Office of Medical Cannabidiol, Iowa Department of Public Health

Laboratory Testing Requirements & Acceptance Criteria

Table of Contents

Document Versions	
Version	Release Date
v1.0	6/5/18
v2.0	10/26/18
v3.0	1/31/19
v4.0	5/1/19
v4.1	7/17/19
V4.2	11/27/19
v4.3	9/7/2020

1.0 Introduction and Purpose

1.1 – Introduction

The vision of the Office of Medical Cannabidiol (OMC) at the Iowa Department of Public Health is to have a high-quality, effective, and compliant medical cannabidiol program for Iowa patients with qualifying, debilitating medical conditions.

The OMC will work to balance a patient's need for access to low-cost treatments with the requirement to ensure the safety and efficacy of the products. Paramount to patient safety and care is making sure that medical cannabidiol products sold to patients are tested for harmful contaminants and that product labels accurately reflect the content and potency of the medical cannabidiol being dispensed.

1.2 – Purpose

The purpose of this document is to provide licensed Iowa medical cannabidiol manufacturers and laboratories with the required and recommended best practices for the testing and analysis of medical cannabidiol. The governing statute of the Office of Medical Cannabidiol is Iowa Code chapter 124E and the associated administrative rules are found in 641 Iowa Administrative Code chapter 154.

1.0 Introduction and Purpose

1.3 – Testing Protocol Overview

Testing of medical cannabidiol products in Iowa occurs at two stages of manufacturing: ***process* lots** and ***package* lots**. A process lot is the cannabis extract used to formulate final products. Process lots can be any amount of cannabinoid concentrate or extract that is uniform, produced from one or more batches, and is tested for pesticides, residual solvents, and heavy metals prior to being used to formulate products. Package lots are the final package products that are ready to be delivered to dispensaries, and are tested for their potency and consistency of cannabinoid content, as well as for microbiological impurities that may have been introduced during the packaging process.

Additionally, process lots and package lots can be in one of two stages of testing status: *standard* testing or *reduced* testing. For standard testing, sampling for both process and package lots is based on the production volume of that process or package lot. Standard testing is more robust, and designed to validate a manufacturer's methods for extraction, as well as their consistency of formulation and cleanliness of final product packaging. Once a manufacturer has successfully passed standard testing for process lots or package lots, they enter into reduced-testing status. Reduced-testing status is different for process and package lots, and further information is provided in **Sections 5.4 and 6.4.** A manufacturing process may remain in reduced-testing status for two years for both process lots and package lots. A manufacturer shall return to standard testing for a given analyte if a failure is reported by a laboratory, or if it is determined by the Department that a process or package lot process has had a material change (Section 4.5 & 6.6). These testing protocols are described in more detail in the following sections.

** This document is subject to revision based on evolving best practices, updated scientific information or standards and guidelines, changes in laws or regulations, and other information relevant to the contents of the protocol. Criteria will not be effective until the Laboratory and Manufacturers have had the opportunity to comment, the Laboratory reviews the document, and it is hosted publicly on the Office of Medical Cannabidiol website.*

**Tests results that include a qualifying statement require department notice, review, and approval before the laboratory issues a certificate of analysis. "Qualify" is defined as a conditional statement to the test result that has the potential to impact the accuracy of the reported test result, i.e., the procedure was not followed as stated. Examples include, but are not limited to: quality control failures, lab accidents, and insufficient sample mass.*

2.0 Definitions

Acceptance criteria*:* The specified limits placed on characteristics of an item or method that are used to determine quality with the exception of microbiological testing. When acceptance criteria for microbiological quality are prescribed, the maximum acceptable counts are as follows:

Colony-Forming Unit (CFU)	Maximum Acceptable Count
10^1	20
10^2	200
10^3	2000

Reference: USP 1111 Microbiological Examination of Nonsterile Products: Acceptance Criteria for Pharmaceutical Preparations and Substances for Pharmaceutical Use.

Action level*:* The threshold value that provides the criterion for determining whether a sample passes or fails a test performed pursuant to 641 IAC 154.

Analyte: A chemical, compound, element, bacteria, yeast, fungus, or toxin to be identified or measured.

Batch: A specifically identified quantity of dried flower and other cannabis plant matter that is uniform in strain or cultivar, harvested at the same time, and cultivated using the same pesticides and other crop inputs.

Certificate of Analysis: A document released by the laboratory to the manufacturer and department that contains the concentrations of cannabinoid analytes and other measures approved by the department, and whether a sample passed or failed in accordance with 641 IAC 154.

Cannabinoid Content Testing: The testing of final medical cannabidiol products for cannabinoid analytes, including THC, THCa, CBD, CBDa (testing for the acid form is not required if a manufacturer uses a decarboxylation process prior to extraction).

Coefficient of variation (CV) = relative standard deviation (RSD) = 100 s/ $\underline{x}$

Department: The Iowa Department of Public Health.

2.0 Definitions

Formulation: A mixture of CBD, THC, and other cannabinoids in specific, determined concentrations or absolute amounts (i.e., mg per capsule). For example, a mixture of 10 mg/ml CBD and 10 mg/ml THC is one formulation, and a mixture of 5 mg/ml CBD and 5 mg/ml THC is a different formulation. Altering the amounts of THC and CBD may be considered a change in formulation.

Laboratory: The State Hygienic Laboratory at the University of Iowa or other independent medical cannabidiol testing facility accredited to Standard ISO/IEC 17025 by an ISO-approved accrediting body, with a controlled substance registration certificate from the Drug Enforcement Administration of the U.S. Department of Justice and a certificate of registration from the Iowa board of pharmacy, and approved by the department to examine, analyze, or test samples of medical cannabidiol or any substance used in the manufacture of medical cannabidiol.

Lot: A specific quantity of medical cannabidiol that is uniform and intended to meet specifications for identity, strength, purity, and composition, and that is manufactured, packaged, and labeled during a specified time period according to a single manufacturing, packaging, and labeling record. For the purposes of this document, there are process lots and package lots.

Lot Number: A unique numeric or alphanumeric identifier assigned to a lot by a manufacturer when medical cannabidiol is produced. The lot number shall contain a sequence to allow for inventory, traceability, and identification of the plant batches used in the production of a lot of medical cannabidiol.

Measurement Uncertainty (MU): A non-negative parameter characterizing the dispersion of the quantity values being attributed to a measurement, based on the information used. An initial estimate of MU is based on the validation data collected. Ongoing laboratory quality control will be used to update the MU estimate as necessary.

Medical Cannabidiol: Any pharmaceutical grade cannabinoid found in the plant *Cannabis sativa* L. or *Cannabis indica* or any other preparation thereof that is delivered in a form recommended by the medical cannabidiol board, approved by the board of medicine, and adopted by rule.

2.0 Definitions

Process Lot: Any amount of cannabinoid concentrate or extract that is uniform, produced from one or more batches, and is tested for pesticides, residual solvents, and heavy metals prior to being formulated into products.

Package Lot: A finished lot of salable medical cannabidiol that has been packaged, but has not been transported or sold to a dispensary.

Qualify or Qualified Result: A conditional statement to the test result that has the potential to impact the accuracy of the reported test result, e.g., the procedure was not followed as stated.

Reduced Testing: The testing procedures for *package lot* formulations that have successfully completed Standard Testing procedures.

Relative Percent Difference or **RPD:** A comparative statistic used to calculate precision or random error. RPD is calculated using the following equation: RPD = absolute value ([primary sample measurement – duplicate sample measurement]) / ([primary sample measurement + duplicate sample measurement] / 2) × 100.

Relative Standard Deviation or **RSD:** The standard deviation expressed as a percentage of the sample mean. It is the coefficient of variation (CV) multiplied by 100. If any results are less than the limit of quantitation, then the absolute value of the limit of quantitation is used in the following equation: RSD = (s / x) × 100, where s = standard deviation and x = sample mean.

Reduced Spot-Check Testing: As referenced in Iowa Code chapter 124E.6 and 124e.7, a laboratory must perform spot-check testing of the medical cannabidiol manufactured by the medical cannabidiol manufacturer as to content, contamination, and consistency. For the purposes of this document, after a manufacturer has completed standard testing for a *process lot*, the manufacturer shall only be required to test *one process lot per quarter* for analytes listed in section 4.1.

Stability Testing: After storage of an unopened package of medical cannabidiol, the contents shall not vary in concentrations of THC and CBD by more or less than 30 percent by weight in milligrams per milliliter (mg/ml) for liquids and milligrams per gram (mg/g) for solids from the concentration indicated on the package label.

2.0 Definitions

Standard Deviation: The standard deviation, s, of n measurements is given by:

$$\sqrt{\sum_{i} \frac{(x_i - \underline{x})^2}{(n-1)}}$$

n= total number of values

$$x_i = each\ individual\ value\ used\ to\ calculate\ the\ mean$$

Standard Testing: Testing performed on process and package lots to determine whether a manufacturing process produces products that are homogenous, free of contamination, and true to a labeled or expected concentration within certain established parameters. Upon satisfactorily completing standard testing for a specific manufacturing process and cannabidiol formulation, a manufacturer enters reduced-testing status for that process and formulation.

Total THC: Eighty-seven and seven-tenths percent (87.7%) of the amount of tetrahydrocannabinolic acid plus the amount of tetrahydrocannabinol:

Total THC = (0.877 * THCA) + THC

Validation Study: A process by which it is established, through laboratory studies, that the performance characteristics of a method meet the requirements for its intended analytical applications. Validation typically evaluates the following analytical characteristics of a method: Accuracy, Precision, Specificity, Detection Limit, Quantitation Limit, Linearity, Range and Robustness. Validation studies may be required for novel product forms.

Verification Study: An assessment whether a method is suitable under actual conditions of use. USP recommends that a method verification be conducted the first time that a laboratory employs a method for testing on a new or altered sample type. Method verification is specific to the laboratory performing the testing and to the sample type being tested. Verification studies are generally required to assess the suitability of an existing method on product forms not previously tested by said method.

3.0 Product Verification and Validation Intake Process

3.1 - Verification and Validation Study Overview

A laboratory must ensure that testing methods are fit for purpose for all process lot and package lot samples submitted for testing by a licensed manufacturer. A manufacturer must complete the 'Laboratory Testing Verification/Validation Form (located on the OMC website).' for any new, novel, or amended process lot or package lot prior to submitting samples for testing. This form is provided on the OMC website at: idph.iowa.gov/omc/For-Manufacturers-and-Dispensaries.

3.2 - Laboratory Testing Verification/Validation Form

This form must initially be completed by a manufacturer and delivered to a laboratory. A manufacturer must disclose the composition of the process or package lot, as well as provide reference materials for the verification or validation study. This allows a laboratory to ensure satisfactory method performance prior to analysis for regulatory compliance. After reference material and documentation has been established, authorized personnel from both the laboratory and manufacturer must execute the form.

This form is used by a laboratory to determine if the process lot or package lot will require a verification or validation prior to testing:

- For novel product forms that a laboratory does not possess a validated method for, a validation study is generally required.
- For existing product forms or iterations of existing product forms, a verification study is generally required.
- If a proposed product form is similar enough to an existing product form, and a laboratory determines an existing method is fit for purpose, a validation or verification study may not be required, and the process lot or package lot can be sampled and delivered for testing.

3.3 - Verification or Validation Study Details

In order for all manufacturers to be able to use methods validated by SHL, the Department will pay for the costs associated with a validation study of a process or package lot. For verification studies, which are generally an iteration of an existing method, it is the intention of the Department that a manufacturer will pay for the costs associated of the verification study.

Any reference materials that are necessary for a laboratory to conduct a verification or validation for a new or amended process or package lot shall be provided to a laboratory by a manufacturer at no cost to a laboratory or the Department.

4.0 Process Lot Sampling

4.1 – Process Lot Sampling Plan Overview

A manufacturer shall submit to the Department for approval a standard operating procedure (SOP) for sampling process lots. The SOP(s) for sampling process lots shall include processes for both standard and reduced sampling as described in **Sections 4.2 and 4.3**. These SOPs shall include methods for drawing samples, homogenizing samples, and compositing samples. Samples submitted for process lot testing should be representative of the entire process lot. Development of sampling strategies is a requirement of licensed manufacturers described in 641 IAC 154.26(2).

Manufacturers must contact the laboratory in advance of sampling. For both standard and reduced-testing process lots, a laboratory shall provide the necessary weighed and designated containers to a manufacturer. In addition, a manufacturer shall notify the Department two business days in advance of all sampling pursuant to 641 IAC 154.26(2)f. The Department shall reserve the right to be present to verify a manufacturer's submitted sampling SOP for process or package lots.

4.2 – Standard Sampling - Process Lots

For sampling at the process lot stage, extracts should be thoroughly mixed before sampling to ensure homogenization of the sample. Samples of medical cannabidiol process lots should be collected following final refinement, but before being used to formulate products. Standard sampling of process lots shall be in accordance with **Table 1.** Sample increments shall include one 2.1 gram sample to be used by a laboratory for matrix spiking, and 1.4 (± 0.2g) for all other samples for a given production volume.

Table 1 – Standard Process Lot Sampling		
Process Lot Weight		**Sample Increments Required**
Pounds	**Kilograms**	**# of Samples**
0-0.50	0-0.23	2
0.50-1.50	0.24-0.68	4
1.51-3.00	0.69-1.36	6
3.10-6.0	1.40-2.72	8
6.10-10.00	2.77-4.54	10
10+	4.58+	15

Example: In Standard Testing, if a manufacturer completes a 4.58+kg process lot, they shall withdraw *15 independent samples* in accordance with **Table 1**, using the example provided in **Table 2**. Once delivered, each sample will have three tests performed, for a total of 45 tests.

4.0 Process Lot Sampling

Example of Standard Process Lot Sampling:

Table 2 – Standard Process Lot Sampling (for a 4.58 kg+ process lot):	
Sample #	**Chemistry & Micro**
1	*2.10
2	1.40
3	1.40
4	1.40
5	1.40
6	1.40
7	1.40
8	1.40
9	1.40
10	1.40
11	1.40
12	1.40
13	1.40
14	1.40
15	1.40
Total Min. Mass	**24.50**

** 2.1g for one sample is necessary for a laboratory to conduct a matrix spiking*

4.3 – Reduced Spot-Check Sampling - Process Lots

Once a manufacturer's method of extraction and purification for process lots has passed standard testing, subsequent process lots produced using that same method will be subject to reduced spot-check testing. A manufacturing process may be subject to reduced spot-check testing for up to two years unless otherwise approved by the Department to continue reduced testing. In Spot-Check Reduced Testing, a manufacturer shall only be required to submit samples from *one process lot per quarter* for testing of analytes listed in **Section 5.1** for an extraction process that has passed standard testing.

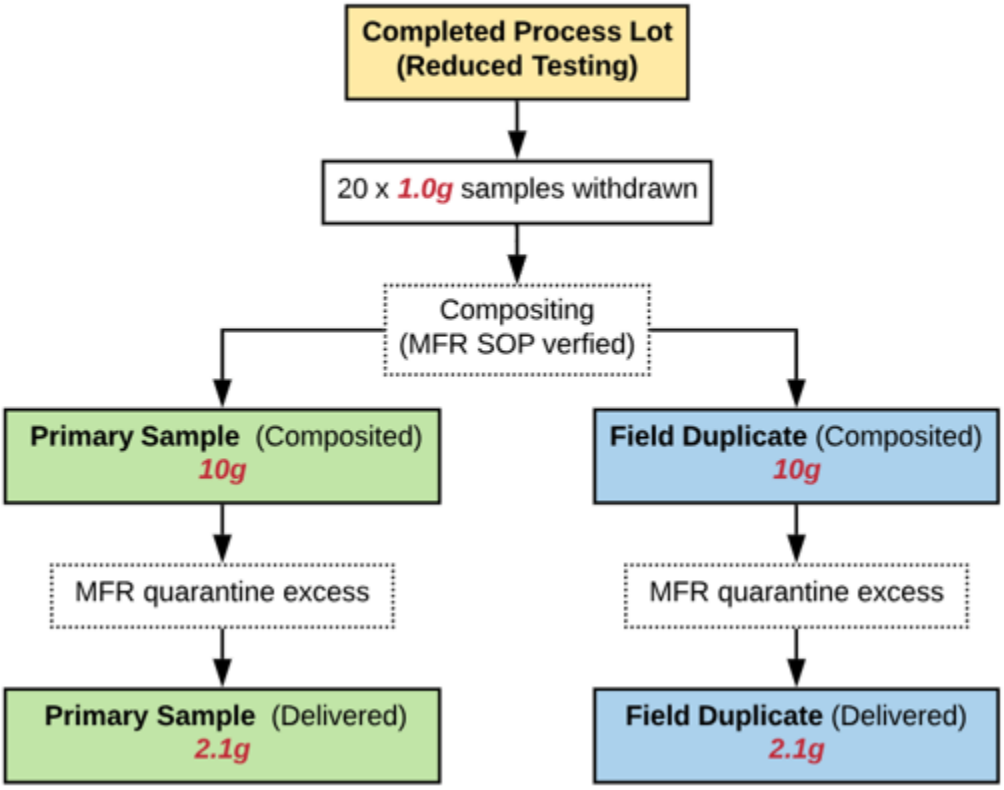
In accordance with **Table 3**, upon completion of a process lot by a manufacturer in reduced spot-check testing, a manufacturer shall withdraw 20, 1.0g samples from the process lot. These 20 samples shall be composited by a manufacturer into a *10.0g primary sample,* and a *10.0g field duplicate*.

Following compositing into the primary sample and field duplicate, a manufacturer shall withdraw the required amount of process lot from the primary sample (*2.1g*) and field duplicate (*2.1g*) necessary for a laboratory to complete the required testing.

4.0 Process Lot Sampling

Quarantine of excess process lot in reduced spot-check testing: The remainder of the primary sample (7.9g) and field duplicate (7.9g) shall be quarantined by a manufacturer. If it is determined that a laboratory requires more material to complete the testing, a manufacturer shall deliver material from the excess process lot that was quarantined by the manufacturer. After the process lot passes all testing, the remainder of the process lot that has been quarantined by the manufacturer may be reintroduced to the original lot from which it was drawn.

Table 3 – Reduced Process Lot Sampling



5.0 Process Lot Testing

5.1 – Process Lot Testing Overview

Process lot testing is designed to determine the safety of process lots produced using a specific extraction process. Once an extraction process successfully passes standard testing, subsequent process lots produced using the same process will be subject to reduced spot-check testing. In Spot-Check Reduced Testing, a manufacturer shall only be required to test *one process lot per quarter* for analytes listed in **Section 5.1** for an extraction process that has passed standard testing.

Hemp-derived CBD isolate is also able to be used as a process lot and incorporated into medical cannabidiol products, and is discussed in **Section 5.5**.
Contaminants tested at the process lot level include:

- Metals
- Pesticides
- Residual Solvents and Processing Chemicals
    - When samples for a process lot are submitted for initial standard testing, a validation study for solvents will be conducted using **Table 8.** Thereafter, a manufacturer's process lots will be held accountable to analytes and action levels identified, but not to analytes in **Table 8** that were not identified.

5.2 – Process Lot Pass Criteria

A laboratory will use the following criteria to determine whether a process lot passes testing for the required analytes at the process lot level:

- Metals cannot be present at or above the action levels described in **Table 5**.
- Pesticides cannot be present at or above the action levels described in **Table 7.**
- If identified in a validation study, residual solvents and processing chemicals cannot be present at or above the action levels described in **Table 8**.

5.3 – Standard Testing - Process Lots

To perform standard testing for process lots, the laboratory will test each sample unit independently. A laboratory shall conduct one test for each required analyte on each independent sample. A laboratory shall report that a process lot passed if no test result meets or exceeds the action levels in the tables referenced in **Section 5.2**.

5.0 Process Lot Testing

5.4 – Reduced Spot-Check Testing - Process Lots

To perform reduced spot-check testing a laboratory shall conduct testing for process lot analytes on both the primary and field duplicate sample, for a total of six tests. A laboratory shall report that a process lot passed if no test result meets or exceeds the action levels in the tables referenced in **Section 5.2**. In Spot-Check Reduced Testing, a manufacturer shall only be required to submit samples from *one process lot per quarter* for the testing of analytes listed in **Section 5.1** for an extraction process that has passed standard testing.

5.5 - Testing of External Hemp-Derived CBD Isolate as a Process Lot

Manufacturers may incorporate hemp-derived CBD isolate or cannabinoids into final package lots. The incorporation of CBD isolate or hemp-derived cannabinoids into final products must comply with the Iowa Hemp Act and HF2581. If manufacturers do not participate in the retail sale or manufacture of hemp-derived products for sale outside of Iowa's Medical Cannabidiol Program, Iowa Code chapter 124E, or 641 Iowa Administrative Code chapter 154, they do not need to register with the Department of Inspections and Appeals (DIA) as outlined in HF2581. Manufacturers intending to incorporate hemp-derived CBD isolate or cannabinoids should communicate with the Department about their intention and plans to do so.

Upon delivery, and before incorporation into final products, any external hemp-derived CBD isolate procured by a manufacturer shall undergo standard testing for process lots as described in **Sections 5.1 and 5.2**. A manufacturer shall notify the Department two business days in advance of all sampling pursuant to 641 IAC 154.26(2)f.

5.6 – Alterations to Processes or Standard Operating Procedures for Process Lots

Material changes to a manufacturing process may require a manufacturer to return to standard testing for that extraction and purification process.

If a manufacturer would like to amend a process lot, they will need to complete a 'Laboratory Testing Verification/Validation Form' as described in **Section 3.0**. A laboratory will determine if a verification or validation study is necessary. If a laboratory determines that no verification or validation study is necessary, a manufacturer may deliver samples of the amended process lot to the laboratory for the type and number of tests as outlined by the Department in the 'Laboratory Testing Verification/Validation Form.'

6.0 Package Lot Sampling

6.1 – Package Lot Sampling Plan Overview

Manufacturers shall submit samples from each package lot of salable medical cannabidiol products prior to delivering the products to dispensaries. Manufacturers must contact the laboratory in advance to schedule a transfer of samples.

6.2 – Standard Package Lot Sampling

Standard package lot sampling shall be random, and follow the strategy as outlined in **Table 4**.

Table 4 – Standard Package Lot Sampling		
Units Produced	**Sample Units**	**Reserve Samples (*retained by the manufacturer*)**
2-15	2	1
16-50	3	1
51-150	5	1
151-500	8	1
501-3,200	13	1
3,201-35,000	20	1

For each package lot, a manufacturer shall retain a uniquely labeled reserve sample, consisting of twice as much material as is necessary to perform all the required tests. The sample shall represent each package lot of medical cannabidiol, and shall be stored for two years under conditions consistent with product labeling and in the same or similar container-closure system in which the product is marketed and sold (641 IAC 154.26(5)).

6.3 – Reduced Package Lot Sampling

Once a manufacturer's process has passed standard testing for package lots and enters into reduced-testing status, a manufacturer shall randomly withdraw *two finished containers* of a given formulation from a completed package lot.

The SOP for withdrawing random samples in reduced-testing status shall be submitted to the Department, and physically verified and approved by the Department and/or a laboratory. There are circumstances for reduced testing (vaporizers, smaller unit containers, etc.) that may require a manufacturer to deliver more than two containers of a package lot for reduced testing. Manufacturers should consult with a laboratory regarding the number of sample units required to complete reduced testing with the package lot samples a manufacturer intends to provide.

7.0 Package Lot Testing

7.1 – Package Lot Testing Overview

Testing of package lots made by a manufacturer is designed to determine the potency and microbiological purity of the lot. Once a manufacturer's formulation and packaging process successfully passes a single round of standard testing, subsequent package lots using the same formulation and packaging process will be subject to reduced testing. A manufacturing process may be subject to reduced testing for up to two years and may be approved by the Department to continue reduced testing beyond this point.

Sampling will be done by formulation. Results for both microbiological impurities and potency will be attached to the unique identifier for the specific formulation of a package lot that a manufacturer delivers to the laboratory.

Testing of a package lot will include:

- Potency – THC, THCa, CBD, CBDa (testing for THCa and CBDa will not be included if a manufacturer uses a decarboxylation process prior to extraction)
    - A laboratory will test samples against a concentration claim for THC (total THC) and CBD that is submitted by the manufacturer. A manufacturer must provide the laboratory with a label claim for total THC and CBD for each formulation.
- Microbiological impurities (tests are based on product matrix, see **Table 6)**.

7.2 – Package Lot Pass Criteria

A laboratory will use the following criteria to determine whether a package lot passes testing:

- All samples test ± 30% of the labeled concentrations for total THC and CBD, in mg/g for solids and mg/ml for liquids.
- The Relative Standard Deviation (RSD) of the mean concentration of total THC and CBD in the samples is less than or equal to 20% for *standard testing.*
- The Relative Percent Difference (RPD) of the mean concentration of total THC and CBD in the samples is less than or equal 20% for *reduced testing*.
- Microbiological impurities do not meet or exceed action levels as described in **Table 6.**

7.0 Package Lot Testing

7.3 – Standard Testing - Package Lots

During standard testing for package lots, a manufacturer will randomly sample units based on **Table 4**. Sampling will be done by formulation. Results for both microbiological impurities and potency will be attached to the unique identifier for the specific formulation of the package lot that a manufacturer delivers to the laboratory.

From the package lot samples of a given formulation that arrive at the laboratory, a laboratory shall choose three individual containers to perform three microbiological impurity suites, which varies by matrix according to **Table 6**. In addition, a laboratory will conduct 30 potency tests per formulation or SKU. The laboratory shall determine the RSD of these 30 samples, which shall not be greater than 20%. This means there will be 36-42 tests per formulation for standard testing of package lots.

Example: If a manufacturer has 700 units of 1:1 CBD:THC capsules in standard testing, the manufacturer shall submit 13 containers of the formulation to the laboratory for testing. A laboratory shall choose 3 containers, and shall conduct a microbiological impurity suite on a sample from each container. In addition, the laboratory will randomly draw 30 capsules from these 13 units to conduct the 30 potency tests, and the laboratory shall report the RSD of these 30 potency tests.

7.4 – Reduced Testing - Package Lots

Once a manufacturer successfully completes standard testing for a formulation and packaging process for a package lot, subsequent package lots produced using the same formulation and packaging process will be subject to reduced testing. A manufacturer's process may remain in reduced-testing status for two years for an approved formulation and packaging process unless otherwise approved by the Department to continue reduced testing. Material changes to a process as outlined in Section 6.6 may also impact reduced testing status. A laboratory shall report that a package lot passed if all criteria in **Section 7.2** are met.

Sampling for reduced-testing status of package lots shall include one primary sample and one field duplicate in the form of two containers from each formulation of package lot. A laboratory shall conduct one microbiological impurities suite on the primary sample. For potency, a laboratory shall test samples from both the primary sample and field duplicate, and calculate the RPD between the two samples. The RPD shall not be greater than 20%. This means there will be a total of 4-6 tests per formulation for reduced testing of package lots.

7.0 Package Lot Testing

Example: If a manufacturer makes 700 units of 1:1 CBD:THC capsules in reduced testing, they shall submit two, randomly sampled units of the formulation or SKU to the laboratory for testing. A laboratory shall conduct a microbiological impurity suite on the primary sample. Additionally, the laboratory will randomly select a capsule from both the primary sample and field duplicate and conduct a potency test on each, and report the RPD of the two tests.

7.5 – Vaporizer Cartridge Validation for Metals Contamination

The following refers to both vaporizer cartridges and disposable vaporizer units. It is recommended that manufacturers perform due diligence on the manufacturer or vendor of the vaporizer cartridges prior to purchasing, and consider requesting available certificates of analysis. When a manufacturer orders a new lot of empty cartridges, the first lot of cartridges that are filled and delivered to the laboratory for package lot testing shall also undergo three tests for metals. These three tests shall be done regardless of the size of the lot of hardware procured, and may be done independent of sending samples for testing potency and microbiological impurities.

These three tests shall be for the following analytes, at the following action levels:

- Lead = 1.0 ppm
- Cadmium = 0.2 ppm
- Arsenic = 0.2 ppm
- Mercury = 0.1 ppm

All three test results must be less than the action level to achieve a pass. Once an order of cartridges passes these three tests, a manufacturer will not have to retest cartridges for metals until it orders a new lot of empty cartridges. Upon report of a failure, that lot of cartridges shall have a single opportunity for a retest. This retest shall include the delivery of enough cartridges from the same lot to perform three tests. If any of the three tests fail, that lot of cartridges shall be destroyed.

A manufacturer shall notify the Department when they order a new lot of cartridges. Manufacturers should be aware that more than three cartridges may be necessary for a laboratory to perform these three tests.

7.0 Package Lot Testing

7.6 – Alterations to Processes or Standard Operating Procedures for Package Lots

Material changes to a manufacturing formulation and packaging process may require a manufacturer to return to standard testing for that formulation and/or process.
If a manufacturer would like to amend a process lot, they will need to complete a 'Laboratory Testing Verification/Validation Form' as described in **Section 3.0** A laboratory will determine if a verification or validation study is necessary. If a laboratory determines that no verification or validation study is necessary, a manufacturer may deliver samples of the amended process lot to the laboratory for the type and number of tests as outlined by the Department in the 'Laboratory Testing Verification/Validation Form.'

8.0 Failure Process – Process and Package Lots

8.1 – Process lot Failure – Standard & Reduced Testing

If a failure occurs for any of the listed contaminants at the process lot stage, pursuant to 641 IAC 156.26(3)"*c*", the manufacturer shall refrain from further formulating any medical cannabidiol products with the failed process lot. Medical cannabidiol from a process lot that fails contaminant testing at the process lot stage may be remediated and resampled in accordance with standard testing procedures (see **Table 2***). During a retest, a laboratory shall only conduct the test for the analyte that failed the initial testing.* A manufacturer will retain this remediation option at the process lot stage in perpetuity, assuming remediation is possible. Upon passing under standard testing conditions for the analyte in question, a laboratory shall report the first test(s) as having failed, and the second test(s) to have passed. A subsequent process lot using the same extraction and purification will be in reduced testing status.

8.2 – Package lot Failure – Standard & Reduced Testing

If a failure for potency or microbiological impurities occurs during the testing of package lots, the following shall apply. For potency, if there is a failure and the lots cannot be remedied by relabeling, or any of the criteria in **Section 7.2** are not met, the manufacturer may have a single opportunity to retest the formulation of package lot as described in the sections below. *During a retest, a laboratory shall only conduct the test for the analyte that failed initial testing.* If a manufacturer chooses not to retest, or the formulation fails the criteria on the retest, the manufacturer shall reject and destroy the products, unless otherwise described in the sections below.

1. Potency Failure
    - 30% criterion (Relabeling)
        - Re-labeling in standard testing may occur if samples consistently fail the ±30% such that they could qualify for an alternative label claim. If any standard testing samples fail the ±30% criterion, it will be determined whether the failure can be remedied by relabeling the package lot such that all samples test within ±30% of the new labeled concentrations. If so, the laboratory will fail the formulation for the original label, but will then pass the formulation for the new label concentration. Such relabeling will still allow the formulation to pass or remain in reduced testing for the new label claim.

8.0 Failure Process – Process and Package Lots

- If samples in standard testing fail the ±30% criterion and cannot be remedied by relabeling, the package lot formulation will have a single opportunity for a retest. Thirty (30) additional, new samples will be taken from the package lot formulation that the lab has on hand. If the lab does not have enough samples to perform 30 tests, the manufacturer shall deliver enough samples of the identical package lot in order to perform these 30 tests. If, upon a retest, the results are within ±30% of a label claim, a laboratory shall report the first test as having failed, and the second as having passed. Upon a reported pass, the formulation shall enter or remain in reduced testing. If upon a retest, there are samples not within ±30% of label claim, the Department reserves the right to determine whether a manufacturer must reject and destroy that package lot, as well as if that package lot formulation will remain in reduced testing status.

- RSD (standard testing) or RPD (reduced testing) >20%
  - If in standard testing the RSD for a formulation of package lot exceeds 20%, or if in reduced testing the RPD exceeds 20%, a laboratory shall conduct 30 new potency tests from the same lot of a given product matrix (capsules, tincture, etc.). If the laboratory does not have enough existing material on-hand to conduct the necessary tests, the manufacturer shall deliver enough new containers of the identical lot to complete the necessary tests. In the event of this failure, a manufacturer shall discuss with a laboratory how much material will be needed to conduct these tests. If, upon a retest, the results are ≤ 20% RSD in standard testing or ≤ 20% RPD in reduced testing, a laboratory shall report the first test as having failed, and the second as having passed.

2. Microbiological Impurities Failure
   - Total Yeast & Mold Count (TYMC), Total Aerobic Microbial Count (TAMC), Aspergillus, Shiga Toxin producing *E. coli* (STEC) and Salmonella
     - If any package lot fails TYMC or TAMC for the action levels described in **Table 6**, a manufacturer will have a single opportunity for a retest.
     - A manufacturer shall deliver two new containers (primary sample and field duplicate) of the formulation(s) in question, drawn from the same lot as the original samples. A laboratory will conduct three new tests total for TYMC from the new primary sample and field duplicate. No one test can be greater than the action levels described in **Table 6**. If any one test exceeds the action levels for microbiological impurities, the package lot of that formulation must be destroyed. If all three tests pass, a laboratory shall report the first test as having failed, and the second to have passed. Upon a reported pass, the formulation shall enter or remain in reduced-testing status.

9.0 Contaminant Analyses and Acceptance Criteria

Approved laboratories and licensed manufacturers should refer to **Table 5** for guidelines for product testing and acceptance criteria.

Table 5 - Contaminant Analysis & Acceptance Criteria			
Analyte	Action Level	Comment	Guideline
Metals		Metals testing is required for every process lot. See **Section 6.5** for vaporizer cartridge validation action levels for metals	FDA Q3D, elemental impurities guidance
Arsenic	1.5 ppm		
Cadmium	0.3 ppm		
Lead	1.0 ppm		
Mercury	0.5 ppm		
Analyte	Action Level	Comment	Guideline
Microbiological Impurities	See **Table 6**	Microbial tests (Total combined yeast and molds) are required for all package lots	American Herbal Pharmacopeia (USP 1111), State of Iowa Hygienic Laboratory
See **Table 6**			
Analyte	Action Level	Comment	Guideline
Pesticides	See **Table 7**	Pesticide Testing is required for every process lot	APHL "Guidance for State Medical Cannabis Testing Programs" (2016)
See **Table 7**			
Analyte	Action Level	Comment	Guideline
Solvents		Solvent testing is required for every process lot	Oregon Administrative Rule (OAR) 333-00710-0410: Table 4
See **Table 8**	See **Table 8**		

**For all contaminants, a test shall be reported as having failed if the analyte concentration is greater than or equal to the action level approved by the department and listed in this document.*

8.0 Contaminant Analyses and Acceptance Criteria

Table 6 – Microbiological Impurities & Acceptance Criteria				
Microbiological Test	**Testing Stage (Lot)**	**Consumable products**	**Inhalable products**	**Non-consumable Products (Topical, Suppositories)**
Total aerobic microbial count	Package	$1x10^3$ CFU/g Max acceptable count: 2000	$1x10^2$ CFU/g Max acceptable count: 200	$1x10^3$ CFU/g Max acceptable count: 2000
Total combined yeasts molds count	Package	$1x10^2$ CFU/g Max acceptable count: 200	$1x10^1$ CFU/g Max acceptable count: 20	$1x10^2$ CFU/g Max acceptable count: 200
Aspergillus (*A.fumigatus, A. flavus, A. niger, A. terreus)**	Package		$1x10^2$ CFU/g Max acceptable count: 200	
Shiga-Toxin Producing *E.coli*	Package	No detection in 1 g	No detection in 1 g	
Salmonella	Package	No detection in 1 g	No detection in 1 g	

**Results for this test will only be reported when mold is found on the Total Combined Yeasts Molds Count.*

8.0 Contaminant Analyses and Acceptance Criteria

Table 7 – Pesticide Analytes and Action Levels		
Analyte	**Chemical Abstract Services (CAS) Registry Number**	**Action Level (ppm)**
Acetamiprid	135410-20-7	0.2
Aldicarb	116-06-3	0.4
Azoxystrobin	131860-33-8	0.2
Bifenazate	149877-41-8	0.2
Boscalid	188425-85-6	0.4
Carbaryl	63-25-2	0.5
Carbofuran	1563-66-2	0.2
Chlorantraniliprole	500008-45-7	0.2
Chlorpyrifos	2921-88-2	0.6
Cypermethrin	52315-07-8	18
Diazinon	333-41-5	2.6
Dichlorvos	62-73-7	0.1
Ethoprophos	13194-48-4	0.4
Etofenprox	80844-07-1	0.4
Fipronil	120068-37-3	1
Flonicamid	158062-67-0	1
Imidacloprid	138261-41-3	0.4
Metalaxyl	57837-19-1	0.2
Methiocarb	2032-65-7	0.4
Methomyl	16752-77-5	0.4
Methyl parathion	298-00-0	8.5
Myclobutanil	88671-89-0	0.3
Oxamyl	23135-22-0	1
Permethrin I	52465-53-1	1.1
Pyridaben	96489-71-3	0.2
Spiroxamine I	118134-30-8	2
Tebuconazole	80443-41-0	0.4
Thiacloprid	111988-49-9	0.2
Thiamethoxam	153719-23-4	0.2

8.0 Contaminant Analyses and Acceptance Criteria

Table 8 – Residual Solvents & Processing Chemicals

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*
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*
Cumene	98-82-8	70
Cyclohexane	110-82-7	3880
Dichloromethane	75-09-2	600
2,2-dimethylbutane	75-83-2	290†
2,3-dimethylbutane	79-29-8	290†
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

Solvent	Chemical Abstract Services (CAS) Registry number	Action level (µg/g)
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*
2-Methylpentane	107-83-5	290†
3-Methylpentane	96-14-0	290†
N,N-dimethylacetamide	127-19-5	1090
N,N-dimethylfromamide	68-12-2	880
Pentane	109-66-0	5000
Propane	74-98-6	5000*
Pyridine	110-86-1	200
Sulfolane	126-33-0	160
Tetrahydrofuran	109-99-9	720
Toluene	108-88-3	890
Xylenes‡	1330-20-7	2170

- * Limit based on similarity to pentane.
- † Limit based on similarity with n-hexane.
- ‡ Combination of: 1,2-dimethylbenzene, 1,3-dimethylbenzene, 1,4-dimethylbenzene, and ethyl benzene

10.0 – Stability Testing

As a part of a quality control program, manufacturers shall develop procedures for performing stability testing of each product type that is manufactured. Stability testing shall be done in the same container-closure system in which the product is sold. Stability testing shall be conducted by the manufacturer. Licensed manufacturers should refer to **Table 9** guidelines for sample size and testing intervals for stability testing.

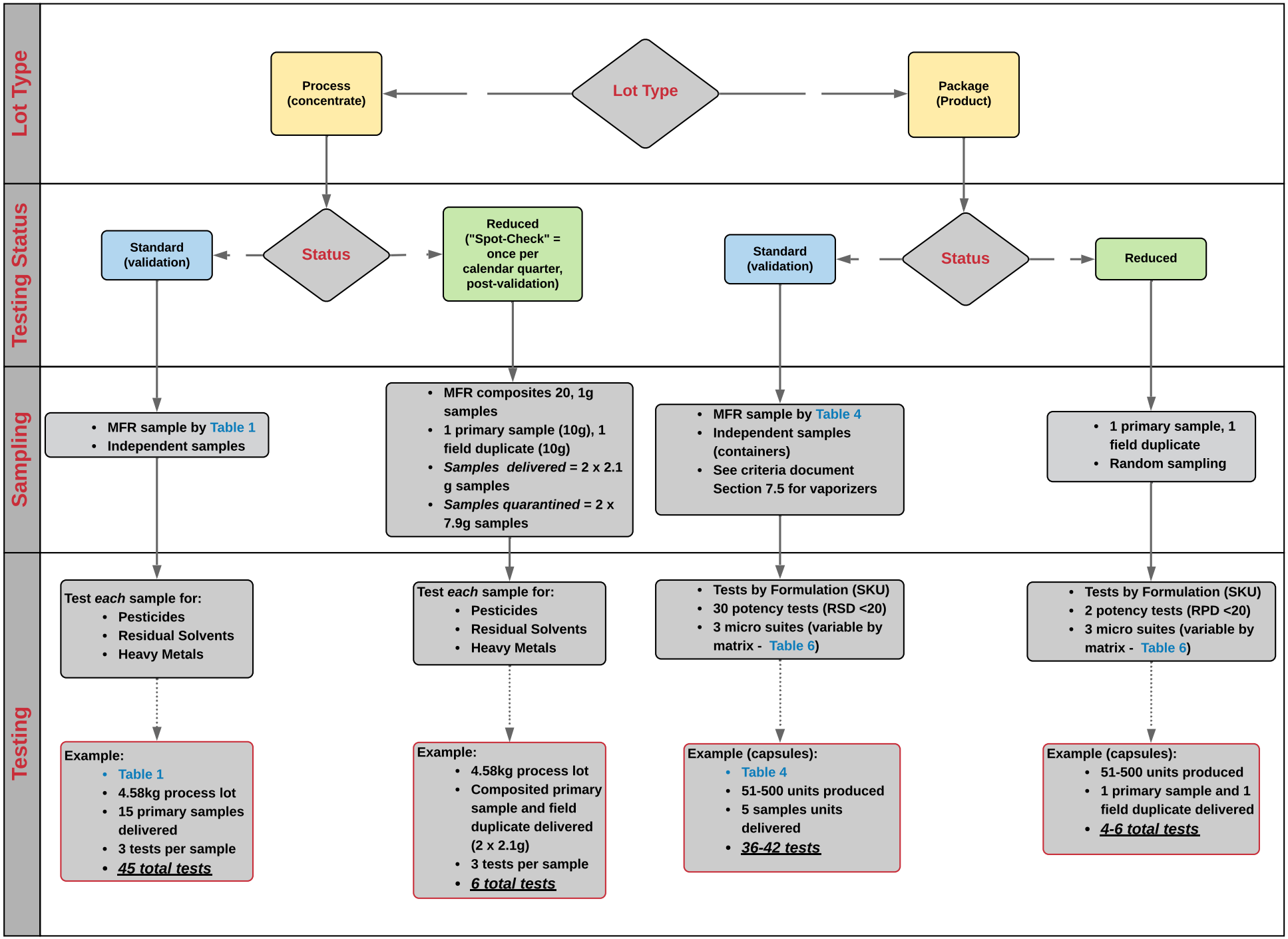
Table 9 – Stability Testing

Product	Sample size tested at each interval	Sample container	Storage Conditions	Intervals (months)					
Capsule	3 capsules	White Plastic Bottle	Room Temp.	0	3	6	9	12	18
Suppository	3 suppositories	Blister Pack	Room Temp.	0	3	6	9	12	18
Tincture	0.5 mL	Amber Glass Bottle	Room Temp.	0	3	6	9	12	18
Lotion	1.0 mL	White Plastic Bottle	Room Temp.	0	3	6	9	12	18
Vaporization	3 cartridges, or disposable units	Cartridge, or disposable units	Room Temp.	0	3	6	9	12	18

If product-expiration-date studies have not been completed before a manufacturer begins delivering products to dispensaries, the manufacturer shall assign a tentative product expiration date, not to exceed one year, based on any available stability information (641 IAC 154.26(4)).

IDPH Medical Cannabidiol Testing Process Flowchart

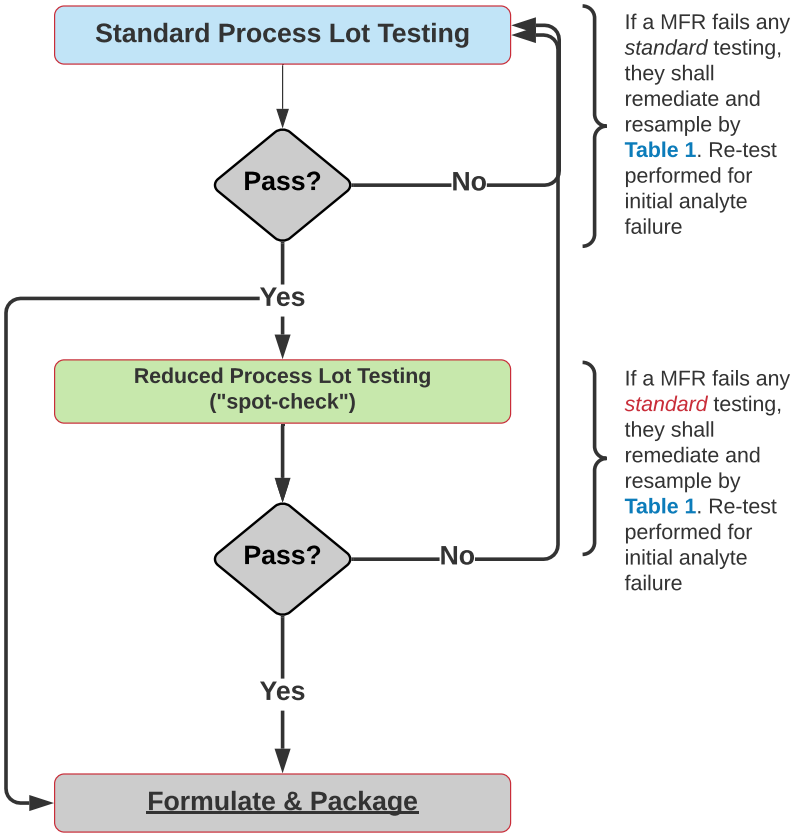
Office of Medical Cannabidiol | Rev. 09/2020



IDPH Medical Cannabidiol Testing Failure Flowchart

Office of Medical Cannabidiol | Rev. 09/2020

Process Lot Failure



Package Lot Failure