capsule

Commonly, these are heat-activated oils in medium-chain triglyceride (MCT) coconut oil diluent that are placed in pharmaceutical grade gel-cap material. Testing would be similar to other extracts, in addition to testing for any potentially harmful materials frequently tested for in the pharmaceutical industry.

The dissolvable pill is meant for oral intake, but not to be swallowed. This is not to say it would not be swallowed, only that it is designed to be absorbed by the oral mucosa, metabolizing like an orally-absorbed tincture. Testing would be similar to extract testing but would also account for relevant ingredients that might be introduced in the unique manufacturing process required for the dissolvable matrix tablet.

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<sup>2</sup> A method for test cannabinoids in urine can be found at Wei B, Wang L, Blount BC. Analysis of Cannabinoids and Their Metabolites in Human Urine. *Anal Chem.* 2015 Oct 20;87(20):10183-7.

### **Tincture**

This form is for oral mucosal absorption (not swallowed) and is typically an extract dissolved in alcohol at a defined percentage. Testing would be similar to extract testing and possibly verifying alcohol content.

### **Spray**

This is similar to tinctures above or extract oils below. When plastic components are used in spray packaging, testing for contaminant related to packaging may be warranted. IF a solvent is used, such as glycol or glycerin, these may also need analysis.

### **Oils for food or cooking**

These are extracts of raw plant, homogenized with an edible lipid. These should be tested as an extract and also tested for biologicals specific to the food manufacturing process.

Oils for combining and swallowing (i.e. for children with seizures) are extracts of raw plant, heat activated and homogenized with an edible lipid, like MCT coconut oil and possibly flavoring. These should be tested as an extract and also tested for biologicals specific to the food-manufacturing process.

### **Oils/ extracts for vaporizing**

These are extracts of raw plant sold in various viscosities for the purpose of placing in a “vaporizer” or “vape pan” and inhaled as vapor (not smoke). The vaporizing device heats the material to a temperature below the combustion point (ideally) and causes the volatile active ingredients (cannabinoids and terpenes) to enter a vapor form available for inhalation. To the extent that the material is not heated to combustion (which can happen with low quality devices), the risks of smoke inhalation are theoretically avoided (i.e., no particulate matter or other products of combustion are inhaled). This is better from a medical standpoint. Additionally, since a homogenized extract can be measured for content per vaporized inhalation, more accurate dosing should theoretically be possible when compared to smoking raw plant material.

Extracts should commonly be tested for active ingredients; residual extraction solvents (hydrocarbons or other); mycotoxins; any pesticides not typically removed in the extraction process; any biological that might be introduced after extraction but before final packaging; and heavy metals (depending on the grow medium).

Some extracts are combined with solvent to make them less viscous. This has generated controversy in the industry since the safety of these solvents for inhalation is debated. Propylene glycol is most commonly used as the solvent and, though it has been considered generally safe for oral consumption, it carries risk when heated and inhaled. Other potentially harmful solvents are sometimes used. Processes that create a homogenized thinner oil for placing in a vape pen or vape pen cartridge (prepackaged) without the use of solvent do exist but are not yet common or cheap—making the debate a fast-evolving one.

Finally, other potentially harmful substances may be found in this form including any flavorings added by the manufacturer and any possible contamination by the device itself (glues, plastics, sealants). These need to be identified and analyzed based on current health data for such compounds. Heating these products to high temperature for combustion should be avoided for reasons similar to smoking other plant material.

### **Plant mixes for vaporizing or smoking**

Some states mandate a homogenization process for plant product which might be then smoked or vaporized with a solvent. These products should be tested in the same way as a raw plant product, ideally before and after homogenization.

### **Plant for smoking**

Testing plant material designed for smoking will mirror what has been studied the most,<sup>3</sup> as this is the most commonly consumed form (recreationally and medically). However, it is the least appropriate form from a medical standpoint due to the particulate and toxic substances created when organic material is burned (heated above combustion temperature) and inhaled.

### **Creams/ointments for skin**

Various topical products exist which combine extracts (heat activated and not) with a cream or ointment base for topical application (to be absorbed through the skin to varying degrees). See discussion on extracts above. Testing should also mirror the pharmaceutical topical cream/ointment standard.<sup>4</sup>

### **Patches**

These are essentially similar to creams or ointments but are more convenient for application and are generally longer-acting. These products contain synthetic elements (adhesive, plastics, synthetic material, etc.) and testing should mirror the pharmaceutical industry standard for medications applied via absorbable patch.<sup>5</sup>

### **Eye drops**

Much like the spray and oil preparations, these extract-based products also contain a solvent or diluent that allow the active oil to be placed safely in the eye for absorption locally. Various techniques using glycol, oils or white petroleum products and cyclodextrans have been described. Testing should mirror that for extracts, sprays and oils as well as for any other possible ingredients introduced in the packaging process (solvents, biological). Standards should mirror that of medications intended for ocular application in the pharmaceutical industry.<sup>2</sup>

### **Suppositories**

Extract is combined with a glycerin or similar matrix in order for it to maintain form and be inserted rectally and absorbed by mucosa. Testing should mirror that of extracts, pills and oils.

### **Air purifier oil inserts**

The intent is for passive inhalation in the local air but not for direct inhalation. Testing should mirror that for vaporized extract.

### **IV/IM Injections**

These are not industry standard forms but are hypothesized and testing standards should be anticipated. Extracts or fractional distillates of raw plant can be combined with solvents that enhance water solubility. Cyclodextrans (such as Captisol) have been used for this purpose in the pharmaceutical industry (Geodon, Abilify, Amiodarone, etc.). Testing would mirror the pharmaceutical IV/IM medication standard as well as the testing standard described in the extracts portion here.

### **Raw plant consumed orally**

Some patients include the leaves in salad or juice them, but often don't wash it to avoid rinsing off the active ingredient. This brings up concerns about residues, especially pesticides that might remain on the product. See above for raw plant, smoked.

<sup>3</sup> Daley, P, et al. Testing Cannabis for Contaminants. BOTEK Analysis Corp. September 12, 2013.

<sup>4</sup> U.S. Pharmacopeial Convention. Topical and Transdermal Drug Products: Product Quality Tests. November 1, 2013. Available at [http://www.usp.org/sites/default/files/usp\\_pdf/EN/USPNF/revisions/topical\\_and\\_transdermal.pdf](http://www.usp.org/sites/default/files/usp_pdf/EN/USPNF/revisions/topical_and_transdermal.pdf)

<sup>5</sup> U.S. Food and Drug Administration/ Center for Drug Evaluation and Research. Guidance for Industry Orally Disintegrating Tablets. December 2008. Available at <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm070578.pdf>.



## Characteristics of Various Forms

The forms described above are usually indicated for one of three reasons. First, ease of use and historical application are considered. This mostly applies to raw plant forms for smoking or oral consumption. Certain forms of extract are also encountered because they are easier or cheaper to manufacture compared to other products (for example butane hash oil or BHO, water hash extracts or using propylene glycol in vape pens). Secondly, the intended use often requires a specific form. Eye drops used for glaucoma or topical products used for skin conditions are good examples. Data for these use indications is variable.

Thirdly, the biochemical process in the human body must also be considered. THC (and other cannabinoids) are metabolized to other compounds—some also active. How the native plant or extract is consumed alters the biochemistry and the biological result. THCA needs to be decarboxylated into  $\Delta^9$ -THC before consumption to achieve certain biological effects. The effects of other forms are less well-studied. Consuming products orally so that they are absorbed in the intestine results in a “first pass metabolism,” where the liver has a chance to significantly alter the active compounds before they have a biological effect.

Absorption rates are highly variable and prolonged when products are orally ingested. But products that are inhaled or absorbed through the mucous membranes of the mouth, eyes, nasal mucosa or rectum enter the blood stream before being metabolized by the liver are absorbed much quicker and have a different set of effects. Inhaled products are the most quickly absorbed. Parenteral (IV or IM) products exist conceptually and would be similar to inhaled products, because you bypass first-pass metabolism in the liver. Topical applications result in a direct absorption (like oral mucosa) but are usually slower and more variable. Some topical products may only have a local reaction and are not systemically absorbed.

Risks for various products are different as well. The biological risks for various product contaminants depend to a degree on whether the product is ingested orally (*E. coli* for example). Certain contaminants might be more harmful if ingested orally or parentally (if they are not absorbed in the GI tract). Topical, oral, rectal or ocular applications might cause local irritation depending on the solvent and product. Smoked products contain a uniquely large amount of harmful byproducts of combustion. Heated vape pen components may contain adhesive or other parts that are toxic when heated beyond a certain degree. IV and IM preparations potentially carry an additional set of risks (biological, allergic and chemical) given the bypass of the blood/endothelium barrier.

Products that are rapidly absorbed (inhaled, absorbed, parenteral) may cause immediate effects and significant side effects which may or may not be tolerated well, but which usually last a shorter period of time. This quick feedback is helpful for dosing in the patient. Orally-ingested products are highly variable in the rate and amount of absorption and are much slower in onset of action, which makes dosing more difficult. This could easily result in an ingestion far beyond what is advised or intended (because you can eat a lot before you feel anything).

All of these considerations indicate the **importance of consulting toxicologists and physicians when deciding which products will be available for use**, and what type of testing should be done on the products.

## Dealing with Schedule I Materials

Marijuana is classified as a schedule I substance under the Controlled Substance Act (CSA) [21 U.S.C. § 801 et seq].<sup>6</sup> This Act requires persons who handle controlled substances to register with

<sup>6</sup> <http://www.deadiversion.usdoj.gov/21cfr/21usc/812.htm>

the Drug Enforcement Agency (DEA) in the Department of Justice, which administers and enforces the Act.

In New York, medical marijuana and related products produced by a registered organization must be examined in a laboratory located in New York State. The laboratory must be licensed by the federal Drug Enforcement Administration (DEA) and approved for the analysis of medical marijuana by the department in accordance with New York law. Relevant language is copied below.

The ordering and use of controlled substances must adhere to the requirements of the Controlled Substance Act of 1970 and any local state enforcement agency, as well as the terms and conditions of any Institutional Research or Analytical Licenses or Registrations issued in accordance with proposed laboratory activities. Each approved facility must be preapproved by both DEA and Local State Codes and have the license/registrations posted on or near the primary inventory storage. A comprehensive standard operating procedures (SOP) covering all aspects of oversight of controlled substances within the laboratory documenting substance receipt to the final depletion or destruction must be addressed.

### **Licenses/Registrations**

will be required for the type of activity being conducted at each facility, including the need to maintain controlled substances and record keeping within the activity.

### **Definitions**

Refer to SPPM IV—Controlled Substance Program for a list of program specific definitions.

### **Responsibilities**

The normal responsibility for security of controlled substances within a facility rests with the individuals granted unescorted access and use of these substances. The following are specific responsibilities for personnel assigned to the facility.

3.1 **Licenseses** will be responsible for the submittal of all internal applications/forms/ requests needed to support this policy. Additionally, they will approve all **usage requests** submitted, to support legitimate, authorized studies or programs.

3.2 All usage of Controlled Substances will require any **usage requests** be submitted by the **Investigator** for approval before controlled substance activity takes place.

3.3 Licensees responsible for storing quantities of controlled substances will act as or appoint an **Inventory Custodian** responsible to coordinate protective requirements including monitoring orders, receipt verification, storage, accountability, and final distribution.

3.4 The **Mail and Receiving Section** is responsible to notify licensees or custodians of the receipt of deliveries containing controlled substances, as identified under state and federal law. All efforts will be made to ensure the rapid transition from the mailroom to the custodian and into secure storage.

3.5 Controlled Substances **Users**, under the guidance of the Principal Investigators and Licensees, are responsible to ensure compliance with Laboratory policy and all other rules, regulations, and orders issued by the state and/or the US Drug Enforcement Administration.

## Approved Storage Areas

The following is a list of approved storage situations for controlled substances designated as Level II and III Assets.

4.1 Each licensed facility will maintain a **Primary Storage** location to support registered activities.

4.2 **Satellite Storage** locations may be approved to support small quantity users and should be coordinated with the Laboratory Director prior to approval.

## Procedures

All controlled substances used in research or diagnostic procedures or as part of research will be requested through the licensee and will refer to the corresponding license or registration on requests.

1. A copy of your current DEA registration (DEA Form 223) along with your request for controlled substances must be submitted. It is the research investigator's responsibility to keep his/her registration current and verify the drug code for drug/compound being requested. For those investigators who request Schedule I drugs must provide DEA documentation that the requested drug is covered under their current DEA registration.
2. Enclose an accurately completed DEA Form 222 (for controlled substances) with the request. Note that a DEA Form-222 is not necessary for drugs in Schedules III V, but a valid registration for the appropriate schedule is.

**NOTE:** No Controlled Substances should be transferred into the facility without the approval of the Licensee responsible for the specific activity. Unregistered Controlled Substances will be reported to DEA and/or state authorities for immediate seizure.

5.1 All purchases of Controlled Substances will be made by the Licensees; purchase requests will list only the licensees or custodians to ensure they are placed into the facility's inventory.

5.1.1 Usage requests will be made using the appropriate facility protocol for laboratory standards and controlled substances.

5.1.2 All requests will be accompanied by a usage protocol and include the following information;

5.1.2.1 Type of activity conducted;

5.1.2.2 Type and form of controlled substances required;

5.1.2.3 Quantity of controlled substances expected to be used.

5.1.3 Controlled substances should be received by the Controlled Substance Custodian, secured and logged into inventory as soon as possible.

5.1.4 The Controlled Substance Inventory Record to maintain an accurate **Inventory** of controlled substances that are maintained by each licensed/registered activity at each facility.

5.1.5 Inventory records will be maintained within the security

container at each location and at an alternate location to ensure they are not compromised during a theft.

5.1.6 Until being used, all controlled substances will be stored in a security container under the control of the licensee or custodian.

5.1.7 All other scheduled substances can be stored in the same area for safekeeping until dispersal to the Principal Investigator or authorized User.

5.2 **Transfer** of Controlled Substances will be based upon a proper usage request, consistent with approved protocols.

5.2.1 The custodian will be responsible to physically open the safe, retrieve the substance and inventory records, and issue them to the authorized User listed upon the Usage Request.

5.2.2 The **Usage Record** will be provided by the custodian along with the controlled substances.

5.2.3 The Controlled Substance Inventory Record will be used to track the program use of each controlled substance.

5.2.4 The completed Usage Records will be checked for accuracy and completeness; any impropriety questioned and upon return used to reconcile the custodial inventory record.

5.2.5 Users will not be issued quantities greater than what would be needed for operational purposes, at the discretion of the licensee.

5.2.6 Controlled substance transfers will be “Hand Delivered” by either the Licensee or Custodian or the requesting Principal Investigator (PI) or Users. Movement within the facility will be coordinated with [sic].

5.2.7 Security escorts will be used whenever transfers are made between the primary and satellite storage locations within a licensed facility/facilities. Contact the Security Control Center at ext. 3-6153, as soon as possible, to request escorts.

5.3 Upon depletion or expiration of the substance, the PI and/or user will return the bottle to the controlled substance custodian, whether empty or not, with the usage record to assure accurate record keeping and/or proper disposal.

5.4 Unused controlled substances being returned to inventory will be “Hand Delivered” as specified above.

5.5 The requesting PI will be required to keep all controlled substances in secure storage and record each use on the corresponding usage sheets as specified below.

5.6 Controlled substances will be returned, to the controlled substance safe from which they were issued, inventoried, and stored, until such time that they are properly used or disposed of.

5.7 Generally, during inventories or before transfer controlled substances should be

checked for expiration dates and items nearing expiration should be replaced and/or recalled.

5.8 The required New York State Bureau of Controlled Substances Forms [DOH-2340](#) and [DOH-166](#) will be completed by the controlled substance custodian, endorsed by the licensee, and submitted for drug disposal approval.

5.8.1 Upon approval, at least two authorized personnel will be present to carry out the approved disposal method.

5.8.2 The controlled substance will be disposed of in the timeframe and by the method agreed to on the request forms.

### **Contamination, Spills or Breakage**

Any time a controlled substance becomes unusable due to one of these unplanned events it will be reported to the responsible PI and/or the issuing Licensee Custodian.

6.1 The cleanup will not begin until the responsible PI and/or Licensee Custodian arrives to witness the cleanup and take a verification sample.

6.2 The absorbent material and/or liquid residue will be placed in an appropriate container which will be secured by the Licensee Custodian until proper disposal can be scheduled.

6.3 The verification sample will be tested, using one of the analytical laboratories, to verify the presence of the regulated substance prior to final destruction.

6.4 The appropriate usage record will be documented under **Purpose** to reflect the loss due to the contamination, spill, or breakage.

### **Suspected Loss**

If for any reason, there is or appears to have been a **Loss of a Control Substance** the PI, Custodian, and Licensee will be immediately notified and supplied with all pertinent information.

7.1 The custodian will contact Security Services, ext 473-6173, who will immediately initiate an internal investigation.

7.2 Upon verification of the loss the Director of Security will submit a [DOH 2094, Loss of Controlled Substance Report](#) specifying all known facts surrounding the loss.

### **Record Keeping**

8.1 Inventory Custodian(s) will maintain accurate records documenting the following:

8.1.1 Records of Receipt (e.g., signed invoice, bill of lading, or packing slip)

8.1.2 Inventory Record, see Attachment I.

8.1.3 Usage Record, see Attachment II.

8.1.4 Copies of approved *Animal and Non-Animal Usage Request Forms*.

8.1.5 Records of Destruction

8.2 The Licensees and/or Principal Investigators shall initiate and monitor record keeping activities to ensure accurate maintenance and inventory control.

8.3 Document all storage container combination changes using the Security Combination Change Record, see Attachment V.

8.4 All records shall be maintained at the permitted premises for a period of not less than three years unless otherwise extended by DOH Records Retention Policies.

## Analytes and Action Levels

While medical cannabis products are often assumed to be inherently safe, **factors such as moisture content, bioburden, potency and the presence of contaminants play a significant role in determining the risk to patient health and safety.** The three major categories of contaminants targeted for testing include pesticides, solvents and microbiological contaminants.

Not all types of cannabis products need testing for all types of contaminants. Below is information on some of the major categories of testing. In evaluating what analysis should be performed, it is important to maintain perspective on the laboratory's role in the product quality ecosystem.

### Pesticides

Pesticides can lead to illness and therefore many states have included them on the list of analytes that need to be tested. There are no pesticides specifically approved for use on cannabis in the US. However, any pesticides meeting the criteria described in the USEPA 40 CFR 180.950(a), (b), or (c)<sup>7</sup> may be used as an inert ingredient in any minimum risk pesticide product applied to cannabis cultivation.

Selections of target pesticides for testing vary by state. For example, Massachusetts' Medical Marijuana Program requires testing prohibited pesticides identified by the American Herbal Pharmacopoeia,<sup>8</sup> which are commonly used in cannabis cultivation. But New Jersey's program selected pesticides for testing based on the EPA pesticide testing method 507,<sup>9,10</sup> with the addition of some representative pesticides of different classes from the USDA's "Pesticide Residue Testing of Organic Produce."<sup>11</sup>

The remainder of this section presents the approach taken by Oregon,<sup>12</sup> which established a list of target analytes related to pesticides. Oregon was not chosen as a model, they simply were chosen because they participated in the drafting of this section. As mentioned above, other states have taken different approaches, and as this document is updated APHL hopes to include more examples here.

Oregon started by compiling lists from three laboratories already involved in testing cannabis products for pesticides. Participating labs were members of a Rules Advisory Committee assembled to guide the state in developing rules for testing cannabis. The first list, was created as described in

<sup>7</sup> <https://www.law.cornell.edu/cfr/text/40/180.950>

<sup>8</sup> AHP. 2013. Cannabis Inflorescence, Cannabis spp., Standards of Identity, Analysis, and Quality Control. American Herbal Pharmacopoeia. 2013. Available at: [http://www.stcm.ch/files/us-herbal-pharmacopoeia\\_cannabis-monography.pdf](http://www.stcm.ch/files/us-herbal-pharmacopoeia_cannabis-monography.pdf)

<sup>9</sup> EPA. Method 507: Determination of Nitrogen- and Phosphorus-containing pesticides in water by gas chromatography with a nitrogen-phosphorus detector. Revision 2.1. Edited by J.W. Munch (1995). Available at <https://www.epa.gov/sites/production/files/2015-07/documents/epa-507.pdf>.

<sup>10</sup> EPA. Inert Ingredients Eligible for FIFRA 25(b) Pesticide Products (Updated December 2015). Available at [https://www.epa.gov/sites/production/files/2015-01/documents/section25b\\_inerts.pdf](https://www.epa.gov/sites/production/files/2015-01/documents/section25b_inerts.pdf).

<sup>11</sup> USDA. 2010 – 2011 Pilot Study: Pesticide Residue Testing of Organic Produce. Available at [https://www.ams.usda.gov/sites/default/files/media/Pesticide%20Residue%20Testing\\_Org%20Produce\\_2010-11PilotStudy.pdf](https://www.ams.usda.gov/sites/default/files/media/Pesticide%20Residue%20Testing_Org%20Produce_2010-11PilotStudy.pdf)

<sup>12</sup> Oregon Health Authority. Technical Report: Oregon Health Authority's Process to Determine which Types of Contaminants to Test for in Cannabis Products, and Levels for Action. Available at <https://public.health.oregon.gov/PreventionWellness/marijuana/Documents/oha-8964-technical-report-marijuana-contaminant-testing.pdf>.

Appendix 1 of “Pesticide Use on Cannabis” from the Cannabis Safety Institute,<sup>13</sup> and contained 123 active ingredients. The Committee generated the second list by selecting compounds that overlapped between various lists including the first list, as well as regulation lists for medical or recreational marijuana from Oregon, Nevada and Colorado. The third list was based on Integrated Pest Management guidance for several crops grown in the Pacific Northwest and a search of Washington State University’s Pesticide Information Center Online (PICOL) database.<sup>14</sup> The third list also included active ingredients available in pesticide products sold at a local hardware store. Removal of duplicates resulted in 188 pesticide analytes.

### **Action Levels<sup>15</sup>**

Ideally, action levels would be based on human health and toxicity thresholds. However, there is insufficient exposure information available to establish toxicity-based tolerances for pesticide residues in cannabis products. The variety of uses and exposure routes is too great, and there is not enough information about the pyrolysis products of target pesticides relevant to cannabis products when smoked.

Therefore, action levels for pesticides in cannabis in Oregon were developed based on laboratory limits of quantification (LOQ) that were deemed reasonably achievable by analytical chemists represented on the testing subcommittee of the rules advisory committee. The criterion for pass/fail was set on whether or not an analyte is detected above the action level.

To set action levels, the Oregon Health Authority (OHA) asked commercial analytical laboratories to submit their LOQs for each analyte on the target list. Two labs submitted LOQs, while a third lab submitted limits of detection on the instrument types from published literature. For each instrument type, OHA multiplied the higher of the LOQs from the two laboratories by a factor of two to get to the action level. For analytes not tested by the laboratories, OHA selected the highest action level from among analytes with the same published detection limits for the relevant analytical laboratory equipment.

Regarding piperonyl butoxide and pyrethrins, OHA adopted Nevada’s action levels. For piperonyl butoxide, the level is based on the Nevada state laboratory’s LOQ. The action level of 1 ppm for pyrethrins is based on the lowest federal food tolerance for pyrethrins in edible plant material. Washington’s Department of Health is also adopting Nevada’s action levels for these two compounds.

For analytes not tested in cannabis by any analytical laboratory in Oregon, OHA used surrogate analytes with similar published detection limits. While not ideal, this represented the best available estimate at the time. Oregon rules requiring that labs submit their limits of detection along with their LOQs will allow OHA to update action levels as appropriate in the future.

The Oregon limits in Table 1 are not thresholds; they are a best guess at the analytical LOQ for that analyte. This is because allowing a detection at all for an off-label compound would violate federal FIFRA laws. These limits are analytical in nature only and will probably be revised when Oregon has enough data to be sure the labs can achieve lower limits.

<sup>13</sup> <http://cannabissafetyinstitute.org/wp-content/uploads/2015/06/CSI-Pesticides-White-Paper.pdf>

<sup>14</sup> <http://cru66.cahe.wsu.edu/LabelTolerance.html>

<sup>15</sup> This pulls almost verbatim from reference 12 above.

**Table 1: Pesticide analytes and their action levels in OR**

Analyte	Chemical Abstract Services (CAS) Registry Number	Action Level ppm
Abamectin	71751-41-2	0.5
Acephate	30560-19-1	0.4
Acequinocyl	57960-19-7	2
Acetamiprid	135410-20-7	0.2
Aldicarb	116-06-3	0.4
Azoxystrobin	131860-33-8	0.2
Bifenazate	149877-41-8	0.2
Bifenthrin	82657-04-3	0.2
Boscalid	188425-85-6	0.4
Carbaryl	63-25-2	0.2
Carbofuran	1563-66-2	0.2
Chlorantraniliprole	500008-45-7	0.2
Chlorfenapyr	122453-73-0	1
Chlorpyrifos	2921-88-2	0.2
Clofentezine	74115-24-5	0.2
Cyfluthrin	68359-37-5	1
Cypermethrin	52315-07-8	1
Daminozide	1596-84-5	1
DDVP (Dichlorvos)	62-73-7	0.1
Diazinon	333-41-5	0.2
Dimethoate	60-51-5	0.2
Ethoprophos	13194-48-4	0.2
Etofenprox	80844-07-1	0.4
Etoxazole	153233-91-1	0.2
Fenoxycarb	72490-01-8	0.2
Fenpyroximate	134098-61-6	0.4
Fipronil	120068-37-3	0.4
Flonicamid	158062-67-0	1
Fludioxonil	131341-86-1	0.4
Hexythiazox	78587-05-0	1
Imazalil	35554-44-0	0.2
Imidacloprid	138261-41-3	0.4
Kresoxim-methyl	143390-89-0	0.4
Malathion	121-75-5	0.2
Metalaxyl	57837-19-1	0.2
Methiocarb	2032-65-7	0.2
Methomyl	16752-77-5	0.4
Methyl parathion	298-00-0	0.2



Analyte	Chemical Abstract Services (CAS) Registry Number	Action Level ppm
MGK-264	113-48-4	0.2
Myclobutanil	88671-89-0	0.2
Naled	300-76-5	0.5
Oxamyl	23135-22-0	1
Paclobutrazol	76738-62-0	0.4
Permethrins <sup>16</sup>	52645-53-1	0.2
Phosmet	732-11-6	0.2
Piperonyl_butoxide	51-03-6	2
Prallethrin	23031-36-9	0.2
Propiconazole	60207-90-1	0.4
Propoxur	114-26-1	0.2
Pyrethrins <sup>17</sup>	8003-34-7	1
Pyridaben	96489-71-3	0.2
Spinosad	168316-95-8	0.2
Spiromesifen	283594-90-1	0.2
Spirotetramat	203313-25-1	0.2
Spiroxamine	118134-30-8	0.4
Tebuconazole	80443-41-0	0.4
Thiacloprid	111988-49-9	0.2
Thiamethoxam	153719-23-4	0.2
Trifloxystrobin	141517-21-7	0.2

## Solvents

Various solvents (Table 2) are used during the manufacturing of cannabis extracts and concentrates to remove cannabinoids from the plant material. The extraction process is a super critical fluid process in which the marijuana plant material is placed in a vessel with the solvent at high pressures. Each solvent used has its own extraction efficiency, toxicity and latency within the extracted product. The compounds used for the extraction of cannabinoids may also pose a health risk.

While no health-based solvent residual limits have been established specifically for cannabis extract or concentrate products, practices around pharmaceutical production and limits provide a reasonable model, particularly for the oral route of exposure.

The US Pharmacopeia's National Formulary<sup>18</sup> Chapter 467 provides guidance for the use of solvents in the manufacturing of pharmaceutical products. This chapter has been adopted by many regulatory agencies in selecting solvents that may be utilized for extraction, as well as in setting the limits for residual solvents allowed in extracted products.

<sup>16</sup> Permethrins should be measured as cumulative residue of cis- and trans-permethrin isomers (CAS numbers 54774-45-7 and 51877-74-8 respectively).

<sup>17</sup> Pyrethrins should be measured as the cumulative residues of pyrethrin 1, cinerin 1, and jasmolin 1 (CAS numbers 121-21-1, 25402-06-6, and 4466-14-2 respectively).

<sup>18</sup> <http://www.usp.org/usp-nf>

The solvents are broken down into three different categories. Category 1 contains solvents that are known or suspected carcinogens, or environmental hazards. Category 2 contains non-genotoxic animal carcinogens or causative agents with irreversible toxicity. Category 3 contains compounds that have low toxicity potential to humans with no health-based exposure limits. The analytes as determined by the US Pharmacopeia are listed in Table 2 with their concentration limits and category.

Solvents found in categories 1 and 2 are either toxic or pose a significant enough health risk not to be utilized in the manufacturing of cannabis concentrates and extracts.

**Table 2: USP Chapter 467 Solvents and their concentration limit**

Solvent	Concentration Limit (ppm)	Category
Benzene	2	1
Carbon tetrachloride	4	1
1,2-Dichloroethane	5	1
1,1-Dichloroethene	8	1
1,1,1-Trichloroethane	1500	1
Acetonitrile	410	2
Chlorobenzene	360	2
Chloroform	60	2
Cyclohexane	3880	2
1,2-Dichloroethene	1870	2
1,2-Dimethoxyethane	100	2
N,N-Dimethylacetamide	1090	2
N,N-Dimethylformamide	880	2
1,4-Dioxane	380	2
2-Ethoxyethanol	160	2
Ethylene glycol	620	2
Formamide	220	2
Hexane	290	2
Methanol	3000	2
2-Methoxyethanol	50	2
Methylbutylketone	50	2
Methylcyclohexane	1180	2
Methylene chloride	600	2
N-Methylpyrrolidone	530	2
Nitromethane	50	2
Pyridine	200	2
Sulfolane	160	2
Tetrahydrofuran	720	2
Tetralin	100	2
Toluene	890	2
Trichloroethylene	80	2

Solvent	Concentration Limit (ppm)	Category
Xylene	2170	2
Acetic acid		3
Acetone		3
Anisole		3
1-Butanol		3
2-Butanol		3
Butyl acetate		3
tert-Butylmethyl ether		3
Cumene		3
Dimethyl sulfoxide		3
Ethanol		3
Ethyl acetate		3
Ethyl ether		3
Ethyl formate		3
Formic acid		3
Heptane		3
Isobutyl acetate		3
Isopropyl acetate		3
Methyl acetate		3
3-Methyl-1-butanol		3
Methylethylketone		3
Methylisobutylketone		3
2-Methyl-1-propanol		3
Pentane		3
1-Pentanol		3
1-Propanol		3
2-Propanol		3
Propyl acetate		3

Action limits for solvents in cannabis products in Oregon (Table 3) are based on the *International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use, ICH Harmonized Tripartite Guideline, Impurities: Guideline for Residual Solvents Q3C(R5) (ICH Q3C)*.<sup>19</sup> The health-based action levels in this guideline are based on the toxicity of individual solvents and the magnitude of exposure expected to occur from consuming 10 grams of a pharmaceutical (which is an unlikely amount of cannabis to consume).<sup>13</sup>

<sup>19</sup> <http://www.pmda.go.jp/files/000156308.pdf>

**Table 3: List of solvents and their action levels**

Solvent	Chemical Abstract Services (CAS) Registry Number	Action Level (µg/g)
1,2-Dimethoxyethane	110-71-4	100
1,4-Dioxane	123-91-1	380
1-Butanol	71-36-3	5000
1-Pentanol	71-41-0	5000
1-Propanol	71-23-8	5000
2-Butanol	78-92-2	5000
2-Butanone	78-93-3	5000
2-Ethoxyethanol	110-80-5	160
2-methylbutane	78-78-4	5000 <sup>20</sup>
2-Propanol (IPA)	67-63-0	5000
Acetone	67-64-1	5000
Acetonitrile	75-05-8	410
Benzene	71-43-2	2
Butane	106-97-8	5000 <sup>20</sup>
Cumene	98-82-8	70
Cyclohexane	110-82-7	3880
Dichloromethane	75-09-2	600
2,2-dimethylbutane	75-83-2	290 <sup>21</sup>
2,3-dimethylbutane	79-29-8	290 <sup>19</sup>
1,2-dimethylbenzene	95-47-6	See Xylenes
1,3-dimethylbenzene	108-38-3	See Xylenes
1,4-dimethylbenzene	106-42-3	See Xylenes
Dimethyl sulfoxide	67-68-5	5000
Ethanol	64-17-5	5000
Ethyl acetate	141-78-6	5000
Ethylbenzene	100-41-4	See Xylenes
Ethyl ether	60-29-7	5000
Ethylene glycol	107-21-1	620
Ethylene Oxide	75-21-8	50
Heptane	142-82-5	5000
n-Hexane	110-54-3	290
Isopropyl acetate	108-21-4	5000
Methanol	67-56-1	3000
Methylpropane	75-28-5	5000 <sup>16</sup>
2-Methylpentane	107-83-5	290 <sup>17</sup>

<sup>20</sup> Limit based on similarity to pentane<sup>21</sup> Limit based on similarity with n-hexane

Solvent	Chemical Abstract Services (CAS) Registry Number	Action Level (µg/g)
3-Methylpentane	96-14-0	290 <sup>17</sup>
N,N-dimethylacetamide	127-19-5	1090
N,N-dimethylformamide	68-12-2	880
Pentane	109-66-0	5000
Propane	74-98-6	5000 <sup>16</sup>
Pyridine	110-86-1	200
Sulfolane	126-33-0	160
Tetrahydrofuran	109-99-9	720
Toluene	108-88-3	890
Xylenes <sup>22</sup>	1330-20-7	2170

Oregon's list was generated by members of their Rules Advisory Committee with analytical chemistry experience as well as knowledge of common cannabis extraction and concentration techniques. They note that selected action levels for solvents in cannabis products may not be sufficiently protective if the product is inhaled. However, there are no studies upon which to base separate action level for products intended for smoking or vaping. ICH Q3C does assume 100% absorption by any route, which would include inhalation.<sup>13</sup>

Several states have developed a list of solvents considered safer for use as extraction solvents. Table 4 lists a few of these solvents, the agency and the maximum concentration levels. Massachusetts Department of Public Health adopted their criteria from the residual solvent recommendations by the Commission of the European Communities, Scientific Committee on Food (SCF, 1999).<sup>23</sup>

**Table 4: Solvent maximum concentration limits by state**

Solvent	Units	State Agency		
		MA	NV	CO
Propane	ppm	1000		
n-Butane	ppm	1000		
Iso butane	ppm	1000		
Butanes	ppm		500	800
Heptanes	ppm		500	500
Propane	ppm		500	
Benzene**	ppm			<1
Toluene**	ppm			<1
Hexane**	ppm			<10

\*\*Note: These solvents are not approved for use.

<sup>22</sup> Combination of: 1,2-dimethylbenzene, 1,3-dimethylbenzene, 1,4-dimethylbenzene, and ethyl benzene

<sup>23</sup> [http://ec.europa.eu/food/fs/sc/scf/out26\\_en.pdf](http://ec.europa.eu/food/fs/sc/scf/out26_en.pdf)

Other solvents such as alcohols and carbon dioxide, which are much less toxic, are becoming more prevalent in the industry, even though these solvents do not have the same extraction efficiency as petroleum hydrocarbon based solvents.

### Microbiologicals<sup>24,25,26</sup>

A review of existing literature shows that the presence of mold on cannabis can result in severe health complications and death.<sup>27,28,29,30</sup> Pathogenic bacteria may also be a cause of under-reported or under-recognized adverse events. For example, in December 2011 a kidney transplant recipient and New Mexico Medical Cannabis Program participant was hospitalized due to a gastrointestinal infection linked to smoking cannabis which had previously failed testing for the presence of enterobacteria and mold. The patient was encouraged to notify the Department of Health but declined due perceived hostility towards patients and industry stakeholders by administration and his relationship with the producer.<sup>31</sup>

Available literature supports the idea of a causal relationship between smoking cannabis and bacterial infections. Numerous human pathogens have been identified on cannabis and research on tobacco products suggests that these organisms are likely not completely destroyed during smoking.<sup>25,32,33</sup>

In general, bacteria cannot survive either the drying or heating processes to which cannabis is subjected. *Salmonella*, however, can survive at very low moisture levels and is highly infectious in humans. *E. coli* itself does not usually pose a significant health risk, but it is an indicator of poor sanitary conditions and the possible presence of other fecal bacteria.

**Aspergillus**, the spores of which can withstand desiccation and high temperatures, can cause respiratory infections in individuals who inhale it if they are severely immune-compromised and there is a known clinical correlation with cannabis smoking. However, some consider it unlikely that Aspergillus testing would be informative because it is so common in the environment. The Oregon Testing Subcommittee recommended that cannabis products intended for smoking and other inhalation uses include a warning about this risk for people with suppressed immune systems.

Some states have required testing of cannabis for aflatoxins produced by certain Aspergillus species.

**Aflatoxins** are highly carcinogenic mycotoxins which pose significant threat to exposed individuals, though concern of their presence on cannabis or in cannabis-derived products is debatable. United States Pharmacopoeial guidelines indicate that mycotoxin quantification is not necessary for all

<sup>24</sup> Dussy FE, Hamberg C, Luginbuhl M, Schwerzmann T. et al. Isolation of  $\Delta^9$ -THCA-A from hemp and analytical aspects concerning the determination of  $\Delta^9$ -THC in cannabis products. *For. Sci. Int.* 2005;149:3-10.

<sup>25</sup> Gargani Y, Bishop P, Denning DW. Too many mouldy joints—marijuana and chronic pulmonary aspergillosis. *Mediterr. J. Hematol. Infect. Dis.* 2011;3:e201105

<sup>26</sup> Szyper-Kravitz M, Lang R, Manor Y, Lahav M. Early invasive pulmonary aspergillosis in a leukemia patient linked to aspergillus contaminated marijuana smoking. *Leukemia and Lymphoma.* 2004;42:1433-1437.

<sup>27</sup> American Society of Addiction Medicine. Medical Marijuana Task Force White Paper Executive Summary. <http://www.ibhinc.org/pdfs/MedicalMarijuanaAGWhitePaper.pdf>

<sup>28</sup> Hamadeh R, Ardehali A, Locksley RM, York MK. Fatal aspergillosis associated with smoking contaminated marijuana, in a marrow transplant recipient. *Chest.* 1988;94:432-433.

<sup>29</sup> Hazekamp A. An evaluation of the quality of medicinal grade cannabis in the Netherlands. *Cannabinoids.* 2006;1:1.

<sup>30</sup> Verweij PE, Kerremans JJ, Voss A, et al. Fungal Contamination of Tobacco and Marijuana. *JAMA.* 2000;22:2875.

<sup>31</sup> Appen, J. Personal communication with patient. December 7, 2011.

<sup>32</sup> Pauly JL, Paszkiewicz G. Cigarette smoke, bacteria, mold, microbial toxins, and chronic lung inflammation. *J. of Onc.* 2011;doi:10.1155/2011/819129.

<sup>33</sup> Sapkota AR, Berger S, Vogel TM. Human pathogens abundant in the bacterial metagenome of cigarettes. *Env. Health. Pers.* 2010;3:351-356.

botanical products. The majority of products which are required to be analyzed for mycotoxins originate from root or rhizome material which THC-containing cannabis products presumably do not possess.

There is no readily available evidence to support the contention that cannabis harbors significant levels of **mycotoxins**. A simple literature search for mycotoxins and cannabis returned only one result: “Examination of fungal growth and aflatoxin production on marihuana” by G.C. Llewellyn and C.E. O’Rear published in *Mycopathologia* in 1977.<sup>34</sup> That paper examined illicitly grown cannabis seized by law enforcement and found that “[a]ll natural flora cultures tested negative for aflatoxins” and the authors concluded “[m]arihuana appears not to yield large quantities of these mycotoxins.”

Given there is no readily available evidence to support the contention that cannabis harbors significant levels of mycotoxins and ongoing advancements in the cannabis industry such as the introduction of requirements to test for microbiological contaminants and improvements in Good Manufacturing Practices (GMP) oversight, it is unlikely that mycotoxins would be identified on flower material.

There is one circumstance under which mandatory mycotoxin testing should be considered. When UV-C light exposure is insufficient to remediate a flower product contaminated with mold, that product is diverted to an extraction process. If the mold/fungi happens to be of a type which produces mycotoxins, those carcinogenic compounds may be concentrated during the extraction process and passed on to patients. **It is strongly advised that concentrate derived from plant material which entered into the extraction process due to mold contamination be tested for the presence of mycotoxins.**

Moisture present in herbal products is a primary determinant of the ability of microorganisms to thrive and rise to harmful levels post distribution. The Dutch Office of Medical Cannabis specifies that the water content of cannabis at the time of quality control (directly after packaging) must be between 5-10%. Testing for water activity, and requiring water activity levels to fall below  $A_w$  0.65, will ensure the absence of microbial growth on cannabis products during storage and prior to sale.

**Table 5: US Pharmacopeia Microbial Limits**

Preparation	Definition	USP Microbial Limits
Chopped or Powdered Botanicals	Hand-picked portions of the botanical (e.g. leaves, flowers, roots, tubers etc.) that are air dried and chopped, flaked, sectioned, ground or pulverized to the consistency of a powder.	Total Aerobic Microbial Count <10 <sup>5</sup> Total Combined Yeast and Mold Count <10 <sup>3</sup> Bile Tolerant Gram-negative Bacteria <10 <sup>3</sup> Absence of <i>Salmonella spp</i> & <i>E. coli</i> in 10 g

<sup>34</sup> <http://link.springer.com/article/10.1007%2FBF01259400>

Preparation	Definition	USP Microbial Limits
Powdered Botanical Extracts	Extracts are solids or semisolid preparations of a botanical that are prepared by percolation, filtration and concentration by evaporation of the percolate. The extracting material may be alcoholic, alkaline, acid hydro-alcoholic or aqueous in nature. Typically an extract is 4-10 times as strong as the original botanical. The extracts may be semisolids or dry powders termed powdered extracts.	Total Aerobic Microbial Count $<10^4$ Total Combined Yeast and Mold Count $<10^3$ Absence of <i>Salmonella spp</i> & <i>E. coli</i> in 10 g
Tinctures	Tinctures are solutions of botanical substances in alcohol obtained by extraction of the powdered, flaked or sectioned botanical.	Total Aerobic Microbial Count $<10^4$ Total Combined Yeast and Mold Count $<10^3$
Infusions	Infusions are solutions of botanical principles obtained by soaking the powdered botanical in hot or cold water for a specified time and straining. Typically infusions are 5% in strength.	Total Aerobic Microbial Count $<10^2$ Total Combined Yeast and Mold Count $<10$
Decoctions	Decoctions are solutions of botanicals prepared by boiling the material in water for at least 15 minutes and straining. Typically decoctions are 5% in strength.	Total Aerobic Microbial Count $<10^2$ Total Combined Yeast and Mold Count $<10$
Fluidextracts	A fluidextract is an alcoholic liquid extract made by percolation so that 1 mL of the fluidextract represents 1 g of the botanical.	Total Aerobic Microbial Count $<10^4$ Total Combined Yeast and Mold Count $<10^3$
Botanicals to be treated with boiling water before use	Dried botanicals to which boiling water is added immediately prior to consumption.	Total Aerobic Microbial Count $<10^5$ Total Combined Yeast and Mold Count $<10^3$ Absence of <i>E. coli</i> in 10 g



Preparation	Definition	USP Microbial Limits
Other raw materials and ingredients		Total Aerobic Microbial Count <math><10^3</math> Total Combined Yeast and Mold Count <math><10^2</math> Absence of <i>E. coli</i> in 10 g
Nutritional products with other highly refined ingredients	Edibles	Total Aerobic Microbial Count <math><10^3</math> Total Combined Yeast and Mold Count <math><10^2</math> Absence of <i>E. coli</i> in 10 g
Rectal Use Products	Rectal Suppositories For nonsterile products for pharmaceutical preparations and substances for pharmaceutical use	Total Aerobic Microbial Count <math><10^3</math> Total Combined Yeast and Mold Count <math><10^2</math>
Vaginal Use	Ointments, Creams, Inserts, etc. For nonsterile products for pharmaceutical preparations and substances for pharmaceutical use	Total Aerobic Microbial Count <math><10^2</math> Total Combined Yeast and Mold Count <math><10</math> Absence of <i>Pseudomonas aeruginosa</i> , <i>Staphylococcus aureus</i> and <i>Candida albicans</i> in 1g or 1mL
Transdermal Patches	For nonsterile products for pharmaceutical preparations and substances for pharmaceutical use	Total Aerobic Microbial Count <math><10^2</math> Total Combined Yeast and Mold Count <math><10</math> Absence of <i>Pseudomonas aeruginosa</i> , <i>Staphylococcus aureus</i>
Oral Mucosal, Gingival, Cutaneous, Nasal or Auricular use	For nonsterile products for pharmaceutical preparations and substances for pharmaceutical use	Total Aerobic Microbial Count <math><10^2</math> Total Combined Yeast and Mold Count <math><10</math> Absence of <i>Pseudomonas aeruginosa</i> , <i>Staphylococcus aureus</i>
Ophthalmic use		Must meet the requirements of USP 771 for Ophthalmic Preparations

## Metals<sup>35</sup>

Metals are present in our soil and water, both naturally and as a result of anthropogenic activities. Some of the activities include mining and smelting of metals, disposal of industrial wastes, burning of fossil fuels, paints, the use of fertilizers and pesticides in agriculture, production of batteries and other metal products, sewage sludge and municipal waste disposal. Metals in soil and water can be absorbed by plants during cultivation, resulting in elevated metals in plants and thus a concern for public health.

Cultivation of cannabis requires soil and water of a certain quality, i.e. it should be free of contaminants. Since this might not always be the case, screening of heavy metals is recommended to safeguard the cannabis user's health. **Heavy metals such as lead, cadmium, mercury, and arsenic are toxic to both plants and humans, and therefore often the focus of testing.**

## Cannabinoids

It is well known that the potency of cannabis products may vary largely by strain. The goal in determining what cannabinoids should be quantified is to support label accuracy. Although cannabis contains more than 150 cannabinoids, delta-9-tetrahydrocannabinol ( $\Delta^9$ -THC) has received the most attention since it is the principal psychoactive component of the plant. Other analytes often required for analysis include cannabidiolic acid (CBD-A), cannabigerolic acid (CBGA), cannabidiol (CBD), cannabigerol (CBG), tetrahydrocannabinol acid (THCA), cannabinol (CBN) and delta-8-THC ( $\Delta^8$ -THC). Information of other cannabinoids can help understand the pharmacological properties of cannabis.

In Oregon, the rule requires testing for THC, THC-A, CBD, and CBD-A. Due to the potential of THC-A decarboxylizing into  $\Delta^9$ -THC during sample processing and analysis, a total THC amount must be calculated,<sup>36</sup> where M is the mass or mass fraction of  $\Delta^9$ -THC or  $\Delta^9$ -THCA:

$$M \text{ total } \Delta^9\text{-THC} = M \Delta^9\text{-THC} + 0.877 \times M \Delta^9\text{-THCA}$$

Total CBD must also be calculated, where M is the mass or mass fraction of CBD and CBDA:

$$M \text{ total CBD} = M \text{ CBD} + 0.877 \times M \text{ CBDA}$$

Oregon acknowledged that as seen analytically, the mass ratio scenario is not perfect. They expect the equation for calculating Total THC to change after data is produced.

## Sampling and Analysis

The potency of cannabis products varies by strain. Also, contaminants may be introduced to the plant materials or cannabis products during growing, manufacturing and storage processes. To ensure the quality of the product and compliance with the standards set forth by each state, testing of cannabis products is recommended.

A comprehensive sampling and testing plan should be developed so that the testing results are representative for the products tested. Although no standardized sampling or testing protocols exist

<sup>35</sup> Tangahu BV, Abdullah SRS, Basri H, Idris M, Anuar N, and Mukhlisin M. International Journal of Chemical Engineering Volume 2011 (2011). <http://dx.doi.org/10.1155/2011/939161>

Chibuike GU and Obiora SC. Applied and Environmental Soil Science, Volume 2014 (2014) <http://dx.doi.org/10.1155/2014/752708>

Stern AH, Gochfeld M, Weisel C, Burger J. Mercury and methylmercury exposure in the New Jersey pregnant population. Arch Environ Health. 2001 Jan-Feb;56(1):4-10. [http://www.nrcs.usda.gov/Internet/FSE\\_DOCUMENTS/nrcs142p2\\_053279.pdf](http://www.nrcs.usda.gov/Internet/FSE_DOCUMENTS/nrcs142p2_053279.pdf)

<sup>36</sup> In Oregon, the total amount of THC must not exceed the maximum allowances for serving and package size even when heated.

for cannabis products, some examples can be found in programs from the United States, Canada and Europe, as well as in peer-reviewed articles.<sup>3,8,12,37,38,39</sup>

Specific sampling and testing approaches are outlined below. An overall reference for testing for contaminants can be found in: Daley, P, et al. *Testing Cannabis for Contaminants*. BOTEC Analysis Corp. September 12, 2013.<sup>3</sup> A quality management system, including validation of methods, is important for assuring the quality of testing and the quality of the product overall.

### Sample Collection

Representative sampling for any form of cannabis product must be conducted. Specific sampling instructions have been developed by different states based on sampling guidance for food products and herbal medicines developed by the Codex Alimentarius Commission<sup>40</sup> and the United States Pharmacopeia<sup>8</sup>.

Generally, a random sample should be conducted. For example, to collect samples from cannabis plant material, New Jersey collects five ~5 g samples from the dry plant materials for each new strain. The results are considered representative since the weight of the total samples collected is approximately 5% of the total products from each harvest. Each sample is tested for potency and the composite of the five samples are also tested for potency, heavy metals, pesticides and mycotoxin. The QA samples (5-10% of the testing samples or a minimum of two samples) are also collected, stored under the same conditions as other products at the center and tested six months later to examine whether there are changes in potency or contamination due to storage.

Massachusetts provides specific guidance for sampling from different matrices, such as cannabis oil, resin or other solid products. The specific sample collection procedures (i.e., documentation) and sampling tools required for sample collection can be found in their guidance<sup>35</sup>.

The homogeneity of liquid products is usually better than solid products. For liquid products, the product should be well-mixed by stirring before sample collection.

Given the concern of homogeneity of solid cannabis products, a quartering method is recommended<sup>41</sup>. Briefly, the procedure includes the following steps:

1. Place the well-mixed ground products into a square shape.
2. Divide the material into four equal parts.
3. Take two parts from the opposite corners, mix them and collect samples needed.
4. Repeat steps until the designated number of samples are collected.

Every manufacturing run should have samples collected during manufacturing, representing 5% of the total dosage units of the sampled lot. To ensure that samples are representative of the entire lot, samples should be collected at random throughout the process. The samples will help determine whether a lot can be released from manufacturing hold and distributed to patients.

<sup>37</sup> <http://www.mass.gov/eohhs/docs/dph/quality/medical-marijuana/lab-protocols/finished-mmj/final-revised-mdph-mmj-mips-protocol.pdf>

<sup>38</sup> Health Canada (2008). Industrial Hemp Technical Manual. B. o. D. Surveillance. Canada, Therapeutic Products Directorate.

<sup>39</sup> [https://www.health.ny.gov/regulations/medical\\_marijuana/docs/regulations.pdf](https://www.health.ny.gov/regulations/medical_marijuana/docs/regulations.pdf)

<sup>40</sup> [http://www.fao.org/fao-who-codexalimentarius/sh-proxy/en/?Ink=1&url=https%253A%252F%252Fworkspace.fao.org%252Fsites%252Fcodex%252Fstandards%252FCAC%2BGL%2B50-2004%252FCXG\\_050e.pdf](http://www.fao.org/fao-who-codexalimentarius/sh-proxy/en/?Ink=1&url=https%253A%252F%252Fworkspace.fao.org%252Fsites%252Fcodex%252Fstandards%252FCAC%2BGL%2B50-2004%252FCXG_050e.pdf)

<sup>41</sup> Sexton M and Ziskind J. 2013. Sampling Cannabis for Analytical Purposes. BOTEC Analysis Corp. I-502 Project #430-1e.

Another resource for sampling is the “Guidance on Obtaining Defensible Samples,” or “GOODSamples,”<sup>42</sup> which includes a systematic approach to developing sampling protocols for defensible decisions. Good sampling is key to improving analytical data equivalency among organizations, a step in facilitating inter-agency data sharing. An archived APHL webinar<sup>43</sup> addresses basic concepts, basic terminology and the need for program-wide understanding of sampling principles for the improvement of data quality, data acceptability and more efficient use of resources.

## Sample Analysis

### Pesticides

Given the wide range of physical properties of pesticides, both liquid chromatography (LC) and gas chromatography (GC) methods are required for testing.

#### Sample Preparation

Pesticides in a cannabis plant material can be extracted by QuEChERS extraction procedure and analyzed by GC-MS. QuEChERS (**Q**uick, **E**asy, **C**heap, **E**ffective, **R**ugged, and **S**afe) is a general purpose extraction procedure for the determination of organic compounds in fruits, vegetables and vegetation.<sup>44</sup> It is applicable to a wide range of organic compounds that are partitioned from a fruit, vegetable or vegetation sample to acetonitrile or other suitable solvents. Substituting acetonitrile with ethyl acetate as an extracting solvent provides adequate recovery of a target pesticide while minimizing extraction of other compounds in cannabis material, therefore minimizing interference. The sample extract can also be used for LC-based analysis after a solvent exchange into an LC mobile-phase-compatible solvent such as acetonitrile or methanol.

#### Sample Analysis

Quantification of pesticides can be performed by EPA Residue Analytical Methods (RAM)<sup>45</sup> or FDA Pesticide Analytical Manual (PAM).<sup>46</sup> GC-MS or GC-MS/MS, LC-MS or LC-MS/MS methods are most common methods for pesticides detection.

### Solvents

The analysis of residual solvents is primarily performed using headspace gas chromatographic flame ionization detection (HS GC-FID). The sample is placed in a septa-sealed volatile vial with a non-interfering less volatile solvent and heated. This causes any solvents that may be present in the sample to dissolve into the septa-sealed volatile vial. The instrument then punctures the septa, removes a portion of the headspace and injects this into the GC-FID instrument for analysis. This method has the potential to be used for the analysis of other cannabis matrices and products after validating the method for a particular matrix or product.

The analysis is dependent on a partition coefficient being developed in the vial to allow the residual solvents to dissolve into the headspace above the sample. The coefficient can be developed either by adding a non-interfering less volatile solvent to the sample. This type of analysis is static headspace analysis and has the potential to have matrix effects. The more complex the matrix becomes, the more difficult it is to develop a partition to allow the residual solvents to migrate into the headspace in the vial. A complex matrix allows the residual solvents to be absorbed into the matrix and affects the quantitative ability of the analysis.

<sup>42</sup> <http://www.aafco.org/Portals/0/SiteContent/Publications/GOODSamples.pdf>

<sup>43</sup> <http://bit.ly/1SJUx8N>

<sup>44</sup> Steven J. Lehotay, Kyung Ae Son, Hyeyoung Kwon, Urairat Koesukwiwat, Wusheng Fu, Katerina Mastovska, Eunha Hoh, Natchanun Leepipatpiboon. *Journal of Chromatography A* Volume 1217, Issue 16, 16 April 2010, Pages 2548–2560 doi:10.1016/j.chroma.2010.01.044

<sup>45</sup> <https://archive.epa.gov/pesticides/methods/rammethods/web/html/ram12b.html>

<sup>46</sup> <http://www.fda.gov/Food/FoodScienceResearch/LaboratoryMethods/ucm2006955.htm>

The alternative to static headspace analysis is Full Evaporation Technique (FET). This type of headspace analysis is where the sample is added to a vial with no solvent. The sample is heated directly and the headspace in the vial is used for analysis. The FET version of the analysis does not rely on the development of a partition, however, the homogeneity of the sample is very important.

The extracted cannabinoid material can be in many forms: liquid, wax or a harder, brittle solid material known as “shatter.” For waxes and solids, the dispersion of solvents may be heterogeneous. As the solid material becomes thinner, the solvent will out gas more readily from the material, this causes diffusion of the solvent, which migrates to the thinner portions of the material, increasing the concentration. When these materials are sampled for analysis, care must be used to take a representative sampling from each thickness region of the sample. This sampling technique will ensure a more representative analysis of the material and avoid high or low biases to the analytical result.

Massachusetts has detailed instructions for testing residual solvents.<sup>47</sup> some of which is copied below:

As discussed in Section 4.2.1, residual solvents testing is required only for cannabis resins and concentrates where solvents have been used in the production process. In particular, a production batch of cannabis oil may be dispensed as a finished medical marijuana product or used to make another medical marijuana product only if:

- Laboratory analysis verifies that all solvents used at any stage of cannabis oil production, except in cleaning equipment, are below the limits provided in Exhibit 6; and
- The production batch passes all other applicable testing requirements.

Only solvents listed in Exhibit 7 may be used in the production of cannabis oil. A RMD is required to test only for those solvents used, and it is not required to test for any residual solvents if it can document that no solvents were used in the cannabis oil production process.

The upper limits for residual solvents in Exhibit 7 are given as milligrams of residual solvent per kilogram of cannabis oil. DPH developed the upper limits based on residual solvent standards provided by the United States Pharmacopeia (USP Chapter <467>), the International Conference on Harmonization (ICH, 2011), and AHP (2013). Consistent with the standards provided by these sources, “Class 1” solvents including benzene, carbon tetrachloride, 1,2-dichloroethane, 1,1-dichloroethene, and 1,1,1-trichloroethane may not be used in the production of any medical marijuana product.

Analyses to determine residual solvent concentrations in medical marijuana products must be performed in accordance with the methods identified in USP Chapter <467>.

#### **Quality Control and Quality Assurance (QC/QA)**

QC/QA plan must be developed and implemented based on the requirement of the testing purposes. For example, full validation of the method must be conducted to achieve accuracy, precision and sensitivity. In addition, secondary sources of the standards for the target analytes should be obtained and included in the testing plan. More, given the complex matrix

<sup>47</sup> <http://www.mass.gov/eohhs/docs/dph/quality/medical-marijuana/lab-protocols/finished-mmj/final-exhibit-7-residual-solvent-limits.pdf>

of the cannabis raw material, preparation of the calibration standards in the same matrix as the sample extract is recommended when testing the plant material.

Currently, there is program established for proficiency testing, which should be established in the near future.

### **Metals**

Atomic absorption and inductively coupled plasma-mass spectrometry (ICP-MS) are commonly-used methods for metal testing, while the US FDA ICP-MS method<sup>48</sup> is widely used for quantification of metals in cannabis products. Analytes required for testing vary by state:

- New Jersey: arsenic, cadmium, iron, lead, manganese, mercury, nickel, selenium and zinc.
- Massachusetts: arsenic, cadmium, lead and mercury.
- New York:<sup>49</sup> arsenic, cadmium, chromium, copper, nickel, zinc, selenium, mercury and lead.

### **Cannabinoid Profile**

The choice of instrumentation used to perform quantification of cannabinoids is important in accurately determining potency and is based on the type of sample. Inaccuracies can cause patients discomfort due to an inappropriate dose.

Several analytical methods have been established to characterize the cannabinoid profile of cannabis products,<sup>8,50,51,52</sup> including thin layer chromatography (TLC), gas chromatography (GC) and high pressure liquid chromatography (HPLC).

Among all of the analytical methods, the most common methods employed for cannabinoid analysis are GC-MS, GC-FID and LC-DAD (diode array detector) methods. However, the analytical method selected needs to match with the application.

In raw plant material, cannabinoids, particularly  $\Delta^9$ -THC, primarily exist in their non-psychoactive acidic form ( $\Delta^9$ -THC-A-A). If characterization of cannabinoids in all forms is needed, the LC-DAD method is recommended. All forms of the cannabinoids, whether in acid or neutral form, are stable during analysis by liquid chromatography, whereas decarboxylation may occur when testing by gas chromatography.<sup>8,47,48</sup>

The GC method employs a high temperature inlet and oven heating program to volatilize, separate and elute the material. Since cannabinoids in acid form are unstable and easily decarboxylated by heating (> 60 °C) this results in their changing from acid form to their neutral form, which in the case of THC, is the psychotropic form.

In addition, if GC temperatures are sufficiently high, the THC may be degraded, resulting in under-reporting of potency. Dussy, F., et. al., determined their GC was reporting THC total values that

<sup>48</sup> FDA. 2011. Analysis of Foods for As, Cd, Cr, Hg and Pb by Inductively Coupled Plasma-Mass Spectrometry (ICP-MS). United States Food and Drug Administration, Center for Food Safety and Applied Nutrition, Current Method CFSAN/ORS/DBC/CHCB April 25, 2011. Available at: <http://www.fda.gov/downloads/Food/FoodborneIllnessContaminants/Metals/UCM272693.pdf>

<sup>49</sup> New York State Department of Health-Wadsworth Center. Metals and Metalloids in Medical Marijuana Products by ICP-MS. <http://www.wadsworth.org/sites/default/files/WebDoc/760769119/LINC-250-01.pdf>

<sup>50</sup> De Backer B, Debrus B, Lebrun P, Theunis L, Dubois N, Decock L, Verstraete A, Hubert P, Charlier C. J Chromatogr B Analyt Technol Biomed Life Sci. 2009 Dec 15;877(32):4115-24. doi: 10.1016/j.jchromb.2009.11.004

<sup>51</sup> Raharjo TJ and Robert Verpoorte, Phytochemical Analysis, Volume 15, Issue 2, pages 79–94, 2004 DOI: 10.1002/pca.753

<sup>52</sup> Giese MW, Lewis MA, Giese L and Smith KM. Journal of AOAC International, Volume 98, Number 6, November-December 2015, pp. 1503-1522(20) DOI: <http://dx.doi.org/10.5740/jaoacint.15-116>

were as much as 30% lower than actual values, and therefore could not provide a full profile of cannabinoids.<sup>2</sup> In order to report cannabinoid content accurately using a GC, samples must first be subjected to a derivatization step and the extent of decomposition must be qualified against a liquid chromatographic method.<sup>8</sup>

Below is an example to illustrate the importance of GC versus LC analysis and differentiating between acidic and neutral for cannabinoids in a manufacturing process:

An infused product manufacturer was having its extract analyzed using GC and was told that it contained approximately 87% w/w THC. When the finished product was distributed, patient feedback suggested that the product was ineffective and did not elicit the desired effect. After the extract was reanalyzed using a liquid chromatographic method, it was discovered that the extract was 49% w/w THC. The difference was due to the GC having decarboxylated the anti-inflammatory THC-A to the psychotropic THC. Due to the error that occurred during the initial analysis, the manufacturer added roughly half of the amount of extract needed to achieve the dose listed on the package label resulting in a misbranded product and dissatisfied patients.

#### *Sample Preparation*

A number of organic solvents are used to extract cannabinoids, including polar solvents such as methanol, ethanol and chloroform, and less polar solvents such as benzene, petroleum ether and n-hexane.<sup>48</sup> Specific sample preparation procedures can be found in AHP (2013), DeBacker et al. (2009), and Giese et al., (2015).<sup>8,47,49</sup>

New Jersey reported that the mixture of methanol and chloroform (9:1) was an optimal solvent for extracting cannabinoids.<sup>53</sup> The sample extract is filtered through a 0.2 µm Nylon, dried by nitrogen without heating and re-dissolved in 200 µL of methanol:water (65:35). Proper dilution is needed to minimize contamination of the instrument by the complex matrix while meeting the sensitivity of the analytical method. Giese et al. (2015) reported an extraction method which includes one single sample preparation, and the extract can be used for the analysis of both cannabinoids and terpenes using HPLC-DAD and GC-FID, respectively.<sup>49</sup>

#### *Analysis by GC Method*

The commonly-used analytical columns for separation of cannabinoids are fused silica non-polar columns such as HP-1 (or DB-1) and HP-5 (or DB-5). Quantitation can be achieved by either flame ionization detection (FID) or mass spectrometry (MS), the latter can provide identification of the constituents as well. If the goal of the analysis is to quantify both acid and neutral compounds by GC, prior derivatization is required.<sup>48</sup> Employment of internal standards, such as 5α-cholestane, docosane and tetracosane are suitable for quantitation by GC-FID method, while deuterated cannabinoids are good internal standards for MS detection.

#### *Analysis by LC method*

The commonly-used column for separation of cannabinoids includes the reversed-phase of the octadecyl type, C<sub>8</sub> and C<sub>18</sub>, and the mobile phase is methanol:water (8:2 or other ratio) running at isocratic condition or gradient.<sup>8,47,49,50</sup> Acetic acid is used to adjust the mobile phase pH to ~4.75.

This method can also be modified for the analysis of other cannabis products, such as foods and cannabis oil. However, appropriate modification in sample preparation is needed and full validation

<sup>53</sup> Patel B, Wene DJ, Hom SS, Parsa B. Quantitative Determination of Cannabinoids in Cannabis Plant Material Using High Performance Liquid Chromatography - UV Diode Array-Mass Spectrometry (Trap) Detector. Abstract #445 available at <http://easinc.org/wordpress/wp-content/uploads/2015/11/EAS-2015-Abstract-Book.pdf>

of the method needs to be conducted according to the US FDA guidance for bioanalytical method validation (2013).<sup>54</sup>

New York provides a method for analysis of the cannabis products in capsules, tinctures or formulations for vaporization. Briefly, approximately 10-200 mg of cannabis product is extracted with methanol. A portion of the extract is then removed for analysis. Internal standard is added, and the extract is diluted up to 100-fold for analysis based on the concentrations of cannabinoids in the samples as declared by the submitting Registered Organization. The targeted analytes are separated by HPLC and subsequently detected online by monitoring UV absorbance using a PDA detector. The separation of ten cannabinoids is achieved on a C18 reverse-phase column 150 mm in length. The limit of quantification for most of the cannabinoids is approximately 0.60 µg/mL. This method can be used to quantify the cannabinoid components that are present as low as 0.04% (percent by weight) in the medical cannabis products. The specific procedures for sample preparation and analysis can be found in NYS DOH MML-301 and NYS DOH MML-300, respectively.<sup>55</sup>

### Laboratory Certification/Registration/Accreditation

Laboratory accreditation is important to the industry as whole and extremely valuable in assuring that data utilized in consumer and public health decisions is of high quality and defensible. It is key to a successful medical cannabis testing program.

Although each state has taken a different approach, the overall process for accreditation remains the same: a laboratory applies for accreditation and provides the appropriate quality and technical standard operating procedures. The state agency performs an onsite assessment, and if deficiencies are observed, the laboratory performs root cause analysis and corrective action.

Below are some state web sites for cannabis testing laboratories:

#### Colorado<sup>56</sup>

“We coordinate the inspection of retail marijuana testing facilities. We review all documentation and practices to ensure the rules set forth by the Colorado Department of Revenue are being met and to determine whether to recommend the testing facilities for certification to the Department of Revenue. The Marijuana Enforcement Division is the certifying body of the Department of Revenue.”

#### New York

This link provides details of the Environmental Laboratory Approval Program’s (ELAP) corresponding application forms and related accreditation information: <http://www.wadsworth.org/labcert/elapcert/appforms.htm>.

For state certification it is necessary to return the completed application (Form 107—Application Form<sup>57</sup>). An inspection by an ELAP Environmental Laboratory Consultant may also be required prior to a laboratory’s certification.

- Develop a checklist for the licensing or certification process
- Decide whether the process will be done by in-house experts or third parties, like the American Association for Laboratory Accreditation (A2LA)

<sup>54</sup> <http://www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm368107.pdf>

<sup>55</sup> <http://www.wadsworth.org/sites/default/files/WebDoc/576578963/MML-300-01.pdf>  
<http://www.wadsworth.org/sites/default/files/WebDoc/1495494332/MML-301-01.pdf>  
<http://www.wadsworth.org/sites/default/files/WebDoc/359205661/MML-303-01.pdf>

<sup>56</sup> <https://www.colorado.gov/pacific/cdphe/inspection-retail-marijuana-testing-facilities>

<sup>57</sup> <http://www.wadsworth.org/labcert/elapcert/appforms.htm>



- Find or develop a proficiency testing program that includes enough information to assure a certain level of accountability (i.e. includes QC data)

New York has a detailed process for certification,<sup>37</sup> the relevant pieces of which are copied below:

(l) For each lot of medical marijuana product produced, the registered organization shall submit a predetermined number of final medical marijuana products (e.g., sealed vials or capsules; with the number of samples submitted, based on statistical analysis, determined to be representative of the lot) to an independent laboratory/laboratories approved by the NYS Department of Health (“department”). The laboratory verifying the cannabinoid content shall be approved for the analysis of medical marijuana product by the department in accordance with section five hundred two of the public health law and subpart 55-2 of this title. Such laboratory, or approved laboratories cumulatively, shall certify the medical marijuana product lot as passing all contaminant testing and verify that the content is consistent with the brand prior to the medical marijuana product being released from the manufacturer to any dispensing facility.

**§1004.14 Laboratory testing requirements for medical marijuana.**

(a) Medical marijuana products produced by a registered organization shall be examined in a laboratory located in New York State that is licensed by the federal Drug Enforcement Administration (DEA) and approved for the analysis of medical marijuana by the department in accordance with article 5 of the public health law and subpart 55-2 of this title.

(b) No board member, officer, manager, owner, partner, principal stakeholder or member of a registered organization shall have an interest or voting rights in the laboratory performing medical marijuana testing.

(c) The registered organization shall submit to the laboratory, and testing shall only be performed on, the final medical marijuana product equivalent to the sealed medical marijuana product dispensed to the patient (e.g., in a sealed vial or intact capsule).

(d) Testing of the final medical marijuana product is mandatory. However, at the option of the registered organization, testing may be performed on components used for the production of the final medical marijuana product including but not limited to water or growing materials. Testing may also be performed on the final marijuana extract prior to packaging e.g. for cannabinoid profile verification or contaminant testing.

(e) Sampling and testing of each lot of final medical marijuana product shall be conducted with a statistically significant number of samples and with acceptable methodologies such that there is assurance that all lots of each medical marijuana product are adequately assessed for contaminants and the cannabinoid profile is consistent throughout.

(f) Testing of the cannabinoid profile shall include, at a minimum, those analytes specified in section 1004.11(c)(2) of this part.

(g) Testing for contaminants in the final medical marijuana product shall include but shall not be limited to those analytes listed below. The department shall make available a list of required analytes and their acceptable limits as determined by the commissioner.

Analyte: *E. coli*, *Klebsiella Pseudomonas* (for products to be vaporized), *Salmonella*, *Streptococcus*, Bile tolerant gram negative bacteria, *Aspergillus Mucor* species, *Penicillium* species, Thermophilic Actinomycetes species, Aflatoxin, Ochratoxin, Antimony, Arsenic,

Cadmium, Chromium, Copper, Lead, Nickel, Zinc, Mercury, Any pesticide/herbicide/fungicide used during production of the medical marijuana product, Any growth regulator used during production of the medical marijuana product, Any other analyte as required by the commissioner

(h) The laboratory shall track and destroy any quantity of medical marijuana product that is not consumed in samples used for testing.

### **Oregon<sup>58,59</sup>**

“It is strongly recommended that laboratories interested in ORELAP accreditation for Cannabis apply as soon as possible. The accreditation process takes several months.

“The final analyte lists are complete. It is possible to apply for some technologies (such as LCMSMS) and matrices (Cannabis plant is in the ‘Biological Tissue’ matrix, Cannabis products will likely be in the ‘Solid’ matrix) and add other technologies later, OR add the technologies that you currently perform with the analyte list.

“If your technology and method are accredited, adding additional analytes that are included in the Rule will not require an additional site visit. However, it will require a document review of your new Standard Operating Procedure (SOP) and method validation.

“Until a lab is fully accredited for all of desired methods, labs can subcontract non-accredited analytes to an ORELAP accredited laboratory, per the TNI 2009 Standard. Laboratories are required to be accredited before OLCC licensing per HB 3400.”

### **Washington<sup>60</sup>**

“Third party testing labs must meet certain accreditation criteria in order to be certified as a lab that is allowed to test useable marijuana and marijuana products under the I-502 regulatory system. The Board has contracted with the Center for Laboratory Sciences on the Campus of the Columbia Basin College to conduct the certification process.”

## **Outreach**

As with any program, a key to success is communication and partnership. Some groups that might benefit from understanding a laboratory’s capabilities and limitations include:

- Legislature
- Regulatory bodies
- State Poison Control Centers
- Epidemiologists
- Emergency Departments

## **Efficacy & Side Effects of the Products**

Data results will need to be stored and analyzed to see what poses a health risk and what doses appear efficacious, so refinements can be made over time. States should consider instituting surveillance to capture both positive and negative effects of cannabis use. New York is planning a

<sup>58</sup> <https://public.health.oregon.gov/LaboratoryServices/EnvironmentalLaboratoryAccreditation/Pages/index.aspx>

<sup>59</sup> <https://olis.leg.state.or.us/liz/2015R1/Measures/Overview/HB3400>

<sup>60</sup> <http://www.liq.wa.gov/mj2015/testing-facility-criteria>

clinical trial involving feedback from the state system through self & physician reporting.<sup>61</sup> Minnesota and Colorado will look at this data as well.<sup>62</sup> This type of data will also be critical to understanding and addressing risk over time.

## Appendix: Links to State Programs, Laws, Regulations

### Maine

Information on Maine's program can be found at [http://legislature.maine.gov/legis/bills/bills\\_127th/billtexts/HP072701.asp](http://legislature.maine.gov/legis/bills/bills_127th/billtexts/HP072701.asp)

### Maryland

Information on Maryland's program can be found at <http://mmcc.maryland.gov/>

### Massachusetts

By way of background, on January 1, 2013, Chapter 369 of the Acts of 2012 became law allowing qualifying patients with certain defined medical conditions the legal authority to obtain and use marijuana for medicinal use in the Commonwealth of Massachusetts. This law required that MDPH develop regulations that provide the regulatory framework to ensure that qualified patients have timely access to safe marijuana for medical use. The purpose of their draft protocol below is to provide Massachusetts Registered Marijuana Dispensaries with a health-protective framework for the collection and analysis of medical marijuana products, and comply with Massachusetts regulation 105 CMR 725.000, Implementation of an Act for the Humanitarian Medical Use of Marijuana.

- For additional information about the Medical Use of Marijuana Program, including the authorizing Medical Marijuana Statute, please visit the MMJ Program website at <http://www.mass.gov/eohhs/gov/departments/dph/programs/hcq/medical-marijuana/>
- Laboratory Testing Protocol: <http://www.mass.gov/eohhs/gov/departments/dph/programs/hcq/medical-marijuana/laboratory-testing-protocols.html>
- <http://www.mass.gov/eohhs/docs/dph/quality/medical-marijuana/lab-protocols/finished-mmj/final-revised-mdph-mmj-mips-protocol.pdf>

### Nevada

Information on Nevada's program can be found at [http://dpbh.nv.gov/Reg/MME/dta/Policies/Medical\\_Marijuana\\_Establishments\\_\(MME\)\\_-\\_Policies/](http://dpbh.nv.gov/Reg/MME/dta/Policies/Medical_Marijuana_Establishments_(MME)_-_Policies/)

### New York

[https://www.health.ny.gov/regulations/medical\\_marijuana/docs/regulations.pdf](https://www.health.ny.gov/regulations/medical_marijuana/docs/regulations.pdf)

<sup>61</sup> <http://www.bizjournals.com/buffalo/news/2016/01/20/childrens-to-serve-as-medical-marijuana-clinical.html>

<sup>62</sup> <http://www.modernhealthcare.com/article/20140911/NEWS/309119931>

## **Association of Public Health Laboratories**

The Association of Public Health Laboratories (APHL) works to strengthen laboratory systems serving the public's health in the US and globally. APHL's member laboratories protect the public's health by monitoring and detecting infectious and foodborne diseases, environmental contaminants, terrorist agents, genetic disorders in newborns and other diverse health threats.



8515 Georgia Avenue, Suite 700  
Silver Spring, MD 20910  
Phone: 240.485.2745  
Fax: 240.485.2700  
Web: [www.aphl.org](http://www.aphl.org)