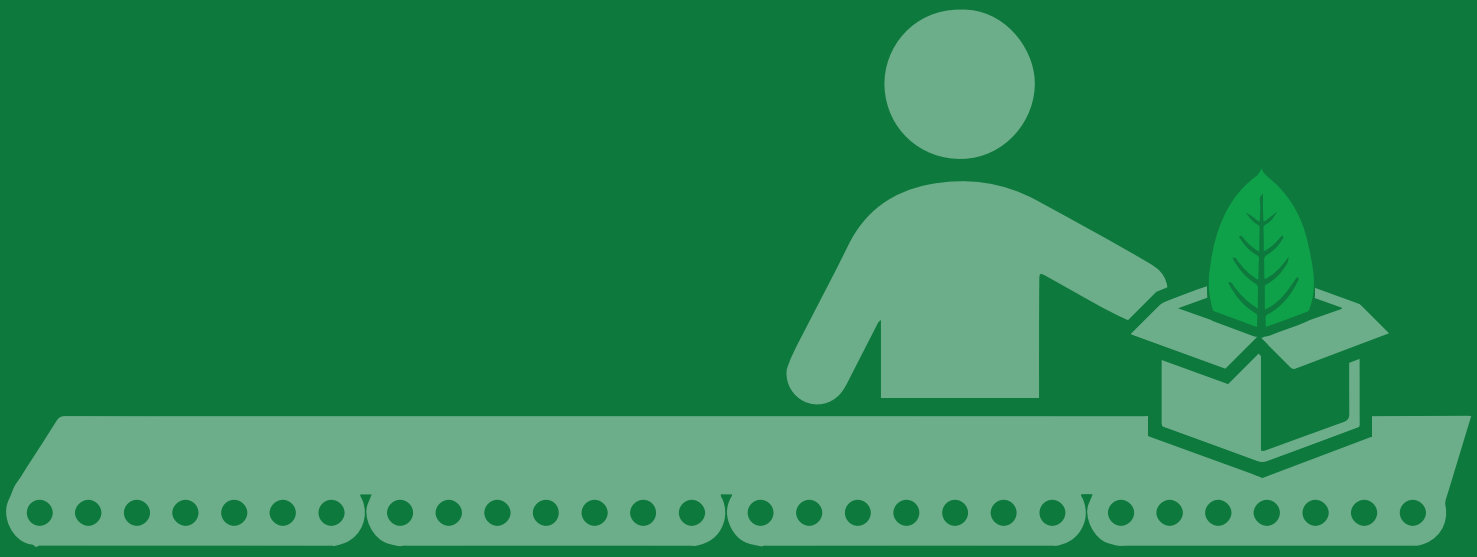
Guide to **Good Manufacturing Practices (GMP)**

KRATOM TRADE ASSOCIATION



Guide to Good Manufacturing Practices

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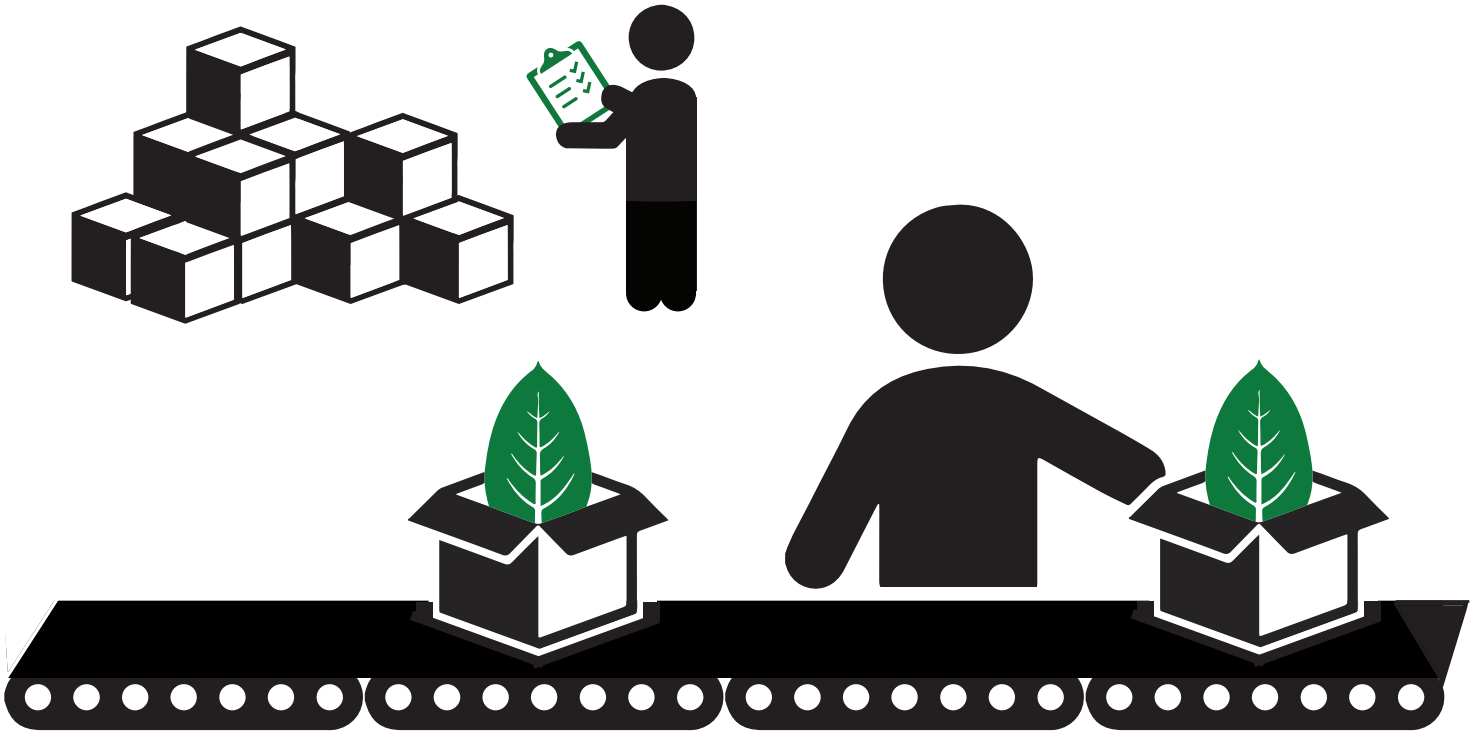
Introduction to **Current Good Manufacturing Practices (cGMPs)**

As the leading Kratom industry association, the Kratom Trade Association (KTA) promotes best practices and quality standards to produce superior botanical products for consumers to manage their well-being.

Consumers expect safe and high-quality products, which is why KTA developed this guide to current Good Manufacturing Practices (cGMPs) standards for our members. cGMPs create an important, highly standardized system to carefully identify, track, and assess deviations from the normal process. Becoming cGMP certified enables manufacturers and distributors to drastically lower the chance of adulteration, leading to an overall safer, more consistent product for consumers. Retailers should also adopt relevant cGMP provisions (personal hygiene, store cleanliness, returned product procedures) and purchase Kratom from cGMP compliant manufacturers and distributors to ensure that their customers recieve the highest quality products.

Kratom manufacturers and distributors need to familiarize themselves and adhere to cGMPs to protect their process and be prepared in case of quality control deviations and recalls. This guide contains the information and resources you need to protect your customers and business by becoming cGMP compliant.



Current Good Manufacturing Practices (cGMP)
Compliance Policy Checklist

Written Procedures

- ☐ Establish written procedures for every aspect of your operation.
- ☐ Make sure records are kept and available for 1 year past the shelf life date, or 2 years beyond the date of distribution of the last batch of products associated with those records.

Qualified and Trained Personnel

- ☐ Establish policies, including an employee handbook, to ensure prevention of contamination by personnel, including mandatory hygienic practices and separating non-manufacturing functions from processing areas.
- ☐ Establish specific recordkeeping and written procedures for ensuring qualified personnel are hired and adequately trained. Maintain a training log for all personnel.

Manufacturing Equipment

- ☐ Ensure your physical plant and grounds for manufacturing, processing, packaging, labeling, and/or storage of ingredients and/or finished product is (1) designed and maintained in a manner conducive to prevent contamination, and (2) is the appropriate size and nature for your operations.
- ☐ Ensure your equipment and utensils are suitable for their intended use and able to be adequately cleaned/sanitized and properly maintained.

Manufacturing Process

- ☐ Establish and implement a system of production and process controls, overseen by qualified quality control personnel, covering all stages of manufacturing, packaging, labeling, and holding of the product to ensure product quality and specification.
- ☐ Quality control personnel must confirm that your manufacturing, packaging, labeling, and holding operations ensure the quality of the product and that the product is packaged and labeled as specified in the master manufacturing record.
- ☐ Establish requirements for components, packaging, and labels for products that are received for packaging or labeling as a dietary supplement.

- ☐ Master Manufacturing Record: Prepare and follow a written master manufacturing record for each unique formulation of product that you manufacture and for each batch size, to ensure uniformity in the finished batch.

- ☐ Batch Production Record: Prepare a batch production record every time you manufacture a batch of a product, which must include complete information relating to the production and control of each batch and must accurately follow the appropriate master manufacturing record, including the performance of each step in the production of the batch.

- ☐ Laboratory Operations: Develop written procedures for laboratory operations, including written procedures for the tests and examinations that you conduct to determine whether specifications are met.

- ☐ Manufacturing Operations: Design or select manufacturing processes ensuring product specifications are consistently met, including adequate sanitation, preventative contamination measures, and rejected products.

Packaging and Labeling Operations:

- ☐ Packaging products and labels must meet specifications to ensure quality of the product, and must be examined prior to packing and labeling to determine whether the packaging and labels conform to the master manufacturing plan and are trackable through distribution.

- ☐ Products must be filled, assembled, packaged, or labeled to ensure quality of products. If a product is rejected for distribution, a sample must be reserved for the appropriate amount of time.

- ☐ You must distribute products under conditions that will protect the products against contamination and deterioration.

Returned Dietary Supplements:

- ☐ Must be identified and quarantined until a material review is conducted.

- ☐ A returned product must be destroyed, unless the outcome of a material review by your quality control personnel determines the product is salvageable.

- ☐ Any reprocessed (deemed salvageable) product must meet all established product specifications and be approved by the quality control personnel prior to distribution.

- ☐ If other batches are implicated, you must conduct an investigation of your manufacturing processes and each of those other batches to determine compliance with specifications.

- ☐ Your quality control personnel must review and document all product complaints, investigate any product complaints that involves a possible failure of a product to meet any of its specifications or any other cGMP requirements, and conduct follow-up actions when necessary.

Current Good Manufacturing Practices (cGMPs) **Compliance Policy**

The Kratom Trade Association (KTA) is dedicated to the safe and responsible use of Kratom botanical products in the U.S. KTA is committed to regulatory compliance and to developing and promoting use of best practices and quality standards for the industry. The following cGMP guidelines reflect this commitment, in conformance with the U.S. Food and Drug Administration (FDA) dietary supplement GMP requirements.

KTA cGMP Membership Requirements

As part of this commitment, KTA member companies that manufacture, package, label, hold/store, or distribute raw Kratom ingredients or finished Kratom products are required to adopt cGMPs and demonstrate cGMP certification or tangible progress toward obtaining certification from a third party quality standards certification entity on a periodic basis.

- For companies already holding third party certification: Evidence of certification in the form of a certificate or certifying audit results must be provided within four weeks of joining KTA and updated upon expiration and renewal.
- For companies in the process of obtaining certification: Proof that the company is in the process of obtaining cGMP compliance, e.g., in the form of an initial audit/assessment report, a gap analysis or a contract/correspondence with the third party certifier or other qualified consultant[1], must be provided within four weeks of joining KTA and an update with documentation must be provided every six months until certification is obtained.

For companies interested in joining KTA and committed to cGMP compliance, but which have not yet begun the process, KTA can provide assistance with identifying an auditor, as discussed further below.

Unlike other organizations, KTA is not offering a “seal of approval” or similar certification at this time because KTA members must comply with all quality requirements and be certified cGMP compliant by a third-party organization qualified to make such a determination. While KTA considered providing such a seal, ultimately it was determined that the potential liability risks and necessary oversight associated with vouching for various products would be too great. Our members instead may advertise the cGMP certification provided by third-parties who are qualified to conduct such reviews, and benefit from being included in KTA membership directories and indices.

[1] As some certification bodies only perform audits of existing systems, KTA will accept evidence that the company has engaged a qualified third-party consultant to assist it with initial creation of its quality system.

KTA Membership Resources

KTA has identified resources that can assist our members with cGMP compliance, as well as examining sampling and testing standards that exceed minimum standards in order to ensure the quality and safety of our members' products.

KTA offers:

- Special member rates for training in compliance with dietary supplement cGMPs
- Special member rates for expert auditing and assistance in setting up your cGMP-compliant quality system
- Access to InstantGMP software to help you manage compliance efforts

KTA Initiatives to Explore Options for Future cGMPs Enhancements

In addition to compliance with cGMPs and best practices among our members, KTA intends to pool member contacts and resources to explore the potential for promotion of cGMP compliance or best practices compliance at the start of the supply chain. KTA is interested in exploring options for incentivizing farmers and suppliers at the source to adopt quality and safety standards.

KTA is also exploring specific standards, including product alkaloid content limits and/or declarations, standard testing requirements and sampling methodology.

KTA Guidelines: Current Good Manufacturing Practices (cGMPs) Standards

The following is an overview of dietary supplement cGMP requirements applicable to companies that manufacture, package, label, hold/store, or distribute raw Kratom ingredients or Kratom products.

The entire set of requirements is found at 21 CFR. Part 111. These requirements are meant to be tailored by each regulated entity to its own particular functions. For example, if an entity only distributes Kratom products (e.g., receives packaged and labeled product from another entity, warehouses that inventory while sales are in process, and then ships to the customer without any processing or re-packaging), then only distribution and holding requirements likely will apply to its facility. Each company's quality system should be appropriately scaled to cover the activities it actually performs.

Many of the responsibilities below may be outsourced to third parties or conducted with assistance from a third party, e.g. the establishment of specifications for your product, or labs that conduct testing for pathogens. However, you ultimately are responsible for ensuring your own compliance, so we recommend conducting appropriate due diligence when selecting any contracting parties. KTA resources, as detailed above, may be useful to members in this regard.

I. Written Procedures

You should have underlying written procedures for every aspect of your operation. This includes not only technical processes like testing, manufacturing, labeling, and packaging, but also underlying aspects that support your operation, such as personnel training and hygiene, facility and equipment standards and maintenance, and record keeping. Third party certification bodies can help you develop these procedures as part of creating and implementing cGMP-compliant quality systems. Where appropriate below, we have included a list of corresponding Standard Operating Procedures (SOPs) that we recommend you have in place, to the extent relevant to your operations.

II. Records and Record keeping

Companies are required to keep certain records of their compliance to comply with cGMPs.

1. **Time period for keeping records required by cGMPs:** 1 year past the shelf life date, if shelf life dating is used, or 2 years beyond the date of distribution of the last batch of products associated with those records.

2. **Making records available to the FDA**: You must have all required cGMP records, or copies of such records, readily available during the retention period for inspection and copying by the FDA when requested (note: records can be electronic and may also be stored off site as long as they can be retrieved within 24 hours).

Each section below includes record keeping requirements specific to particular quality system elements. All record keeping requirements are subject to the timing and availability requirements in this section.

Reference: 21 CFR Part 111, Subpart P

III. Personnel

The DS cGMP rule requires that each person who is identified to perform quality control operations have distinct and separate responsibilities related to performing such operations from those responsibilities that the person otherwise has when not performing such operations.

We recommend that, whenever practical, the person performing a given quality control operation be a different person than the person who performed the operation subject to quality control oversight .

References: 21 CFR Part 111, Subpart 12(b) and 72 FR 34752 at 34867

Personnel requirements cover three broad areas:

1. **Personnel qualifications**
    a. You should appoint a quality control manager with adequate education, training or experience and assign that manager specific quality control responsibilities (e.g., conducting internal audits and mock recalls, supervision of training, etc.)
    b. You should assign qualified personnel to supervise all manufacturing, packaging, labeling, holding, or distribution tasks.
    c. Employees engaged in manufacturing, packaging, labeling, or holding, or in performing any quality control operations, must have the education, training, or experience to perform the assigned functions.
    d. Part of ensuring that personnel have the requisite level of education to perform their jobs is providing training.

2. **Prevention of contamination by personnel**
    a. You should have policies, including in the employee handbook, requiring employees handling any component of the products, or packaging/labeling that could come into contact with the product, to inform a manager in the event they feel ill and encouraging employees not to come into work while sick.
    b. You must require and enforce hygienic practices (e.g., requiring appropriate protective clothing like hair nets, gloves and smocks, requiring hand washing, etc.).
    c. You must separate non-manufacturing functions from processing areas (e.g., requiring personnel to eat, drink and smoke in designated areas).

3. **Specific record keeping requirements and required written procedures**
    a. You must maintain written procedures for ensuring qualified personnel are hired, appropriately trained and effective.
    b. You must maintain a training log that includes the name of the person trained, the date of the training, and the type of training provided.

4. **Recommended written SOPs**
    a. Written job descriptions for any position with a safety/quality role, including required qualifications.
    b. Written training program (can be third party program, but you must vet the quality of

the program).
c. SOP outlining system for ensuring timely initial and refresher training is accomplished.
d. Employee handbook/SOP containing requirements for hygiene and behavior to prevent contamination.

Reference: 21 CFR Part 111, Subpart B

IV. Physical Plant and Grounds

You are responsible for ensuring that your facilities for manufacturing, processing, packaging, labeling, and/or storage of ingredients and/or finished products are designed and maintained in a manner conducive to preventing contamination. This includes the following responsibilities:

1. **Ensuring adequate drainage in the facility and on the grounds**

2. **Preventing conditions that attract or harbor pests** (e.g., ensuring timely removal of garbage and debris from facility and grounds, carrying out written pest control procedures)

3. **Providing adequate waste treatment and disposal**

4. **Maintaining clean and sanitary facilities, including upkeep of the building**

5. **Prohibiting the use or holding of toxic materials in your facility unless the materials are used for cleaning, lab testing, or other operational uses —** if such materials are present, you must take precautions to protect against the contamination of components, products, or surfaces which may come into contact with the product or ingredients.

6. **Ensuring that water used during any part of the manufacturing/handling process is safe and sanitary —** if the water may become a component of the product, (e.g. the water comes into contact with the product or its packaging), then it must, at a minimum, comply with applicable Federal, State, and local requirements and not contaminate the product.

7. **Providing adequate plumbing and sewage disposal to avoid conditions that could contaminate the product**

8. **Making available to your employees adequate, readily accessible restrooms and hand-washing facilities —** such facilities must include running water at a suitable temperature and must be kept clean to avoid becoming a source of potential contamination.

9. **Ensuring your facilities are appropriate to the size and nature of your operations, including the following:**
    a. Suitable in size, construction, and design to facilitate maintenance, cleaning, and sanitizing operations
    b. Adequate space for the orderly placement of equipment and holding of materials as necessary for maintenance, cleaning, and sanitizing operations and to prevent contamination and mix-ups of components and products during manufacturing, packaging, labeling, or holding
    c. Separate or defined areas of adequate size or other control systems, such as

computerized inventory controls or automated systems of separation, to prevent contamination and mix-ups of components and products (e.g., ensuring returned products are not mixed up with incoming ingredients, separating different types of product, quarantining product not yet tested, and ensuring correct placement of labels)

d. Designed and constructed in a manner that prevents contamination of components, products, or contact surfaces. The design and construction must include:
    i. Floors, walls, ceilings, ducts and pipes that can be adequately cleaned and kept in good repair;
    ii. Appropriate ventilation and temperature controls;
    iii. Sufficient space to perform manufacturing functions (to minimize opportunities for contamination);
    iv. Adequate lighting (to assess cleanliness and conditions, as well as accurately perform manufacturing duties).
e. Ability to control access to pests

10. Specific record keeping requirements and written procedures

a. Must have written procedures for cleaning the physical plant and for pest control
b. Must make and keep records that show that water, when used in a manner such that the water may become a component of the product, meets the requirements of 21 CFR. §111.15(e)(2) (compliance with applicable Federal, State, and local requirements)

11. Recommended written SOPs

a. Manufacturing/packaging/labeling process flow diagram
b. Building maintenance inspection schedule and procedures
c. Pest control
d. Facility cleaning requirements and schedule, including checklists

Reference: 21 CFR Part 111, Subpart C

V. Equipment and Utensils

1. Equipment and utensil requirements

a. You must use equipment and utensils that are suitable for their intended use and able to be adequately cleaned and properly maintained.
b. Instruments or controls used in the manufacturing, packaging, labeling, or holding of a product, and instruments or controls that you use to measure, regulate, or record temperatures, hydrogen-ion concentration (pH), water activity, or other conditions, to control or prevent the growth of microorganisms or other contamination must be:
    i. Accurate and precise;
    ii. Adequately maintained; and
    iii. Adequate in number for their designated uses.
c. You must calibrate instruments and controls you use in manufacturing or testing a component or product. You must calibrate:
    i. Before first use; and
    ii. As specified by the manufacturer; or
    iii. At routine intervals or as otherwise necessary to ensure the accuracy and precision of the instrument and control.

d. You must maintain, clean, and sanitize, as necessary, all equipment, utensils, and any other contact surfaces used to manufacture, package, label, or hold components or products.
e. FDA cGMPs contains specific additional requirements for automated, mechanical, or electronic equipment at 21 CFR. § 111.30

2. Specific record keeping and written procedure requirements

You must make and keep the following records:

a. Written procedures for fulfilling the requirements in this section, including written SOPs for:
    i. Calibrating instruments and controls that you use in manufacturing or testing a component or product;
    ii. Calibrating, inspecting, and checking automated, mechanical, and electronic equipment; and
    iii. Maintaining, cleaning, and sanitizing all relevant equipment, utensils, and any other contact surfaces that are used to manufacture, package, label, or hold components or products;
d. Documentation, in individual equipment logs, of the date of the use, maintenance, cleaning, and sanitizing of equipment;
e. Documentation of calibration for instruments and controls that you use in manufacturing or testing a component or product;
f. Written records of calibrations, inspections, and checks of automated, mechanical, and electronic equipment, as well as any backup electronic files or data;
g. Documentation of the controls that you use to ensure that equipment functions in accordance with its intended use.

Reference: 21 CFR Part 111, Subpart D

VI. Requirement to Establish a Production and Process Control System

You must implement a system of production and process controls, including quality controls, that covers all stages of manufacturing, packaging, labeling, and holding of the product to ensure the quality of the product and that the product is packaged and labeled as specified in the master manufacturing record.

This system must be overseen by qualified quality control personnel (“QC”). Any deviation must be reviewed by QC before disposition of ingredients or product is determined.

1. Requirement to establish specifications

a. You must establish a specification for any point, step, or stage in the manufacturing process where control is necessary to ensure the quality of the product and that the product meets the specifications in the master manufacturing record. For example: when receiving raw Kratom from overseas, you must have a process in place to determine whether the product is safe and not contaminated and/or to treat the product to ensure there is no adulteration.
b. For each component that you use in the manufacture of a product, you must establish component specifications as follows:
    i. You must establish an identity specification;

ii. You must establish component specifications that are necessary to ensure that specifications for the purity, strength, and composition of finished products manufactured using the components are met; and
iii. You must establish limits on those types of contamination that may adulterate or may lead to adulteration of the finished batch of the product to ensure the quality of the finished product.

Note that for pure Kratom products, there will only be one component – the Kratom itself

c. For the in-process production:
    i. You must establish in-process specifications for any point, step, or stage in the master manufacturing record where control is necessary to help ensure that specifications are met for the identity, purity, strength, and composition of the products and, as necessary, for limits on those types of contamination that may adulterate or may lead to adulteration of the finished batch of the product;
    ii. You must provide adequate documentation of your basis for why meeting the in-process specifications, in combination with meeting component specifications, will help ensure that the specifications are met for the identity, purity, strength, and composition of the products and for limits on those types of contamination that may adulterate or may lead to adulteration of the finished batch of the product; and
    iii. Quality control personnel must review and approve this documentation.
d. You must establish specifications for product labels (label specifications) and for packaging that may come in contact with the product (packaging specifications). Packaging that may come into contact with products must be safe and suitable for its intended use and must not be reactive or absorptive or otherwise affect the safety or quality of the product.
e. For each finished product that you manufacture you must establish product specifications for the identity, purity, strength, and composition of the finished batch of the product, and for limits on those types of contamination that may adulterate, or that may lead to adulteration of, the finished batch of the product to ensure the quality of the product.
f. If you receive a product from a supplier for packaging or labeling as a dietary supplement (and for distribution rather than for return to the supplier), you must establish specifications to provide sufficient assurance that the product you receive is adequately identified and is consistent with your purchase order.
g. You must establish specifications for the packaging and labeling of the finished packaged and labeled products, including specifications that ensure that you used the specified packaging and that you applied the specified label.

2. Requirements to ensure established specifications are met

You are responsible for determining whether the specifications you establish pursuant to number 1 above are met.

a. Before you use a component/ingredient, you must:
    i. Conduct at least one appropriate test or examination to verify the identity of any component that is a dietary ingredient (i.e., Kratom leaf/powder);
    ii. Confirm the identity of any other components and determine whether other applicable component specifications you established are met. To do so, you must either:

(1) Conduct appropriate tests or examinations; or
(2) Rely on a certificate of analysis from the supplier of the component that you receive, provided that proper qualification of the supplier and documentation has been performed per 21 CFR. § 111.75(a).

b. You must monitor the in-process points, steps, or stages where control is necessary to ensure the quality of the finished batch of product to:
    i. Determine whether the in-process specifications are met; and
    ii. Detect any deviation or unanticipated occurrence that may result in a failure to meet specifications.
c. For a subset of finished product batches that you identify through a sound statistical sampling plan (or for every finished batch), you must verify that your finished batch of the product meets finished product specifications for identity, purity, strength, composition, and for limits on those types of contamination that may adulterate or that may lead to adulteration of the finished batch of the product.
    To do so:
    i. You must select one or more established specifications for identity, purity, strength, composition, and the limits on those types of contamination that may adulterate or that may lead to adulteration of the product that, if tested or examined on the finished batches of the product, would verify that the production and process control system is producing a product that meets all product specifications;
    ii. You must conduct appropriate tests or examinations to determine compliance with the specifications selected;
    iii. You must provide adequate documentation, approved by QC, of your basis for determining that compliance with the specification(s) selected will ensure that your finished batch of the product meets all product specifications for identity, purity, strength, and composition, and the limits on those types of contamination that may adulterate the product; and
d. Before you package or label a product that you receive for packaging or labeling as a dietary supplement (and for distribution rather than for return to the supplier), you must visually examine the product and have documentation to determine whether the specifications that you established are met.
e. Before you use packaging and/or labels, you must, at a minimum, conduct a visual identification of the containers and closures and/or labels and review the supplier's invoice, guarantee, or certification to determine whether the packaging specifications are met.
f. Before you use labels, you must, at a minimum, conduct a visual examination of the label and review the supplier's invoice, guarantee, or certification to determine whether label specifications are met.
g. You must, at a minimum, conduct a visual examination of the packaging and labeling of the finished packaged and labeled products to determine whether you used the specified packaging and applied the specified label.
h. You must ensure that the tests and examinations that you use to determine whether the specifications are met are appropriate, scientifically valid methods. The tests and examinations that you use, or a third party uses on your behalf, must include at least one of the following:
    i. Gross organoleptic analysis
    ii. Macroscopic analysis

iii. Microscopic analysis
iv. Chemical analysis
v. Other scientifically valid methods

You must establish corrective action plans for use when an established specification is not met.

3. Required action if established specifications are not met

a. If a product component/ingredient does not meet identity specifications, you must reject the component and it must not be used in manufacturing the product.
b. If a product does not meet the other specifications described above, you must reject the component, product, package or label unless QC approves a treatment, an in-process adjustment, or reprocessing that will ensure the quality of the finished product and that the product is packaged and labeled as specified in the master manufacturing record.
c. No finished batch of products may be released for distribution unless it meets specifications.

4. Collecting representative samples You must collect representative samples, including:

a. Representative samples of each unique lot of components, packaging, and labels that you use to determine whether the components, packaging, and labels meet your established (including when you receive components, packaging, or labels from a supplier, collecting representative samples of each unique shipment, and of each unique lot within each unique shipment);
b. Representative samples of in-process materials for each manufactured batch at points, steps, or stages, in the manufacturing process as specified in the master manufacturing record where control is necessary to ensure the identity, purity, strength, and composition of products to determine whether the in-process materials meet your established specifications;
c. Representative samples of a subset of finished batches of each product that you manufacture, which you identify through a sound statistical sampling plan (or otherwise every finished batch), before releasing for distribution to verify that the finished batch of product meets your established product specifications;
d. Representative samples of each unique shipment, and of each unique lot within each unique shipment, of product that you receive for packaging or labeling as a dietary supplement (and for distribution rather than for return to the supplier) to determine whether the received product meets your established specifications; and
e. Representative samples of each lot of packaged and labeled products to determine whether the packaging and labeling of the finished packaged and labeled products meet your established specifications.

5. Holding reserve samples

You must collect and hold reserve samples of each lot of packaged and labeled products that you distribute.

a. The reserve samples must:
    i. Be held using the same container-closure system in which the packaged and labeled product is distributed, or if distributing products to be packaged and labeled, using a container-closure system that provides essentially the same characteristics to protect against contamination or deterioration as the one in

which it is distributed for packaging and labeling elsewhere;
   ii. Be identified with the batch, lot, or control number;
   iii. Be retained for 1 year past the shelf life date (if shelf life dating is used), or for 2 years from the date of distribution of the last batch of products associated with the reserve sample, for use in appropriate investigations; and
   iv. Consist of at least twice the quantity necessary for all tests or examinations to determine whether or not the product meets product specifications.

6. Requirements applicable to treatments, in-process adjustments, and reprocessing when there is a deviation or unanticipated occurrence or when an established specification is not met

   a. You must not reprocess a rejected product or treat or provide an in-process adjustment to a component, packaging, or label to make it suitable for use in the manufacture of a product unless quality control personnel conduct a material review and make a disposition decision to approve the reprocessing, treatment, or in-process adjustment.
   b. You must not reprocess any product or treat or provide an in-process adjustment to a component to make it suitable for use in the manufacture of a product, unless quality control personnel conduct a material review and make a disposition decision that is based on a scientifically valid reason and approves the reprocessing, treatment, or in-process adjustment.
   c. If the established identity specification is not met, you may not reprocess or treat the component or finished product; it must be rejected.
   d. Any batch of product that is reprocessed, that contains components that you have treated, or to which you have made in-process adjustments to make them suitable for use in the manufacture of the product must be approved by quality control personnel before releasing for distribution.

7. Specific record keeping requirements and written procedures

You must make and keep the following records:

   a. The specifications established;
   b. Documentation of your qualification of a supplier for the purpose of relying on the supplier's certificate of analysis;
   c. Documentation for why meeting in-process specifications, in combination with meeting component specifications, helps ensure that the product meets the specifications for identity, purity, strength, and composition; and for limits on those types of contamination that may adulterate or may lead to adulteration of the finished batch of the product; and
   d. Justification for the tests or examinations selected to confirm product specifications ensure that the product meets those specifications.

8. Recommended SOPs

   a. Lab Sampling Log
   b. Procedures for retaining, storage of and disposition of samples
   c. SOPs and logs for receiving components, finished product for distribution, packaging and labels
   d. Out of specification investigation

Reference: 21 CFR Part 111, Subpart E

VII. Production and Process Control System: Requirements for Quality Control

1. Responsibilities of quality control personnel

Quality control personnel must ensure that your manufacturing, packaging, labeling, and holding operations ensure the quality of the product and that the product is packaged and labeled as specified in the master manufacturing record. To do so, quality control personnel must perform operations that include:

a. Approving or rejecting all processes, specifications, written procedures, controls, tests, and examinations, and deviations from or modifications to them, that may affect the identity, purity, strength, or composition of a product;
b. Reviewing and approving the documentation setting forth the basis for qualification of any supplier;
c. Reviewing and approving the documentation setting forth the basis for why meeting in-process specifications, in combination with meeting component specifications, will help ensure that the identity, purity, strength, and composition of the product are met;
d. Reviewing and approving the documentation setting forth the basis for why the results of appropriate tests or examinations you selected for each product specification will ensure that the finished batch of the product meets product specifications;
e. Ensuring that required representative samples are collected;
f. Ensuring that required reserve samples are collected and held; and
g. Determining whether all established product specifications are met.

2. Required QC operations for laboratory operations associated with the production and process control system

Quality control operations for laboratory operations associated with the production and process control system must include:

a. Reviewing and approving all laboratory control processes associated with the production and process control system;
b. Ensuring that all required tests and examinations are conducted; and
c. Reviewing and approving the results of all tests and examinations.

Note: If you choose to use a third party lab, appropriate vetting of these factors and retention of results is required.

3. Required QC Operations for a material review and disposition decision

Quality control personnel must conduct a material review and make a disposition decision if:

a. An established specification is not met.
    i. Must reject the component, product, package or label, unless QC approves a treatment, an in-process adjustment, or reprocessing, where permitted.
b. A batch deviates from the master manufacturing record.
c. There is any unanticipated occurrence during the manufacturing operations that adulterates or may lead to adulteration of the component, product, or packaging, or could lead to the use of a label not specified in the master manufacturing record.
    i. Must reject the component, product, packaging, or label unless QC approves a treatment, an in-process adjustment, or reprocessing to correct the applicable deviation or occurrence.
d. Calibration of an instrument or control suggests a problem that may have resulted in a

failure to ensure the quality of a batch or batches of a product
e. A product is returned.

The person who conducts a material review and makes the disposition decision must, at the time of performance, document that material review and disposition decision. The DS CGMP rule requires quality control personnel to reject a component, dietary supplement, packaging, or label when:

a. There is a deviation or unanticipated occurrence during the production and in-process control system that results in or could lead to adulteration of a component, dietary supplement, or packaging, or could lead to the use of a label not specified in the master manufacturing record (unless quality control personnel approve a treatment, an in-process adjustment, or reprocessing to correct the applicable deviation or occurrence) (21 CFR 111.113(b)(1)).
b. When a specification that you are required to establish is not met (unless quality control personnel approve a treatment, an in-process adjustment, or reprocessing, as permitted in 21 CFR 111.77) (21 CFR 111.113(b)(2)).

4. Required QC operations for equipment, instruments, and controls

Quality control operations for equipment, instruments, and controls must include:

a. Reviewing and approving all processes for calibrating instruments and controls;
b. Periodically reviewing all records for calibration of instruments and controls;
c. Periodically reviewing all records for calibrations, inspections, and checks of automated, mechanical, or electronic equipment; and
d. Reviewing and approving controls to ensure that automated, mechanical, or electronic equipment functions in accordance with its intended use.

5. Required QC operations for components, packaging, and labels before use in the manufacture of a dietary supplement

Quality control operations for components, packaging, and labels before use in the manufacture of a dietary supplement must include:

a. Reviewing all receiving records for components, packaging, and labels;
b. Determining whether all components, packaging, and labels conform to established specifications;
c. Conducting any required material review and making any required disposition decision;
d. Approving or rejecting any treatment and in-process adjustments of components, packaging, or labels to make them suitable for use in the manufacture of a dietary supplement; and
e. Approving, and releasing from quarantine, all components, packaging, and labels before they are used.

6. Required QC operations for the master manufacturing record, the batch production record, and manufacturing operations

Quality control operations for the master manufacturing record, the batch production record, and manufacturing operations must include:

a. Reviewing and approving all master manufacturing records and all modifications to the master manufacturing records;
b. Reviewing and approving all batch production-related records;

c. Reviewing all required monitoring;
d. Conducting any required material review and making any required disposition decision;
e. Approving or rejecting any reprocessing;
f. Determining whether all established in-process specifications are met;
g. Determining whether each finished batch conforms to established product specifications; and
h. Approving and releasing, or rejecting, each finished batch for distribution, including any reprocessed finished batch.

Quality control personnel must not approve and release for distribution:

i. Any batch of product for which any component in the batch does not meet its identity specification;
j. Any batch of finished product, including any reprocessed batch, that does not meet all established product specifications;
k. Any batch of finished product, including any reprocessed batch, that has not been manufactured, packaged, labeled, and held under conditions to prevent adulteration; and
l. Any product received from a supplier for packaging or labeling as a dietary supplement (and for distribution rather than for return to the supplier) for which sufficient assurance is not provided to adequately identify the product and to determine that the product is consistent with your purchase order.

7. Required QC operations for packaging and labeling operations

Quality control operations for packaging and labeling operations must include:

a. Reviewing the results of any visual examination and documentation to ensure that established specifications are met for all products that you receive for packaging and labeling as a dietary supplement (and for distribution rather than for return to the supplier);
b. Approving, and releasing from quarantine, all products that you receive for packaging or labeling as a dietary supplement (and for distribution rather than for return to the supplier) before they are used for packaging or labeling;
c. Reviewing and approving all records for packaging and label operations;
d. Determining whether the finished packaged and labeled product conforms to established specifications;
e. Conducting any required material review and making any required disposition decision;
f. Approving or rejecting any repackaging of a packaged product;
g. Approving or rejecting any relabeling of a packaged and labeled product;
h. Approving for release, or rejecting, any packaged and labeled product (including a repackaged or relabeled product) for distribution.

8. Required QC operations for returned products

Quality control operations for returned products must include:

a. Conducting any required material review and making any required disposition decision; including:
    i. Determining whether tests or examination are necessary to determine compliance with established product specifications
    ii. Reviewing the results of any tests or examinations that are conducted to

determine compliance with established product specifications

b. Approving or rejecting any salvage and redistribution of any returned product;
c. Approving or rejecting any reprocessing of any returned product; and
d. Determining whether the reprocessed product meets product specifications and either approving for release, or rejecting, any returned product that is reprocessed.

9. Required QC operations for product complaints

Quality control operations for product complaints must include:

a. Reviewing and approving decisions about whether to investigate a product complaint; and
b. Reviewing and approving the findings and follow-up action of any investigation performed.

10. Specific record keeping requirements and written procedures

You must make and keep the following records:

a. Written procedures detailing the responsibilities of the quality control operations, including:
    i. Written procedures for conducting a material review and making a disposition decision
    ii. Written procedures for approving or rejecting any reprocessing
b. Written documentation, at the time of performance, that QC performed the review, approval, or rejection requirements by recording the following:
    i. Date that the review, approval, or rejection was performed
    ii. Signature of the person performing the review, approval, or rejection
c. Documentation of any material review and disposition decision and follow-up. Such documentation must be included in the appropriate batch production record and must include:
    i. Identification of the specific deviation or the unanticipated occurrence;
    ii. Description of your investigation into the cause of the deviation from the specification or the unanticipated occurrence;
    iii. Evaluation of whether or not the deviation or unanticipated occurrence has resulted in or could lead to a failure to ensure the quality of the product or a failure to package and label the product as specified in the master manufacturing record;
    iv. Identification of the action(s) taken to correct, and prevent a recurrence of, the deviation or the unanticipated occurrence;
    v. Explanation of what you did with the component, product, packaging, or label;
    vi. A scientifically valid reason for any reprocessing of a product that is rejected or any treatment or in-process adjustment of a component that is rejected; and
    vii. The signature of the individual(s) designated to perform the quality control operation, who conducted the material review and made the disposition decision, and of each qualified individual who provides information relevant to that material review and disposition decision.

11. Recommended SOPs

a. Complaint handling
b. Packaging and labeling approval procedures and version control
c. Returned product disposition

Reference: 21 CFR Part 111, Subpart F

VIII. Production and Process Control System: Requirements for Components, Packaging, and Labels and for Product That You Receive for Packaging or Labeling as a Dietary Supplement

1. **Requirements for components of dietary supplements and packaging and labeling received**
    a. You must visually examine each immediate container or grouping of immediate containers in a shipment that you receive for appropriate content label, container damage, or broken seals to determine whether the container condition may have resulted in contamination or deterioration of the components;
    b. You must visually examine the supplier's invoice, guarantee, or certification in a shipment you receive to ensure the components are consistent with your purchase order;
    c. You must quarantine components before you use them in the manufacture of a dietary supplement until:
        i. You collect representative samples of each unique lot of components (and, for components that you receive, of each unique shipment, and of each unique lot within each unique shipment)
        ii. Quality control personnel review and approve the results of any tests or examinations conducted on components
        iii. Quality control personnel approve the components for use in the manufacture of a dietary supplement, including approval of any treatment of components to make them suitable for use, and releases them from quarantine
    d. You must identify each unique lot within each unique shipment of components that you receive and any lot of components that you produce in a manner that allows you to trace the lot to the supplier, the date received, the name of the component, the status of the component (e.g., quarantined, approved, or rejected); and to the product that you manufactured and distributed.
        i. You must use this unique identifier whenever you record the disposition of each unique lot within each unique shipment of components that you receive and any lot of components that you produce
    e. You must hold components under conditions that will protect against contamination and deterioration, and avoid mix-ups.

2. **Requirements for a product received for packaging or labeling as a dietary supplement (and for distribution rather than for return to the supplier)**
    a. You must visually examine each immediate container or grouping of immediate containers in a shipment of product that you receive for packaging or labeling as a dietary supplement (and for distribution rather than for return to the supplier) for appropriate content label, container damage, or broken seals to determine whether the container condition may have resulted in contamination or deterioration of the received product.
    b. You must visually examine the supplier's invoice, guarantee, or certification in a shipment of the received product to ensure that the received product is consistent with your purchase order.
    c. You must quarantine the received product until:

i. You collect representative samples of each unique shipment, and of each unique lot within each unique shipment, of received product
ii. Quality control personnel review and approve the documentation to determine whether the received product meets the specifications that you established under §111.70(f)
iii. Quality control personnel approve the received product for packaging or labeling as a dietary supplement and release the received product from quarantine

d. You must identify each unique lot within each unique shipment of received product in a manner that allows you to trace the lot to the supplier, the date received, the name of the received product, the status of the received product (e.g., quarantined, approved, or rejected), and to the product that you packaged or labeled and distributed as a dietary supplement.
e. You must use this unique identifier whenever you record the disposition of each unique lot within each unique shipment of the received product.
f. You must hold the received product under conditions that will protect against contamination and deterioration, and avoid mix-ups.

3. Requirements for rejected components, packaging, and labels, and rejected products that are received for packaging or labeling as a dietary supplement

You must clearly identify, hold, and control under a quarantine system for appropriate disposition any component, packaging, and label, and any product that you receive for packaging or labeling as a dietary supplement (and for distribution rather than for return to the supplier), that is rejected and unsuitable for use in manufacturing, packaging, or labeling operations.

4. Specific record keeping requirements and written procedures

a. You must make and keep the following records:
   i. Written procedures for fulfilling these receiving requirements
   ii. Receiving records (including records such as certificates of analysis, suppliers' invoices, and suppliers' guarantees) for components, packaging, and labels and for products that you receive for packaging or labeling as a dietary supplement
b. The person who performs the required operation must document, at the time of performance, that the required operation was performed, including:
   i. The date that the components, packaging, labels, or products that you receive for packaging or labeling as a dietary supplement were received
   ii. The initials of the person performing the required operation
   iii. The results of any tests or examinations conducted on components, packaging, or labels, and of any visual examination of product that you receive for packaging or labeling as a dietary supplement
   iv. Any material review and disposition decision conducted on components, packaging, labels, or products that you receive for packaging or labeling as a dietary supplement

Reference: 21 CFR Part 111, Subpart G

IX. Production and Process Control System: Requirements for the Master Manufacturing Record

1. **Requirement to establish a master manufacturing record**
    a. You must prepare and follow a written master manufacturing record for each unique formulation of product that you manufacture, and for each batch size, to ensure uniformity in the finished batch from batch to batch.
    b. The master manufacturing record must:
        i. Identify specifications for the points, steps, or stages in the manufacturing process where control is necessary to ensure the quality of the product and that the product is packaged and labeled as specified in the master manufacturing record
        ii. Establish controls and procedures to ensure that each batch of product that you manufacture meets these specifications

2. **Required contents of the master manufacturing record**

The master manufacturing record must include:

    a. The name of the product to be manufactured and the strength, concentration, weight, or measure of each dietary ingredient for each batch size;
    b. A complete list of components to be used;
    c. An accurate statement of the weight or measure of each component to be used;
    d. The identity and weight or measure of each dietary ingredient that will be declared on the Supplement Facts label and the identity of each ingredient that will be declared on the ingredients list of the product;
    e. A statement of any intentional overage amount of a dietary ingredient;
    f. A statement of theoretical yield of a manufactured product expected at each point, step, or stage of the manufacturing process where control is needed to ensure the quality of the product, and the expected yield when you finish manufacturing the product, including the maximum and minimum percentages of theoretical yield beyond which a deviation investigation of a batch is necessary and material review is conducted and disposition decision is made;
    g. A description of packaging and a representative label, or a cross-reference to the physical location of the actual or representative label;
    h. Written instructions, including the following:
        i. Specifications for each point, step, or stage in the manufacturing process where control is necessary to ensure the quality of the product and that the product is packaged and labeled as specified in the master manufacturing record
        ii. Procedures for sampling and a cross-reference to procedures for tests or examinations
    i. Specific actions necessary to perform and verify points, steps, or stages in the manufacturing process where control is necessary to ensure the quality of the product and that the product is packaged and labeled as specified in the master manufacturing record, including:
        i. Such specific actions must include verifying the weight or measure of any component and verifying the addition of any component
        ii. For manual operations, such specific actions must include:
            (1) One person weighing or measuring a component and another person verifying the weight or measure
            (2) One person adding the component and another person verifying the addition
        iii. Special notations and precautions to be followed

iv. Corrective action plans for use when a specification is not met

Reference: 21 CFR Part 111, Subpart H

X. Production and Process Control System: Requirements for the Batch Production Record

1. Requirement to establish a batch production record

a. You must prepare a batch production record every time you manufacture a batch of a product;
b. Your batch production record must include complete information relating to the production and control of each batch; and
c. Your batch production record must accurately follow the appropriate master manufacturing record and you must perform each step in the production of the batch.

2. Required contents of the batch record

The batch production record must include the following:

a. The batch, lot, or control number of the finished batch of product that you assign in accordance with 21 CFR. §111.415(f) for the following:
    i. Each lot of packaged and labeled product from the finished batch of product
    ii. Each lot of product, from the finished batch of product, that you distribute to another person for packaging or labeling
b. The identity of equipment and processing lines used in producing the batch;
c. The date and time of the maintenance, cleaning, and sanitizing of the equipment and processing lines used in producing the batch, or a cross-reference to records, such as individual equipment logs, where this information is retained;
d. The unique identifier that you assigned to each component (or, when applicable, to a product that you receive from a supplier for packaging or labeling as a dietary supplement), packaging, and label used;
e. The identity and weight or measure of each component used;
f. A statement of the actual yield and a statement of the percentage of theoretical yield at appropriate phases of processing;
g. The actual results obtained during any monitoring operation;
h. The results of any testing or examination performed during the batch production, or a cross-reference to such results;
i. Documentation that the finished product meets established specifications;
j. Documentation, at the time of performance, of the manufacture of the batch, including:
    i. The date on which each step of the master manufacturing record was performed
    ii. The initials of the persons performing each step, including:
        (1) The initials of the person responsible for weighing or measuring each component used in the batch
        (2) The initials of the person responsible for verifying the weight or measure of each component used in the batch
        (3) The initials of the person responsible for adding the component to the batch
        (4) The initials of the person responsible for verifying the addition of

components to the batch

m. Documentation, at the time of performance, of packaging and labeling operations, including:
    i. The unique identifier that you assigned to packaging and labels used, the quantity of the packaging and labels used, and, when label reconciliation is required, reconciliation of any discrepancies between issuance and use of labels
    ii. An actual or representative label, or a cross-reference to the physical location of the actual or representative label specified in the master manufacturing record
    iii. The results of any tests or examinations conducted on packaged and labeled dietary supplements (including repackaged or relabeled dietary supplements), or a cross-reference to the physical location of such results
n. Documentation at the time of performance that quality control personnel:
    i. Reviewed the batch production record, including:
        (1) Review of any monitoring operation
        (2) Review of the results of any tests and examinations, including tests and examinations conducted on components, in-process materials, finished batches of products, and packaged and labeled products
        (3) Approved or rejected any reprocessing or repackaging
        (4) Approved and released, or rejected, the batch for distribution, including any reprocessed batch
        (5) Approved and released, or rejected, the packaged and labeled product, including any repackaged or relabeled product
o. Documentation at the time of performance of any required material review and disposition decision; and
p. Documentation at the time of performance of any reprocessing.

Reference: 21 CFR Part 111, Subpart I

XI. Production and Process Control System: Requirements for Laboratory Operations

You must develop written procedures for laboratory operations, including written procedures for the tests and examinations that you conduct to determine whether specifications are met. If you use a third party to conduct laboratory operations, you should have written procedures for qualifying the lab, and records of all testing methodologies and results.

1. Requirements for the laboratory facilities that you use

You must use adequate laboratory facilities to perform whatever testing and examinations are necessary to determine whether:

a. Components that you use meet specifications;
b. In-process specifications are met as specified in the master manufacturing record; and
c. Finished products that you manufacture meet specifications.

2. Requirements for laboratory control processes

You must establish and follow laboratory control processes that are reviewed and approved by quality control personnel, including the following:

a. Use of criteria for establishing appropriate specifications;
b. Use of sampling plans for obtaining representative samples of:

i. Components, packaging, and labels
ii. In-process materials
iii. Finished batches of products
iv. Product that you receive for packaging or labeling as a dietary supplement (and for distribution rather than for return to the supplier)
v. Packaged and labeled products

c. Use of criteria for selecting appropriate examination and testing methods;
d. Use of criteria for selecting standard reference materials used in performing tests and examinations; and
e. Quality control personnel must review and approve lab control processes.

3. Requirements for laboratory methods for testing and examination

a. You must verify that the laboratory examination and testing methodologies are appropriate for their intended use.
b. You must identify and use an appropriate scientifically valid method for each established specification for which testing or examination is required to determine whether the specification is met.

4. Specific record keeping requirements and written procedures

You must make and keep the following records:

a. Written procedures for laboratory operations, including written procedures for the tests and examinations that you conduct to determine whether specifications are met.
b. Documentation that established laboratory methodology is followed.
c. The person who conducts the testing and examination must document, at the time of performance, that the established laboratory methodology is followed.
d. The documentation for laboratory tests and examinations must include the results of the testing and examination.

Reference: 21 CFR Part 111, Subpart J

XII. Production and Process Control System: Requirements for Manufacturing Operations

1. Design requirements for manufacturing operations

You must design or select manufacturing processes to ensure that product specifications are consistently met.

2. Requirements for sanitation

You must conduct all manufacturing operations in accordance with adequate sanitation principles.

3. Precautions you must take to prevent contamination

You must take all the necessary precautions during the manufacture of a product to prevent contamination of components or products. These precautions include:

a. Performing manufacturing operations under conditions and controls that protect against the potential for growth of microorganisms and the potential for contamination;
b. Washing or cleaning components that contain soil or other contaminants;

c. Using water that, at a minimum, complies with the applicable Federal, State, and local requirements and does not contaminate the product when the water may become a component of the finished batch of product;
d. Performing chemical, microbiological, or other testing, as necessary to prevent the use of contaminated components;
e. Sterilizing, pasteurizing, freezing, refrigerating, controlling hydrogen-ion concentration (pH), controlling humidity, controlling water activity (a w), or using any other effective means to remove, destroy, or prevent the growth of microorganisms and prevent decomposition;
f. Holding components and products that can support the rapid growth of microorganisms of public health significance in a manner that prevents the components and products from becoming adulterated;
g. Identifying and holding any components or products, for which a material review and disposition decision is required, in a manner that protects components or products that are not under a material review against contamination and mix-ups with those that are under a material review;
h. Performing mechanical manufacturing steps (such as cutting, sorting, inspecting, shredding, drying, grinding, blending, and sifting) by any effective means to protect the products against contamination, by, for example:
    i. Cleaning and sanitizing contact surfaces
    ii. Using temperature controls
    iii. Using time controls
i. Using effective measures to protect against the inclusion of metal or other foreign material in components or products, by, for example:
    i. Filters or strainers
    ii. Traps
    iii. Magnets
    iv. Electronic metal detectors
j. Segregating and identifying all containers for a specific batch of products to identify their contents and, when necessary, the phase of manufacturing; and
k. Identifying all processing lines and major equipment used during manufacturing to indicate their contents, including the name of the product and the specific batch or lot number and, when necessary, the phase of manufacturing.

4. Rejected products

You must clearly identify, hold, and control under a quarantine system for appropriate disposition any product that is rejected and unsuitable for use in manufacturing, packaging, or labeling operations.

5. Specific record keeping requirements and written procedures

You must make and keep records of the written procedures you develop for manufacturing operations.

6. Recommended SOPs

a. Manufacturing process flow and steps
b. Log of rejected product/component and disposition

Reference: 21 CFR Part 111, Subpart K

XIII. Production and Process Control System: Requirements for Packaging and Labeling Operations

1. Requirements for packaging and labels

a. You must take necessary actions to determine whether packaging for products meets specifications so that the condition of the packaging will ensure the quality of your products;
b. You must control the issuance and use of packaging and labels and reconciliation of any issuance and use discrepancies;
c. You must examine, before packaging and labeling operations, packaging and labels for each batch of product to determine whether the packaging and labels conform to the master manufacturing record; and
d. You must be able to determine the complete manufacturing history and control of the packaged and labeled product through distribution.

2. Requirements for filling, assembling, packaging, labeling, and related operations

You must fill, assemble, package, label, and perform other related operations in a way that ensures the quality of the product and that the product is packaged and labeled as specified in the master manufacturing record. You must do this using any effective means, including the following:

a. Cleaning and sanitizing all filling and packaging equipment, utensils, and product packaging, as appropriate;
b. Protecting manufactured products from contamination, particularly airborne contamination;
c. Using sanitary handling procedures;
d. Establishing physical or spatial separation of packaging and label operations from operations on other components and products to prevent mix-ups;
e. Identifying, by any effective means, filled product containers that are set aside and held in unlabeled condition for future label operations, to prevent mix-ups;
f. Assigning a batch, lot, or control number to:
    i. Each lot of packaged and labeled product from a finished batch of product
    ii. Each lot of product, from a finished batch of product, that you distribute to another person for packaging or labeling
g. Examining a representative sample of each batch of the packaged and labeled product to determine whether the product meets established specifications; and
h. Suitably disposing of labels and packaging for products that are obsolete or incorrect to ensure that they are not used in any future packaging and label operations.

3. Requirements for repackaging and relabeling

a. You may repackage or relabel products only after quality control personnel have approved such repackaging or relabeling.
b. You must examine a representative sample of each batch of repackaged or relabeled products to determine whether the repackaged or relabeled products meet all specifications established in accordance with §111.70(g).
c. Quality control personnel must approve or reject each batch of repackaged or relabeled product prior to its release for distribution.

4. Requirements for packaged and labeled products that are rejected for distribution
You must clearly identify, hold, and control under a quarantine system for appropriate disposition any packaged and labeled product that is rejected for distribution.

5. Specific record keeping requirements and written procedures
You must make and keep records of the written procedures you develop for packaging and labeling operations.

Reference: 21 CFR Part 111, Subpart L

XIV. Holding and Distributing

1. Requirements for holding components, dietary supplements, packaging, and labels
- a. You must hold components and dietary supplements under appropriate conditions of temperature, humidity, and light so that the identity, purity, strength, and composition of the components and products are not affected.
- b. You must hold packaging and labels under appropriate conditions so that the packaging and labels are not adversely affected.
- c. You must hold components, products, packaging, and labels under conditions that do not lead to the mix-up, contamination, or deterioration of components, products, packaging, and labels.

2. Requirements for holding reserve samples of product
- a. You must hold reserve samples of products in a manner that protects against contamination and deterioration. This includes:
  - i. Holding the reserve samples under conditions consistent with product labels or, if no storage conditions are recommended on the label, under ordinary storage conditions
  - ii. Using the same container-closure system in which the packaged and labeled product is distributed, or if distributing products to be packaged and labeled, using a container-closure system that provides essentially the same characteristics to protect against contamination or deterioration as the one in which you distribute the product for packaging and labeling elsewhere
- b. You must retain reserve samples for 1 year past the shelf life date (if shelf life dating is used), or for 2 years from the date of distribution of the last batch of products associated with the reserve samples, for use in appropriate investigations.

3. Requirements for distributing products
You must distribute products under conditions that will protect the products against contamination and deterioration.

4. Specific record keeping requirements and written procedures
- a. You must make and keep the following records:
  - i. Written procedures for holding and distributing operations; and
  - ii. Records of product distribution.

5. Recommended SOPs
- a. Warehousing specifications

Reference: 21 CFR Part 111, Subpart M

XV. Returned Dietary Supplements

1. Requirements applicable to a returned product you receive
You must identify and quarantine returned products until quality control personnel conduct a material review and make a disposition decision.

2. Destruction or disposal of a returned product
You must destroy, or otherwise suitably dispose of, any returned product unless the outcome of a material review and disposition decision is that quality control personnel do the following:

a. Approve the salvage of the returned product for redistribution; or
b. Approve the returned product for reprocessing.

3. Requirements for salvage of a product
You may salvage a returned product only if quality control personnel conduct a material review and make a disposition decision to allow the salvage.

4. Requirements for a returned product that quality control personnel approve for reprocessing

a. You must ensure that any returned products that are reprocessed meet all established product specifications; and
b. Quality control personnel must approve or reject the release for distribution of any returned product that is reprocessed.

5. Required investigation of your manufacturing processes and other batches
If the reason for a product being returned implicates other batches, you must conduct an investigation of your manufacturing processes and each of those other batches to determine compliance with specifications.

6. Specific record keeping requirements and written procedures
You must make and keep the following records:

a. Written procedures for fulfilling these requirements. We recommend these include procedures for clearing quarantined products and returns procedures and log.
b. Any material review and disposition decision on a returned product;
c. The results of any testing or examination conducted to determine compliance with established product specifications; and
d. Documentation of the reevaluation by quality control personnel of any product that is reprocessed and the determination by quality control personnel of whether the reprocessed product meets established product specifications.

Reference: 21 CFR Part 111, Subpart N

XVI. Product Complaints

1. Review and investigation of a product complaint

a. A qualified person must:
    i. Review all product complaints to determine whether the product complaint

involves a possible failure of a product to meet any of its specifications, or any other cGMP requirements, including those specifications and other requirements that, if not met, may result in a risk of illness or injury

ii. Investigate any product complaint that involves a possible failure of a product to meet any of its specifications, or any other requirements of this part, including those specifications and other requirements that, if not met, may result in a risk of illness or injury

b. Quality control personnel must review and approve decisions about whether to investigate a product complaint and review and approve the findings and follow-up action of any investigation performed.

c. The review and investigation of the product complaint by a qualified person, and the review by quality control personnel about whether to investigate a product complaint, and the findings and follow-up action of any investigation performed, must extend to all relevant batches and records.

2. Specific record keeping requirements and written procedures

You must make and keep the following records:

a. Written procedures for complaint handling; and

b. A written record of every product complaint that is related to good manufacturing practice:

i. The person who performs these requirements must document, at the time of performance, that the requirement was performed

ii. The written record of the product complaint must include the following:

(1) The name and description of the product

(2) The batch, lot, or control number of the product, if available

(3) The date the complaint was received and the name, address, or telephone number of the complainant, if available

(4) The nature of the complaint including, if known, how the product was used

(5) The reply to the complainant, if any

(6) Findings of the investigation and follow up action taken when an investigation is performed

Reference: 21 CFR Part 111, Subpart O

Appendix

Sanitation
Best Practices

KTA members have asked for guidance on appropriate methods for sanitizing product as an extra measure against potential contaminants. The following is an analysis of the various methods available.

Note: KTA advises against reliance on any sanitation/sterilization process without testing for confirmation.

Irradiation - Prohibited

Kratom should not be sterilized using ionizing radiation because the FDA may deem any Kratom that is sterilized with radiation to be adulterated.

The FDA regulates radiation as a food additive. To date, the FDA has approved three types of ionizing radiation (gamma ray, e-beam, and x-ray) for the treatment of specific food products.[1] Only 14 types of food may be irradiated under limits imposed by specific regulation, none of which include herbal or botanical supplements.[2]

Any source of ionizing radiation or any recipient food that are not specifically approved by FDA would be deemed "intentionally irradiated" food, i.e., the food would be adulterated in violation of the Federal Food, Drug and Cosmetic Act.[3]

Companies previously have filed Food Additive Petitions asking the FDA to approve irradiation of dietary supplements. However, these requests have been unsuccessful. This may be in part because the American Herbal Products Association has strongly opposed irradiation of supplements and has expressed this to the FDA by filing a letter in opposition of petitions to allow irradiation of supplements.

[1] *See* 21 C.F.R. 179.26.
[2] *See id*. We note that one category of food permitted to be irradiated includes "ingredients in small amounts solely for flavoring or aroma: culinary herbs, seeds, spices, vegetable seasonings that are used to impart flavor but that are not either represented as, or appear to be, a vegetable that is eaten for its own sake." This does not include botanicals used as dietary ingredients.
[3] *See* 21 U.S.C. 341.

Accordingly, you must not use irradiation as a method of sanitizing your ingredients or product.

Ethyl Oxide (EtO) Sterilization - Prohibited

Ethylene oxide fumigation is permitted for raw herbs and spices, but it is unclear whether it is permitted for sterilization of all botanicals. Additionally, the Environmental Protection Agency limits EtO residue in herbs and spices to 7 ppm.[4] Because EtO is listed under California's Proposition 65 as a carcinogen and the World Health Organization has declared EtO to be a carcinogen, KTA does not support its use in sterilization.

Steam Sterilization – Permitted

There are various types of steam sterilization available and it is our understanding that these techniques do not result in the addition of any chemical or radiation to the product, or any change to the composition of the product, meaning it would not be regulated as a food additive.

[4] 40 C.F.R. 180.151.

Sampling and Testing
Best Practices

As noted in Section VI of the KTA cGMP Guidelines, you are required to establish product specifications for the following:

- **Identity**
- **Purity**
- **Strength**
- **Composition**
- **Limits on contaminants**

Before your product can be sold in the U.S., you must ensure that it consistently meets these established specifications.

The FDA cGMPs require you to identify a subset of finished dietary supplement batches through a "sound statistical sampling plan" that should be tested to verify that the above product specifications are met.

1. Sampling

KTA encourages the most inclusive sampling procedure practicable, understanding that factors such as shipment or batch volume and container size may vary widely depending on your operation.

A. For bulk raw Kratom received for repackaging/relabeling/distribution without further processing:

i. Whenever practicable, KTA recommends obtaining a sample from the top, middle and bottom of each container of Kratom

ii. At a minimum, KTA requires that you sample as follows:

No. of Containers in Batch	No. of Containers to Be Sampled
1-20	All
21-50	50%
>51	25%

This sample size is modified from the USP sampling requirements for articles of botanical origin.

KTA requires increased sampling due to the recent high profile salmonella cases and because U.S. entities are not always able to determine the exact origin of the raw product and/or the conditions under which it was handled prior to delivery.

iii. Samples must be taken from the upper, middle, and lower sections of each container.

(1) If the crude material consists of ingredients that are 1 cm or less in any dimension, as is the case of all powdered or ground materials, withdraw the sample by means of a sampling device that removes a core from the top to the bottom of the container, at least two cores being taken from different angles.

(2) For materials with ingredients over 1 cm in any dimension (like whole or crushed leaf), withdraw samples using gloved hands.

(3) For kilos, large bales or packs, samples should be taken from a depth of 10 cm, because the moisture content of the surface layer may be different from that of the inner layers.

(4) Prepare the gross sample by combining and mixing the individual samples taken from each opened container, taking care not to alter or crush the material any further (eg. leaf) or significantly affect the moisture content.

(5) For articles in containers holding between 1 and 5 kg, withdraw equal portions from the upper, middle, and lower parts of the container, each of the samples being sufficient to carry out the necessary tests. Thoroughly mix the samples, and withdraw an amount sufficient enough to carry out the required tests.

(6) For containers holding more than 5 kg, withdraw three samples, each weighing at least 250 g, from the upper, middle, and lower parts of the container. Thoroughly mix the samples, and withdraw a portion sufficient to carry out the tests.

B. For bulk raw Kratom that will be further processed or manufactured by you prior to distribution:

i. You must conduct a test or examination to verify that the substance received is actually Kratom.

ii. You may not accept a supplier Certificate of Analysis (“COA”) in lieu of identity testing/examination. (COAs are permitted for other ingredients that may be added to the Kratom, such as fillers.)

iii. Once the finished product is complete, it must be sampled for testing as described in Section A above.

2. Testing

KTA requires that all finished products be tested for *at a minimum*:

A. Elemental contaminants

Element	Permitted Daily Exposure (µg /day)
Arsenic	15
Cadmium	5
Lead	10
Mercury	15
Methylmercury (as Hg)	2

Reference: USP <2232> Elemental Contaminants in Dietary Supplements

B. Microbiology and Mycotoxins

Specification	Limit for dried, unprocessed herbs[1]	Limits for Powdered extracts and soft extracts[2]
Total aerobic plate count	10^7 colony forming units/gram	10^4 colony forming units/gram
Total yeasts and molds	10^5 colony forming units/gram	10^3 colony forming units/gram
Total coliforms	10^4 colony forming units/gram	10^2 colony forming units/gram
Salmonella spp	Not detected in 25 grams	Not detected in 25 grams
Escherichia Coli	Not detected in 10 grams	Not detected in 10 grams
Total aflatoxins (B1 + B2 + G1 + G2)	20 µg/kg (ppb)	20 µg/kg (ppb)
Aflatoxin B 1	5 µg/kg (ppb)	5 µg/kg (ppb)

Reference: AHPA Guidance on Microbiology and Mycotoxins.

[1] Or solid form herbal supplements consisting of dried, unprocessed herbs.
[2] Or solid form herbal supplements consisting of Powdered extracts and soft extracts

New Dietary Ingredient (NDI) Notification **Checklist**

If you manufacture or distribute Kratom as a dietary supplement, you must notify FDA at least 75 days before marketing the dietary supplement in the U.S.

The NDI must include:

- ☐ The name and complete address of the manufacturer or distributor.
- ☐ The name of the new dietary ingredient (Kratom) that is the subject of the premarket notification, including Latin binomial name.
- ☐ A description of the dietary supplement that contains the new dietary ingredient, including:
  a. The level of the dietary ingredient in the dietary supplement;
  b. The conditions of use recommended or suggested in the labeling, or if no conditions of use are recommended or suggested, the ordinary conditions of use of the dietary supplement.
- ☐ The history of use or evidence of safety establishing that the dietary ingredient, when used under the conditions recommended or suggested on the labeling of the dietary supplement, will reasonably be expected to be safe.
- ☐ The signature of the person designated by the manufacturer or distributor.

FDA recommends the NDI information be presented in the following format:

- ☐ Cover Letter
- ☐ Table of Contents
- ☐ Body of the Notification
  a. Administrative Information
    i. Description of the NDI
    ii. Information believed to be trade secret or confidential commercial information
    iii. Safety narrative
  b. Attachments Used to Establish Identity
    i. Detailed description of the identity of the NDI and the dietary supplement
    ii. Manufacturing methods and practices to establish identity and safety
    iii. Specifications to identify dietary ingredients
    iv. Identity references

c. Safety and Toxicology Attachments
    i. Comprehensive safety profile for the NDI
    ii. Toxicology studies
    iii. Human studies
    iv. History of use
    v. Other evidence of safety
d. Complete List of References

The NDI may be submitted electronically at https://www.access.fda.gov or by mail to the Consumer Safety Officer, Office of Dietary Supplement Programs (HFS-810), Center for Food Safety and Applied Nutrition, Food and Drug Administration, 5001 Campus Drive, College Park, MD 20740.

90 days after the filing date of the NDI, all information in the notification will be placed on public display, except any information that is trade secret or confidential commercial information.

Within 75 days after the FDA files your notification, they will respond through:

- A letter of acknowledgment without objection;
- A letter listing deficiencies that make the notification incomplete;
- An objection letter raising safety concerns based on the information in the notification or identifying gaps in the history of use or other evidence of safety;
- A letter raising other regulatory issues with the NDI or dietary supplement.

References:

21 CFR Part 190, Subpart B
FDA Draft Guidance: New Dietary Ingredient Notifications and Related Issues