

## Docket No. FDA-2019-N-1482

### Scientific Data and Information about Products Containing Cannabis or Cannabis-Derived Compounds; Public Hearing; Request for Comments.

#### A. Health and Safety Risks

1. **Based on what is known about the safety of products containing cannabis and cannabis-derived compounds, are there particular safety concerns that FDA should consider regarding its regulatory oversight and monitoring of these products?**

While cannabis and cannabis-derived products themselves have largely been shown to be safe, cannabis and cannabis-derived compounds do have safety concerns that can arise around the cultivation and manufacturing processes. States with inclusive cannabis regulations have been tasked with determining the products best suited for pest management as well as determining safe levels of cannabinoid content, particularly delta-9-tetrahydrocannabinol (THC), as it is the primary psychoactive component of the cannabis plant. Safety concerns also extend to the manufacturing of extracts and the products being used in the extraction process as the extracts may then be used in the production of food and non-food items.

#### Pesticides

A review of recall notices from [Colorado](#), [Oregon](#), [Washington](#), [Appendices 1-3] and California shows that the majority of recalls were issued because of either the use of non-permitted pesticides or the presence of pesticides at levels above the state-implemented limit. [California](#) also experienced a recall due to a laboratory falsifying testing results for 22 pesticides that it was unable to detect at the state-specified limits. [Appendix 4] According to the Environmental Protection Agency (EPA), there are no pesticides that have been approved for use on cannabis crops. In a [memo](#) from November 1, 2017, the EPA noted that four states submitted Special Local Needs registrations to use tolerance-exempt pesticides on cannabis and that all four registrations were denied or withdrawn after the EPA informed the states of their intent to disapprove the registrations. [Appendix 5]

#### *Recommendation:*

*Americans for Safe Access urges the FDA to work with the EPA to identify and set limits on the types of pesticides that are approved for use in the cultivation of cannabis and hemp and also establish limits on any residual pesticides that could be present in cannabis and hemp flowers, extracts, or manufactured products, specifically for non-permitted pesticides. We also urge the EPA to require all persons who are applying pesticides to take appropriate training courses related to safe application, proper personal protective equipment, and permissible entry limits/re-entry intervals.*

#### Solvents

In [Colorado](#), a recall was also required for products that exceeded the allowable amount of residual solvents. [Appendix 6] The use of solvents for the extraction of cannabinoids and terpenes from cannabis is permitted in some states, however those states place limits on the type of solvent that can be used and, where necessary, limits on any solvents remaining in the extract

post-processing. Carbon dioxide (CO<sub>2</sub>) is the solvent most typically permitted for use in cannabis extractions and has no residual solvent testing limits. Hydrocarbons such as butane are also used as solvents where permitted, but limits are imposed on hydrocarbon solvent residue. The Colorado recall involved products that exceeded the allowable amount of ethanol, another solvent effective in cannabinoid extractions.

*Recommendation:*

*ASA urges the FDA to set limits on the types of solvents that may be used to produce cannabis and hemp extracts and establish limits on any residual solvents that may be present in these extracts. ASA also recommends that the FDA work closely with the Department of Labor and the Occupational Safety and Health Administration to develop regulations related to the safe handling, storage, and use of solvents in extractions and the facilities needed for such activities.*

Potency of THC-rich Products

Another potential safety concern the FDA should consider is the potency of cannabis-derived products due to some of the side effects of THC and how its effects vary between people. THC's effects can vary based on a number of different factors, including rate of metabolization, amount consumed, type consumed, and method of consumption as well as factors such as the person's height, weight, and experience with cannabis. California, Colorado, and Washington limit the THC in their adult-use edible products to 10mg THC/serving and 100mg THC/package, with no restrictions placed on the CBD or additional cannabinoid content of either medical or adult-use products. Washington and California limit the amount of THC permitted in medical cannabis products, with California setting a package limit of either 100mg/package (non-orally dissolving) or 500mg/package (orally dissolving) and Washington establishing a limit of 100mg THC/package. Colorado has no THC limit on medical cannabis products.

*Recommendation:*

*The potency of cannabis products should be limited with respect to the concentration of THC in edible products. This is of particular importance in order to attempt to prevent adverse reactions from people who may not understand how their body reacts to THC. There should be no limits on any other cannabinoids present in products, and manufacturers should be encouraged to produce products that contain a wide range of cannabinoids. These products would then be available for further use in research studies to help identify various cannabinoid combinations that could have therapeutic benefits.*

Homogeneity

An additional issue that has been addressed by a number of states is the homogeneity of the manufactured product. Colorado, for example, defines homogeneity as not more than 20% of the total THC being located in 10% of the product.

*Recommendation:*

*The FDA should require homogeneity testing to promote consistent product content, appropriate distribution of all cannabinoids, not just THC, throughout manufactured products, and accurate packaging and labeling, making cannabinoid-containing products safer for those consuming them.*

*Further recommendations:*

*Laboratory standards should be established for all types of testing that may be done on cannabis, including safety tests and informational tests (e.g., analyses of cannabinoid and terpene content). To ensure that cannabis and cannabis products intended for sale and consumption are not contaminated with banned or excess levels of pesticides or solvents and that potency is accurately measured, independent laboratory testing must be required. Cannabis products must also be tested for homogeneity. The laboratories licensed to perform these analyses must have validated methodologies that are capable of detecting the required compounds and quantifying their results, as discussed in question B1 below.*

**3. What are the characteristics of a successful system to collect representative safety information at the national or State level about products containing cannabis and cannabis-derived compounds?**

**a. Are there systems that currently exist for the collection of this information (other than FDA's systems)?**

At the state level, there are a variety of systems in place that are collecting health and safety information about cannabis and cannabis products. Each state that has enacted cannabis regulations includes provisions for seed-to-sale tracking protocols that not only track the number of plants grown and the products manufactured from those plants, but also the test results from any health and safety tests conducted as well as product recall information. There are three software platforms being used principally by many states: METRC (11 states), BioTrackTHC (seven states), and MJ Freeway (two states). Each platform is not without its problems, as highlighted by a September 11, 2018 [article](#) published in Slate. [Appendix 7] As with many major software platforms, scalability, functionality, and performance were all issues requiring attention from each company.

Each of these platforms includes functions for tracking any state-mandated testing that is conducted on cannabis and cannabis-derived products. By requesting access to this data, rates may be determined for the percentage of failed batch testing as well as the various types of contaminants that have been found. According to data provided by a licensed cannabis testing laboratory located in California, from March 2018 through March 2019, 14.8% of samples submitted to the lab failed testing (n=45,000). The failures were for the following: pesticides (5.3%), heavy metals (4.3%), residual solvents (4.1%), and microbiological contaminants (0.5%). [Appendix 8]

The various state departments of health and environment are also tasked with tracking the results of product testing and handling notices of adverse events and recalls. These departments should be able to provide current information regarding any adverse events and recalls, including why recalls were issued. By tracking and trending this data, limits may be placed on compounds that may affect health and safety such as pesticides, heavy metals, microbiological contaminants, residual solvents, and THC potency.

This testing information is currently only available for cannabis and cannabis-derived products as there are no current testing requirements for hemp and hemp-derived products other than to ensure the content of THC is  $\leq 0.3\%$ .

*Recommendation:*

*ASA recommends the FDA work with state governments to collect safety data that may not be available to the public from these seed-to-sale tracking systems. By utilizing this data, the FDA can determine the safety tests and limits that would be most effective in protecting the public from harm.*

*ASA also urges the FDA to implement testing of hemp and hemp-derived products to the same standards recommended in question B1 below, and that are already in place in some states for cannabis and cannabis-derived products.*

## **B. Manufacturing and Product Quality**

### **1. Are there particular standards needed to address any safety issues related to the manufacturing, processing, and holding of products containing cannabis and cannabis-derived compounds (e.g., genotoxic impurities, degradation of active compounds)? Please identify or describe those standards.**

The American Herbal Products Association (included in Appendix 10) and the American Herbal Pharmacopoeia [Appendix 9] have addressed these issues in their Recommendations for Regulators and Cannabis Inflorescence monograph, respectively. These standards address issues of purity and safety and the recommended production, handling, storage, and testing practices to be used, as applicable, by cannabis cultivators, processors, manufacturers, holding operations, labeling operations, distributors, and independent testing laboratories.

These standards have been adopted by numerous states as they present a comprehensive set of guidelines that can be used by every type of cannabis operation, including laboratories. The AHPA Recommendations for Regulators discusses the following topics for cultivation, manufacturing, holding, packaging, labeling, distribution, and laboratory operations:

- Types of activities
  - Cultivation and processing operations
  - Ancillary operations
  - Cultivation best practices
  - Processing best practices
  - Distribution best practices
  - Quality systems
  - Product acquisition and distribution
  - Laboratory functions
  - Dispensing best practices
- Personnel
- Facilities
  - General compliance

- Fire prevention
- Sanitation practices
- Electrical systems
- Ventilation systems
- Disposal and waste practices
- Security
- Water resource management
- Inventory and Recordkeeping
- Product complaints, adverse events, and recalls
- Packaging and labeling process controls
- Holding controls
- Sample analysis
- Compliant individuals
  - Requirements for purchase
  - Compliant individuals

The AHP monograph *Cannabis Inflorescence: Standards of Identity, Analysis, and Quality Control* also provides information about commercial cultivation, manufacturing, processing, and handling as well as more details around the types of laboratory testing that should be conducted, including:

- Potency testing
- Foreign organic matter
- Loss on drying
- Pesticide limits
- Microbial and fungal limits
- Heavy metals limits
- Solvent residues

Additionally, Americans for Safe Access has produced a Regulator's Program Guide, which discusses the AHPA and AHP guidebooks as well as provides detailed information on implementing these programs. [Appendix 10]

*Recommendation:*

*ASA recommends that these guides be followed when implementing regulations around consumer health and the safety of cannabis and cannabis-derived products. These standards include provisions for good agricultural practices, good manufacturing practices, and good laboratory practices as well as information for the safe dispensing of products that are not covered by GXP rules and regulations.*

It is also imperative that manufactured goods be appropriately sampled using sound statistical practices in order to determine accurate potency and homogeneity results. These two tests are of utmost importance as the other contaminants may be addressed through the rulemaking process. For instance, states may ban the use of pesticides and limit the solvents approved for extractions, and therefore these become less of a public health and safety concern; but, all of these products

will contain cannabinoids, the amount and distribution of which will affect public health and safety.

Additionally, some states allow their cultivators and manufacturers to submit their own samples to the testing laboratory conducting the mandatory tests. This type of practice creates an opportunity for businesses to take selective (rather than representative) samples or tamper with samples to ensure that they will pass product testing. For example, a business may treat its samples with adulterants such as ozone, bleach, or hydrogen peroxide in order to pass microbiological testing.

*Recommendation:*

*ASA recommends that the FDA evaluate the most reliable statistical methods for representative sampling of cannabis and cannabis-derived products and require that independent testing laboratories obtain the samples for testing. We also implore the FDA to set standards around the potency and homogeneity of products as well as develop a representative sampling scheme that ensures an entire batch of manufactured product can be deemed safe.*

It is important, when developing rules around cannabis and cannabis-derived product, to ensure that there are adequate numbers of inspectors that have received the proper education and training in order to ensure safe cultivation and manufacturing practices. States with a significant number of cultivation and manufacturing licensees may not employ enough staff to adequately and regularly inspect each facility. A small labor pool resulting from a lack of individuals with the education and training required to inspect these operations may compound potential staffing shortages.

*Recommendation:*

*Americans for Safe Access urges the FDA to ensure all inspectors receive adequate training around cannabis and cannabis-derived products and to also ensure that there is a sufficient number of inspectors to conduct assessments on a regular basis.*

**2. Are there particular standards or processes needed to ensure manufacturing quality and consistency of products containing cannabis or cannabis-derived compounds, including standards applied to evaluate product quality? Please identify and describe those standards.**

Most states that have enacted regulations around cannabis and cannabis-derived products have established inspection protocols and manufacturing standards to be used during the cultivation and manufacturing processes to ensure consistent and safe products. These standards include those issued in the AHPA Recommendations for Regulators and the AHP Cannabis Inflorescence monograph.

Facilities are regularly inspected by members of state departments of health, environment, and agriculture along with other state and local departments, including fire and police departments. These inspections are intended to identify any potential risks to the product, environment, and employee safety.

At this time, each state that has approved the use of cannabis and cannabis-derived products has implemented a testing program except Arizona. Each testing program is different in regard to the specific testing that must be done and the limits that are set on tests such as pesticides. The table below includes 69 different pesticides for which testing may or may not be required, with four different states' testing requirements listed to highlight the variations in state requirements.

<b>Pesticide Testing Requirements</b>	<b>California</b>	<b>Colorado</b>	<b>Oregon</b>	<b>Washington</b>
Abamectin	0.3ppm	0.07ppm	0.5ppm	Screen
Acephate	5ppm		0.4ppm	
Acequinocyl	4ppm		2ppm	
Acetamiprid	5ppm		0.2ppm	
Aldicarb	0.1ppm		0.4ppm	
Azoxystrobin	40ppm	0.02ppm	0.2ppm	
Bifenazate	5ppm	0.02ppm	0.2ppm	
Bifenthrin	0.5ppm		0.2ppm	Screen
Boscalid	10ppm		0.4ppm	
Captan	5ppm			
Carbaryl	0.5ppm		0.2ppm	
Carbofuran	0.1ppm		0.2ppm	
Chlormequat chloride				Screen
Chlorantraniliprole	40ppm		0.2ppm	
Chlordane	0.1ppm			
Chlorfenapyr	0.1ppm		1ppm	
Chlorpyrifos	0.1ppm		0.2ppm	
Clofentezine	0.5ppm		0.2ppm	
Coumaphos	0.1ppm			
Cyfluthrin	1ppm		1ppm	
Cypermethrin	1ppm		1ppm	
Daminozide	0.1ppm		1ppm	Screen
DDVP (Dichlorvos)	0.1ppm		1ppm	Screen
Diazinon	0.2ppm		0.2ppm	
Dimethoate	0.1ppm		0.2ppm	
Dimethomorph	20ppm			
Ethoprophos	0.1ppm		0.2ppm	
Etofenprox	0.1ppm		0.4ppm	

Etoazole	1.5ppm	0.01ppm	0.2ppm	
Fenhexamid	10ppm			
Fenoxycarb	0.1ppm		0.2ppm	
Fenpyroximate	2ppm		0.4ppm	
Fipronil	0.1ppm		0.4ppm	
Flonicamid	2ppm		1ppm	
Fludioxonil	30ppm		0.4ppm	
Hexythiazox	2ppm		1ppm	
Imazalil	0.1ppm	0.04ppm	0.2ppm	
Imidacloprid	3ppm	0.02ppm	0.4ppm	Screen
Kresoxim Methyl	1ppm		0.4ppm	
Malathion	5ppm	0.05ppm	0.2ppm	
Metalaxyl	15ppm		0.2ppm	
Methiocarb	0.1ppm		0.2ppm	
Methomyl	0.1ppm		0.4ppm	
Methyl Parathion	0.1ppm		0.2ppm	
Mevinphos	0.1ppm			
MGK-264			0.2ppm	
Myclobutanil	9ppm	0.04ppm	0.2ppm	Screen
Naled	0.5ppm		0.5ppm	
Oxamyl	0.2ppm		1ppm	
Paclobutrazol	0.1ppm		0.4ppm	Screen
Pentachloronitrobenzene	0.2ppm			
Permethrin (cis + trans)	20ppm	0.04ppm	0.2ppm	Screen
Phosmet	0.2ppm		0.2ppm	
Piperonyl Butoxide	3ppm		2ppm	
Prallethrin	0.4ppm		0.2ppm	
Propiconazole	20ppm		0.4ppm	Screen
Propoxur	0.1ppm		0.2ppm	
Pyrethrins	1ppm		1ppm	
Pyridaben	3ppm		0.2ppm	
Spinetoram	3ppm			
Spinosad	3ppm	0.06ppm	0.2ppm	Screen
Spiromesifen	12ppm	0.03ppm	0.2ppm	Screen
Spirotetramat	13ppm	0.02ppm	0.2ppm	

Spiroxamine	0.1ppm		0.4ppm	
Tebuconazole	2ppm	0.01ppm	0.4ppm	
Thiacloprid	0.1ppm		0.2ppm	
Thiamethoxam	4.5ppm		0.2ppm	
Trifloxystrobin	30ppm		0.2ppm	
Uniconazole				Screen

*Recommendation:*

*To ensure consistency and safety of cannabis and cannabis-derived products, ASA recommends that all standards and processes used to ensure manufacturing quality should be consistent state-to-state. This recommendation would apply to all safety testing, including residual solvents, microbiological contamination, pesticides, mycotoxins, potency, and homogeneity.*

### **3. What validated analytical testing is needed to support the manufacturing of safe and consistent products?**

Validated analytical testing is a key facet of ensuring safe products in the marketplace. There are laboratory safety standards addressed by the AHP Cannabis Inflorescence monograph, ISO/IEC 17025, the Code of Federal Regulations, and Patient Focused Certification as well as other third-party certification/accreditation services. The following testing protocols should be validated by each testing lab performing them:

- Cannabinoid potency
- Residual solvents
- Pesticides
- Mycotoxins (Ochratoxin A, Aflatoxins G<sub>1</sub>, G<sub>2</sub>, B<sub>1</sub>, B<sub>2</sub>)
- Heavy metals
- Terpenes
- Microbiological and fungal contaminants

*Recommendation:*

*ASA recommends that the FDA follow the testing suggestions listed in the AHP Cannabis Monograph. ASA also recommends that the FDA permit proficiency testing providers to develop PT samples using actual cannabis matrix and spiked cannabis matrix, and ship those samples to testing laboratories, regardless of the state they are located in.*

In addition to validated analytical testing, proficiency testing (PT) is a key component in determining that laboratories are meeting performance metrics for the assays that they are certified or accredited to conduct. A challenge for current proficiency testing programs is the lack of standardized materials to use. Because of federal restrictions on controlled substances, proficiency testing programs must send sample extracts that are at a low enough concentration to not be in violation of the Controlled Substances Act. This is problematic because a key aspect of proficiency testing is utilizing the correct sample matrix so that laboratories may prove that their extraction and testing methods meet the requirements of the PT program.

There are currently a limited number of PT providers, and due to strict federal regulations, the PT samples do not contain actual matrix, but are a small amount of solvent spiked with <1mg THC and CBD. The spiked solvent does not need to be diluted and is therefore merely a check of the laboratory's calibration curve. The PT samples also only contain THC and CBD, and do not measure any additional cannabinoids. PT samples are also not available for any other tests such as residual solvents, pesticides, heavy metals, or microbiological contaminants.

In June 2018, the Alaska Marijuana Control Board released a study that evaluated the testing results of a flower sample between two different labs. Each lab reported significant differences in their results. Each lab also passed the PT sample provided to them by Emerald Scientific. This type of discrepancy highlights the need for a more robust PT program as accurate and precise results are paramount in accurately labeling products. [Appendix 11]

*Recommendation:*

*ASA recommends that the FDA permit PT providers to develop matrix-based PT samples to include the various types of matrices that laboratories will receive including flower, concentrate, and food-based products and permit higher quantities of cannabinoids that are more representative of commercially available products. PT programs should also be expanded to include other types of analyses that laboratories are performing in order to better evaluate the laboratory's extraction and analysis techniques, including pesticide, residual solvent, heavy metals, and microbiological contaminants.*

**4. Are there any currently used standardized definitions for the ingredients in cannabis products (e.g., “hemp oil”)? If standardized definitions would be helpful, what terms should be defined and what should the definition(s) be?**

Cannabis and cannabis-derived products have ingredients that must be identified. Most commonly, many states opt to provide definitions of specific cannabinoids such as THC and CBD, as these are listed in the testing requirements and should be defined. Additional standardized definitions are proposed below.

- **Cannabinoid distillate** - a type of highly purified cannabis concentrate that is created by running a relatively less potent concentrate through a distillation process to separate the desired cannabinoid from the other components within the concentrate
- **Cannabinoid isolate** - cannabinoid molecules that have been isolated from all other components of the cannabis plant, such as through chromatography
- **Coconut oil** - oil extracted from the kernel or meat of coconuts
- **Concentrate** (adapted from the State of Alaska) – resin, oil, wax, or any other substance produced by extracting or isolating one or more cannabinoids from cannabis plant material
- **Hemp extract** - a cannabis concentrate (e.g., resin, oil, wax) produced by processing hemp flowers to capture and concentrate the desired compounds within them
- **Hemp oil** - oil obtained by pressing the seeds of hemp flowers to express the resinous oil

- **MCT oil** - medium-chain triglyceride oil, such as coconut or palm oil, used to extract cannabinoids from cannabis or hemp flowers and as a carrier oil in some cannabinoid-containing products.

More broadly, the definitions section of any set of regulations is a key factor in the successful implementation and enforcement of regulations. A lack of clear definitions can lead to confusion and delays in rolling out programs. The following is a list of suggested terms and their definitions:

- **Adverse event** (adapted from AHPA) – a health-related event associated with use of cannabis or a cannabis-derived product that is injurious, and that is unexpected or unusual.
- **Batch** (adapted from AHPA) – a specific quantity of cannabis or cannabis-derived products harvested or manufactured during a specified time period from a specified cultivation area or production run.
- **Batch number** (adapted from AHPA) – any distinctive group of letters, numbers, or symbols, or any combination thereof, from which the complete history of the manufacturing, packaging, labeling, or holding of a batch or lot of cannabis or cannabis-derived products can be determined. (This definition also applies to lot number and control number.)
- **Cannabis waste** (from AHPA) – cannabis or cannabis-derived product discarded by a cultivation, manufacturing, packaging, labeling, holding, dispensary, or laboratory operation.
- **Chemovar** - a chemotaxic variety of a plant family, it is determined by examining the chemical makeup of the plant including the cannabinoids and terpenes.
- **Child-resistant packaging** (adapted from the State of Colorado) – packaging that is:
  - Designed or constructed to be significantly difficult for children under five years of age to open and not difficult for normal adults to use properly, as defined by 16 CFR 1700.20 (1995).
  - Opaque so that the packaging does not allow the product to be seen without opening the packaging material; and
  - Resealable for any product intended for more than a single use or containing multiple servings.
- **Compliant individual** (adapted from AHPA) – an individual who has met all applicable legal requirements to obtain and use cannabis or cannabis-derived products.
- **Control number** - see Batch number.
- **Cultivar** - a cultivated variety of a plant family, it is developed by various genetic breeding strategies.
- **Edible product** (adapted from the State of Colorado) – any cannabis-infused product that is intended to be consumed orally, including but not limited to any type of food, drink, or pill.
- **Exit package** (adapted from the State of Colorado) – a sealed container or package provided at the retail point of sale in which any cannabis or cannabis-containing product already within a container is placed.

- **Harvest batch** (adapted from the State of Colorado) – a specifically identified quantity of processed cannabis that is uniform in cultivar, grown using the same pesticide(s) or other agricultural chemicals, and harvested at the same time.
- **Homogeneous** (from the State of Alaska) – a component or quality, such as THC, is spread evenly throughout the product, or can be found in equal amounts in each part of a multi-serving unit.
- **Lot** (from AHPA) – a batch, or a specific identified portion of a batch, that is uniform and that is intended to meet specifications for identity, purity, strength, and composition.
- **Lot number** - see Batch number.
- **May** (from AHPA) – is used to indicate an action or activity that is permitted.
- **Must** (from AHPA) – is used to state a requirement.
- **Production batch** (adapted from the State of Colorado) – (a) any amount of cannabis concentrate of the same category and produced using the same extraction methods and standard operating procedures and an identical group of harvest batches of cannabis; or (b) any amount of cannabis product of the same exact type, produced using the same ingredients, standard operating procedures, and production batch(es) of cannabis concentrate.
- **Purity** (from AHPA) – the relative freedom from extraneous matter, contaminants, or impurities, whether or not harmful to the consumer or deleterious to the product.
- **Representative sample** (from AHPA) – a sample that consists of an adequate quantity of material or number of units that is collected in a manner intended to ensure that the sample accurately portrays the material being sampled.
- **Reprocessing** (from AHPA) – the performance of a treatment, adjustment, repackaging, relabeling, or other deviation from standard procedures or from the applicable manufacturing protocol in order to render a nonconforming material suitable for use.
- **Scientifically valid method** (from AHPA) – an analytical method that has been subjected to accepted method validation processes and has been demonstrated to be fit for purpose in the analysis of cannabis, cannabis-derived products, hemp, or hemp-derived products.
- **Should** (from AHPA) – is used to state recommended or advisory procedures.
- **Tamper-evident** (adapted from the State of California) – sealed in a manner that prevents the packaging from being opened without obvious destruction of the seal.
- **Unrecognizable** (adapted from the State of Colorado) – in the context of cannabis waste, cannabis plant material rendered indistinguishable from any other plant material.
- **Water activity** ( $a_w$ ) (adapted from AHPA) – a measure of the free moisture in a component or product expressed as the quotient of the water vapor pressure of the substance divided by the vapor pressure of pure water at the same temperature.

### C. Marketing/Labeling/Sales

1. **How should consumers be informed about the risks associated with such products (e.g., directions for use, warnings)? What specific risks should consumers be informed about? Are there any subpopulations for which additional warnings or restrictions are appropriate? Please explain your reasoning.**

Consumers should be informed about the risks associated with cannabis and cannabis-derived products through educational campaigns and proper labeling on all products, including the use of

warning labels as appropriate. Educational campaigns should be aimed at different target audiences, depending on the information being conveyed. For instance, it is known that CBD is an inhibitor of Cytochrome P450 enzymes,<sup>1</sup> so physicians and pharmacists should be made aware of this information when prescribing medications to patients. Additionally, subpopulations such as children and teenagers should be educated about the effects of cannabinoids on developing brains and correct usage for medical purposes. Pregnant and breastfeeding women should receive scientifically accurate information about the potential effects of cannabinoids on fetal health and should be aware that cannabinoids can be excreted in breast milk.<sup>2</sup>

Cannabis-naïve individuals should be advised to consume cannabis and cannabis-containing products with due caution until they know how they react to cannabinoids. It should be noted that cannabis-naïve individuals may be more susceptible to short-term adverse effects from the use of cannabis, which can include, inter alia, elevated heart rate, changes in blood pressure, impairment of short-term memory, impairment of motor skills, dizziness, and anxiety or paranoia.<sup>3</sup> Warning statements should be developed around sound scientific evidence and should alert consumers to potential side effects.

2. What conditions, restrictions, or other limitations on the manufacturing and distribution of these products have been put in place under State or local law, particularly with respect to food products containing cannabis-derived compounds such as CBD (which may, in some cases, be lawful at the State level but not the Federal level)? What other conditions, restrictions, or other limitations might be appropriate to ensure adequate consumer information and to protect the public health?

At the state level, most states that have approved cannabis and cannabis-derived products for use by patients and adult consumers have put in safeguards at all levels of production and distribution, from cultivation through the purchase of a final product. These safeguards include applying GXP principles to cultivation, manufacturing, and laboratory analysis. Additionally, most states require manufacturing employees to take courses related to safe food handling that include topics such as foodborne illness and sanitation practices.

Best-by, use-by, sell-by, and/or expiration dates for all food products should be used by manufacturers to inform and help protect consumers. Product labels should also include information on the date the product was manufactured and the manufacturer name and license number and what storage conditions should apply, such as “keep away from light,” “store in a refrigerator,” “refrigerate after opening,” “store in a cool, dry place,” etc.

3. What statutory or regulatory restrictions are in place under State or local law to warn about the use of these products by certain vulnerable human populations (e.g., children,

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<sup>1</sup> Harvey, D.J. Absorption, distribution, and biotransformation of the cannabinoids Marijuana and medicine. Springer; 1999. p. 91-103.

<sup>2</sup> Bertrand, K.A., Hanan, N.J., Honerkamp-Smith, G., et al. (2018) Marijuana Use by Breastfeeding Mothers and Cannabinoid Concentrations in Breast Milk. *Pediatrics*, 142(3): e20181076. doi:10.1542/peds.2018-1076.

<sup>3</sup> Cohen, K. and Weinstein, A.M. (2018) Synthetic and Non-synthetic Cannabinoid Drugs and Their Adverse Effects-A Review from Public Health Perspective [sic]. *Frontiers in Public Health*, 6, 162. doi:10.3389/fpubh.2018.00162.

adolescents, pregnant and lactating women) or animal populations (e.g., species, breed, or class)? Are there other steps that should be taken to warn about use by vulnerable populations? Please identify such steps and how they would apply to a particular subpopulation.

Below are some of the warning statements that are required in a selection of states. Among these states, only Alaska's regulations require the use of warning labels that are specific to vulnerable human populations (specifically, children, adolescents, and pregnant or breastfeeding women.)

- Alaska
  - "Marijuana has intoxicating effects and may be habit forming and addictive."
  - "Marijuana impairs concentration, coordination, and judgement. Do not operate a vehicle or machinery under its influence."
  - "There are health risks associated with consumption of marijuana."
  - "For use only by adults twenty-one and older. Keep out of the reach of children."
  - "Marijuana should not be used by women who are pregnant or breastfeeding."
- California
  - Universal symbol (in black)
  - "Cannabis-Infused" for edible products
  - Allergens (if applicable for manufactured products)
  - Artificial food colorings (if applicable for manufactured products)
  - Expiration, use-by, or best-by date (if applicable for manufactured products)
  - "KEEP REFRIGERATED" or "REFRIGERATE AFTER OPENING (if perishable after opening)
  - "FOR MEDICAL USE ONLY" (if applicable)
  - Prop 65 Warning (if applicable)
- Colorado
  - Universal symbol
  - "The marijuana contained within this package has not been tested for contaminants" (where applicable)
  - "This product contains medical marijuana and was produced without regulatory oversight for health, safety or efficacy and there may be health risks associated with the consumption of the product."
- Michigan
  - Allergens labeling as specified by the Food and Drug Administration (FDA), Food Allergen Labeling and Consumer Protection Act of 2004 (FAKCPA), 21 USC 343.

In addition to the warning statements required by some states, there are also educational campaigns aimed at informing the public about cannabis and the various cannabis regulations in place in that state. These include information about use by teenagers and pregnant and breastfeeding women. Parents and teenagers should be educated about the potential effects of THC on developing brains.

4. What other information should FDA consider in the labeling of specific product categories of cannabis and cannabis-derived products?

In addition to warning statements, product information, and manufacturing history, FDA should consider harmonizing nomenclature, definitions, and product identities such that they are consistent from state to state. Currently, states use either marijuana, marihuana, or cannabis in their rules and regulations. For scientific accuracy, it is recommended that all rules and regulations use the word *cannabis* as this is the correct taxonomic identification of the plant, whereas marijuana is a slang term, as written about in this [article](#) published by Leafly.

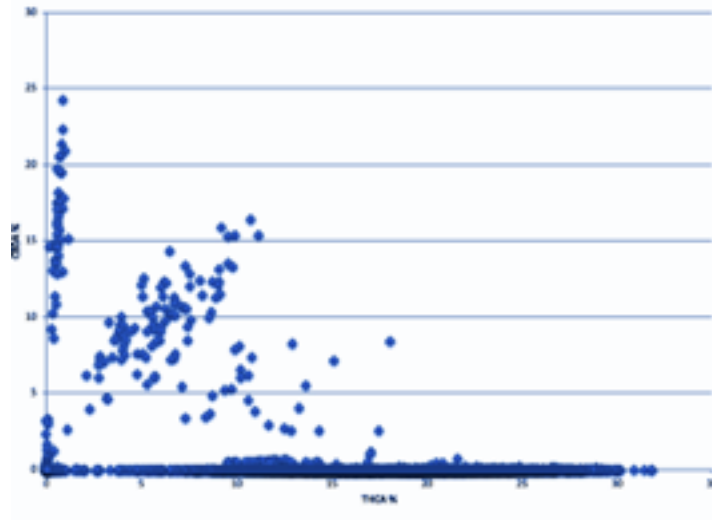
**[Appendix 12]**

The cannabis plant is classified as follows:

- Family – Cannabaceae
  - Genus – *Cannabis*
    - Species - *Cannabis sativa* L.
    - Species - *Cannabis indica* Lam.
    - Species - *Cannabis ruderalis* Janisch

As cannabis is the common name in each species, it is best identified as such and not by slang. It is also recommended that the word “cultivar” be used rather than “strain,” which is better suited to describing a genetic variant or subtype of a microorganism. Cultivars are cultivated varieties of cannabis<sup>4</sup>, and at least 700 have been developed through selective breeding programs.

Cultivars can be grouped into chemovars (chemical varieties of cannabis<sup>5</sup>) based on their cannabinoid and terpene profiles.



<sup>4</sup> Hazekamp, A. and Fishedick, J.T. (2012). [Cannabis – from cultivar to chemovar](#). Drug Testing and Analysis. Wiley Online Publishing

<sup>5</sup> Russo EB (2019) The Case for the Entourage Effect and Conventional Breeding of Clinical Cannabis: No “Strain,” No Gain. *Front. Plant Sci.* 9:1969. doi: 10.3389/fpls.2018.01969

Figure 1: Plot of THC:CBD Ratios of Cannabis Samples (n=4663)<sup>6</sup>

Figure 1 is a plot of cannabis samples that highlights how varied the THC:CBD ratio of flower products that are available to consumers can be. From this chart, we can see that there are varieties that are CBD dominant, varieties that are THC dominant, and varieties that exhibit relatively even ratios of THC:CBD. Scientists have classified these as Type I (THC dominant), Type II (containing both THC and CBD), and Type III (CBD dominant).<sup>7</sup> Given that THC is the cannabinoid most responsible for intoxication and that CBD exhibits a modulating effect on THC, classifying cannabis and cannabis-derived products by chemotype can help patients and consumers determine the products' intoxication potential, if any.

While THC and CBD are the primary major cannabinoids, cannabis is capable of producing a wide range of chemical constituents, including at least 113 cannabinoids and 120 terpenes.<sup>8</sup> Terpenes are aromatic compounds that are generally present in concentrations of less than 2% by dry weight. Studies have shown that terpenes and cannabinoids interact synergistically to produce therapeutic effects; this therapeutic interplay is often referred to as the “entourage effect.”<sup>9</sup>

Regardless of chemotype, a specific plant's chemical profile will be influenced not only by the plant's genetics, but by the conditions under which it was cultivated, including but not limited to temperature, humidity, light exposure, and nutrient availability or scarcity. Clones taken from the same mother plant but grown under different conditions are likely to display different chemical profiles, including different concentrations of cannabinoids and terpenes. Further complicating matters, the potency of a single cannabis plant's flowers can vary based on where on the plant a given flower grew, as discussed in this [article](#) by Orange Photonics. **[Appendix 13]** Those who are under the impression that a cultivar with a given name (e.g., Blue Dream) can be counted on to reliably produce the same effect across batches, or who believe that a Blue Dream product in California is the same as a Blue Dream product in Massachusetts, are mistaken; it is clear that cultivar name is an unreliable indicator of a product's potential effects in consumers and patients.

Helpfully, laboratory analyses of representative samples from every batch of cannabis and cannabis-derived products can be used to group products by chemovar. These chemovar classifications can be made by associating markers within chemical profiles with therapeutic effects. For example, clinical testing may show that Type I cannabis that is relatively high in myrcene and terpinolene is particularly effective at promoting sleep and that Type III cannabis that is high in limonene and linalool is helpful for those seeking to start the day with feelings of inspiration and calm while relieving chronic neuropathic pain. If products are labeled by chemovar group in addition to type and cultivar name, patients and consumers can make

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<sup>6</sup> Marcu, J. and Despres, H. (2015) Report on Medical Cannabis Potency From Colorado Using UPLC Analysis. 25th Annual Symposium on the Cannabinoids, International Cannabinoid Research Society, Research Triangle Park, NC, USA, Page 137

<sup>7</sup> Lewis, M.A., Russo, E.B., and Smith, K.M. (2017) Pharmacological Foundations of Cannabis Chemovars. Planta Med © Thieme Publishing. Published online. DOI <https://doi.org/10.1055/s-0043-122240>.

<sup>8</sup> Aizpurua-Olaizola, et al. (2016, February 2). Evolution of the Cannabinoid and Terpene Content during the Growth of Cannabis sativa Plants from Different Chemotypes. Journal of Natural Products, 79(2), 324-331.

<sup>9</sup> Russo, EB. (2019) The Case for the Entourage Effect and Conventional Breeding of Clinical Cannabis: No “Strain”, No Gain. Front. Plant Sci. 9:1969.

informed decisions about which products to use and when to use them. Without laboratory analyses and clinical trials to tie plant chemovars to therapeutic effects - and without corresponding labeling - it would be difficult for patients to find reliable, consistent relief and for patients and consumers to otherwise be able to reliably predict products' effects.

*Recommendation:*

*ASA urges the FDA to conduct a study to evaluate the therapeutic effects that various chemical profiles of cannabis and hemp are capable of producing and to use this information to identify, name, and set the parameters for chemovar classifications (i.e., establish for each chemovar the amount or allowable range of each cannabinoid and terpene that must be present in concert). Once these chemovar classifications have been established, the FDA should mandate that the labels on cannabis and cannabis-derived products clearly identify the chemovar into which each product falls to allow patients and consumers to obtain consistent, reliable products.*

*Given the nature of the product, the FDA should allow slight (i.e., not medically important) variance between labeled potency and test results. In the absence of clinical testing, we recommend an allowable variance of +/-10% for edible products and +/-15% for flower products. We urge that the medical importance of variance be evaluated as a secondary objective of the chemovar classification study and that the allowable variance be modified (if necessary) according to the results of that study.*

Labels should also contain information about where to learn more about the testing that was done on the products and whether those test results were passing or failing. This is a way to educate the public about the processes used in the cultivation and manufacture of the products they are consuming. Some states allow for the reprocessing of flower samples that have failed testing for microbiological contamination into concentrates as it is believed that processing by CO<sub>2</sub> or hydrocarbon extraction will eliminate aerobic contaminants. Because cannabis is a plant with varying potencies, labeling requirements should include provisions for some allowable amount of variance between the testing lab results and the packages contents. We recommend 15% for flower and flower products and 10% for all manufactured products.

*Recommendation:*

*Labeling requirements should be standardized across all states so that the same information is required and available for every cannabis, hemp, cannabis-derived, and hemp-derived product. Labels should also include information regarding whether the product has been remediated and what method was used to remediate it. At a minimum, labels should include:*

- *Product name*
- *Cannabinoid content in appropriate units for THC, THCA, CBD, CBDA, CBN, CBG, CBGA, THCV, CBDV*
- *Terpene content in appropriate units*
- *Manufacturer's name, address, and license number*
- *Net weight or net volume in appropriate units*

- *Allergen labeling (where appropriate)*
- *Nutritional labeling (where appropriate)*
- *Testing and remediation information*