Voluntary Guideline for the Dietary Supplement Industry
No.2

Certificate of Analysis for Dietary Supplement Components: A Voluntary Guideline

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Prepared by:

SIDI Work Group
www.sidiworkgroup.com

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ACKNOWLEDGEMENTS

The Certificate of Analysis Dietary Supplement Component Voluntary Guideline is based on the IPEC Certificate of Analysis Guide[1] and was developed by representatives of many of the member companies of the SIDI Work Group, an industry coalition consisting of representatives and members of the five trade associations that represent the dietary supplement industry (see **Appendix 2**). The individuals who contributed to this Guideline are listed below.

Amy Caplette, Nutrilite/Amway
Mike Chansilp, NBTY
Elinor Hitchner, Bayer
Reddy Kal, Aaron Industries
Jay Lee, Beijing Gingko Group
Anthony Palmieri, DSM Nutritional Products
Devon Powell, AHPA
Patricia Rohr, Albion
Scott Rosenbush, PL Thomas
Andrew Shao, CRN
Al Shoemaker, NBTY
Stephanie Sigler, Indiana Botanic Gardens
Alexa Smith, Colorcon
Zhigang Tian, Perrigo Company

FDA observers:
Carl Reynolds, CFSAN, FDA
Brad Williams, CFSAN, FDA

[1] The IPEC-Americas® Certificate of Analysis Guide for Bulk Excipients www.ipecamericas.org

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1. INTRODUCTION

1.1 Purpose

This document serves as a guideline for the preparation by suppliers and appropriate use by their customers of a Certificate of Analysis (COA) for Dietary Supplement Components (components). The goal is to standardize the content and format of COAs for dietary supplement components, and to clearly define the roles and responsibilities for component suppliers, distributors, dietary supplement manufacturers and other users who need to meet the dietary supplement current Good Manufacturing Practice (cGMP) requirements of the US FDA, that is, 21 CFR Part 111[2]. The detailed definitions and thorough explanations are intended to establish uniform considerations regarding COAs for component suppliers and dietary supplement manufacturers. It is hoped that, with use of this guideline as a foundation for mutual understanding, greater assurance of regulatory compliance will be achieved for components used in the manufacture of dietary supplement products.

1.2 Use of a Certificate of Analysis in Dietary Supplement Manufacturing Operations

Through long-established industry practice, a component supplier provides to its customers a COA with each delivered lot. COAs prepared in accordance with this guideline document will contain information on numerous aspects of the component's qualities, as detailed in Section 3.

For a dietary supplement manufacturer, certain aspects of the qualities described in a COA that accompanies a component may be "specifications," as that term is used in 21 CFR §§ 111.70, 111.73, and 111.75. This regulation allows the option for a dietary supplement manufacturer to rely on a COA from a component supplier to confirm the identity of any component that is not a dietary ingredient (the manufacturer must conduct at least one appropriate test or examination on each batch of dietary ingredient to verify the identity of the dietary ingredient) and to determine whether other specifications that the manufacturer has established for purity, strength, composition and contaminants of any component – including a dietary ingredient – are met.

If a dietary supplement manufacturer chooses to use the option of having a COA from a component supplier serve any such specification-determining role (other than identity for dietary ingredients), the manufacturer must meet several specified requirements, stated in § 111.75 (a)(2)(ii):

> "(A) You first qualify the supplier by establishing the reliability of the supplier's certificate of analysis through confirmation of the results of the supplier's tests or examinations;

[2] Code of Federal Regulations, Title 21, Part 111: Current Good Manufacturing Practice in Manufacturing, Packaging, Labeling, or Holding Operations for Dietary Supplements.

(B) The certificate of analysis includes a description of the test or examination method(s) used, limits of the test or examinations, and actual results of the tests or examinations
(C) You maintain documentation of how you qualified the supplier;
(D) You periodically re-confirm the supplier's certificate of analysis; and
(E) Your quality control personnel review and approve the documentation setting forth the basis for qualification (and requalification) of any supplier."

Some manufacturers of dietary supplements choose not to rely on the COAs that accompany components to determine whether specifications are met, and instead conduct their own appropriate tests or examinations to evaluate compliance with all specifications. In such cases there is no regulatory requirement to comply with any of the elements of § 111.75 (a)(2)(ii) described above, though some manufacturers may choose to follow some of these same practices.[3]

1.3 Scope

This guideline is applicable to all dietary supplement components (defined as both dietary ingredients and other ingredients) used in the manufacture of a dietary supplement product.

1.4 Principles Adopted

This guideline focuses on compliance with US regulations, but has international application, acknowledging that components used in the manufacture of dietary supplements are diverse and are sourced globally. However, it neither specifies all national legal and/or regulatory requirements nor covers in detail the particular characteristics of every component.

When considering how to use this guide, each component supplier, distributor or user should consider how it may apply to specific products and processes. The diversity of components means that some principles of the guideline may not be applicable to certain products and processes. The terminologies "should" and "it is recommended" do not mean "must" and emphasis on the intended use of the component is advised in the interpretation and application of this guideline.

1.5 Layout

The guideline is divided into several sections. The first part provides background discussion necessary for understanding the design and recommended elements of a COA. In addition to the template provided in this guideline, example formatted templates are

[3] According to 21 CFR Part 111 §111.75 (a)(2)(ii)(A) dietary supplement manufacturers must qualify component suppliers before relying on the component COA. If the manufacturer chooses not to rely on the COA for a given component and instead chooses to perform full testing to confirm that all established specifications have been met for said component, this fulfills the requirement of 21 CFR Part 111 §111.75 (a)(2)(ii)(A), and minimizes the supplier qualification burden. However, full testing alone of a component for established specifications may not be adequate to assure the identity, purity, strength and composition of the dietary supplement in which the component will be included. Therefore, it is recommended that users consider qualifying component suppliers using a risk-based approach irrespective of the decision to rely on the component COA.

provided separately to illustrate suggested placement of information in the COA. Detailed discussion follows to ensure an understanding of the purpose and meaning of the specific information contained in the COA. This is followed by references and a glossary of terms used in this document. Where it first appears in the guide, a term is hyperlinked to its definition in the glossary which appears at the end of the document.

2. GENERAL GUIDANCE

2.1 Dietary Supplement Component Manufacture

A component is often used with a variety of other components (dietary ingredients and other ingredients) and in a diverse range of finished dosage forms. The component is often a natural substance, mixture, or extract whose chemical and physical properties are difficult to quantify. Each component must have specifications for identity, purity, strength, composition and appropriate limits for pertinent contaminants[4].

2.2 Preparation and Appropriate Use of a Certificate of Analysis

The COA for a component should be prepared and issued by the supplier of the component, following the general guidelines discussed below. It is critical that a complete and accurate COA is provided to the user for each specific lot or batch of a component intended for use in dietary supplements. (See Section 9 for additional considerations that must be made for the preparation and issuance of a COA by a distributor of components).

2.3 Use of Contract Facilities

Contract facilities are frequently used in the manufacture, testing and distribution of dietary supplement components. When such facilities are used, the supplier of the component should ensure that the facilities operate under appropriate quality standards (i.e., cGMP, etc.).

3. DESIGN AND ELEMENTS OF A CERTIFICATE OF ANALYSIS

Currently, there are few standardized requirements for the content or format of COAs for components. The recommendations contained in this guideline are in conformance with the Dietary Supplement cGMPs[5].

The recommended elements of a COA listed below are included in the following "Certificate of Analysis Template" Section of the guideline. The component supplier may organize the recommended elements on the COA at their discretion; however, the

[4] 21 CFR Part 111 §111.70
[5] 21 CFR, Part 111, Subpart E § 111.75(a)(2)(ii)(B)

following “Template" sections are designed to present the recommended and optional information in a logical manner.

The following information is typically included in a *Header Section*:

- The name and address of the supplier and contact information for the supplier
- The name and address of the manufacturer and manufacturing site of the component if different from the supplier and supplier location. Although the component manufacturer should be made known to the user, the use of confidentiality/non-disclosure agreements to protect that information may be considered.

The following information is typically included in a *General Information Section*:

- The trade name, grade of the material (if any) and applicable compendial designations (if any).
- A lot/batch number, code or other means of uniquely identifying the material quantity covered by the COA.
- The date of manufacture.
- The date of testing.
- If applicable, the expiration date, recommended re-evaluation date, or other relevant statement regarding the stability of the component. (A detailed discussion of dates on the COA is contained in Section 6).
- Additional customer required information.

The actual test results applicable to the material quantity covered by the COA are included in an *Analysis Section*. The test name, the result, the acceptance criteria or specifications, and a reference to the test method used should be included for each characteristic listed. If the test method is non-compendial, not an AOAC Official Method of Analysis or is a modified version of these, or is in-house, the principle of the method should be stated (e.g., HPLC, TLC, etc.). Actual data and observations should be recorded[6] rather than non-specific “passes” or “conforms” statements. Results derived from a Skip-Lot or Reduced Frequency Testing Program, average or in-process test should be noted on the COA. (See Section 7 for a detailed discussion of considerations).

An *Other Information Section* can be used to list various types of statements that may be required depending on the component and specific user requirements or specifications. These statements are usually negotiated between supplier and user based on specific application requirements. (Examples of statements sometimes used are included in Section 4). Any declaration of supplier compliance to additional compendial and/or other regulatory requirements may be typically included in this section.

[6] 21 CFR, Part 111, Subpart E § 111.75(a)(2)(ii)(B)

Many components have applications other than dietary supplements, such as foods, cosmetics, or industrial products. Any product listed as being in compliance with a specific regulation must meet the specifications and requirements of that regulation and should be manufactured under appropriate good manufacturing practices.

The identity of the individual that approves the content of the COA should appear on the COA. (See Section 8 for a discussion of electronic signature considerations). The page number and total number of pages should also appear on the COA. This information is usually included in a *Footer Section*.

4. CERTIFICATE OF ANALYSIS TEMPLATE

Below is a template for the content and format of a COA.

4.1 Header

- Titled "Certificate of Analysis"
- Company Name, Address, Phone Number, and Identity of Manufacturer and Manufacturing Site

4.2 General Information

- Name (compendial/trade) of Component
- Grade of Component (if applicable)
- Compendial Designation (if applicable)
- Latin Name (if applicable)
- Lot/Batch Number
- Date of Manufacture
- Product Code or Number
- Expiration Date (if applicable)
- Recommended Re-Evaluation Date (if applicable)
- Stability Statement (if applicable)
- Customer Required Information

4.3 Analysis

4.3.1 – Basic parameters

All tests should be accompanied with the following information:

- Test Name
- Test Results
- Acceptance Criteria (i.e., Specifications)
- Reference to the Test Method (including principle of the method, e.g., HPLC, TLC, etc…)

- Reference to Skip-lot Testing (if appropriate[7])
- Reference to Average or In-process Test Results (if appropriate)
- Date Retested (if appropriate)

4.3.2 – Product Characteristics (if applicable, e.g., botanicals)
- Plant Part used
- Carrier used
- Plant:Extract ratio

4.3.3 – Physical Tests
- Appearance
- Color
- Texture (if appropriate)
- Aroma (if appropriate)
- Taste (if appropriate)
- Particle Size (if applicable)
- Total Solids (if applicable)
- Refractive Index (if applicable)
- Viscosity (if applicable)
- Plant Part used (botanicals)
- Solubility (state solvent)
- Carrier used (if applicable)
- Density loose/tapped

4.3.4 – Chemical Tests
- Marker Compound
- Additional Marker Compounds (as appropriate)
- Moisture
- Ash
- Total Heavy Metals (if appropriate)
  - Arsenic
  - Lead
  - Mercury
  - Cadmium
- OVI/Residual Solvents (if applicable)
- Pesticides (if applicable, e.g., botanicals)

4.3.5 – Microbiological Tests (if applicable)
- Total Plate Count
- Yeast & Mold
- Salmonella
- E. coli
- Total Count Enterobacteriacea

[7] *Schedule for reduced frequency testing should be specified; documentation justifying reduced testing should be maintained*

4.4 Other information (if applicable)

- Type of Extract/Solvent System
- Country of Origin for the botanical if different from the manufacturing location
- Certification and Compliance Statements or a statement regarding sterilization (irradiation/ETO) treatment (if appropriate)
- Aflatoxins
- Allergens
- Melamine Testing
- Storage Recommendations

4.5 Footer

- Identity of authorized individual responsible for approval
- Date of Approval
- Page Number (i.e., 1 of 10)

5. ADHERENCE TO SPECIFICATIONS

5.1 General Information

The component should be manufactured according to recognized principles of good manufacturing practices. Component suppliers should establish relevant specifications for their products. These can be established by the supplier alone and/or in conjunction with the user, and the COA should demonstrate adherence to those specifications.

The component user should evaluate the supplier's specifications and methods to ensure that they are appropriate and acceptable for the quality control needed for the manufacturing process of its dietary supplement product. The user should determine which of the supplier's specifications and methods are required for release of the component for use in its process. If additional tests or alternate methods are required by the user, appropriate specifications and methods, along with responsibility for performing the testing, should be agreed upon by the component supplier and user.

5.2 Compendial Designation

For a supplier to claim a compendial grade on the COA for a component, there are two requirements that must be met. The first requirement is that the component is manufactured according to the principles of good manufacturing practices specified by the applicable compendium. Adequate conformance to GMPs must also be demonstrated for subsequent steps in the distribution of the component. The second requirement is that the component meets all of the specifications contained in the identified compendial monograph. When a component is listed as compendial grade,

it is understood that the above requirements have been met for the component, and the user would be able to confirm this through an appropriate audit of the supplier.

Many dietary supplement components are listed in the United States Pharmacopeia USP), Food Chemicals Codex (FCC), European Pharmacopoeia (EP), Japanese Pharmacopoeia (JP), Joint FAO/WHO Expert Committee on Food Additives (JECFA), or other standard reference, and the product specifications can be set by the supplier to include all parameters listed in the monograph, including the use of analytical methods.

Compendial standards can be relied on to define what is an acceptable component. If relied on, these standards apply at any time in the life of the component from production to consumption. If adherence to compendial standards is claimed, the supplier's release specifications and compliance with good manufacturing practices are developed and followed to assure that the component, when stored correctly, will comply with compendial standards until it reaches the expiration or recommended re-evaluation date.

If adherence to a compendial monograph is claimed, the component must meet all the requirements in the monograph defining it, as well as any provision of the General Notices, General Chapters or Rules, as applicable.

6. DATES ON A CERTIFICATE OF ANALYSIS

6.1 General Guidance

Part of the overall goal to standardize COAs for dietary supplement components is a provision for the consistent reporting of appropriate, meaningful, and well-defined dates. The discussion below centers on specific dates that are expected on the COA, along with definitions of the dates, in order to provide suppliers and users of components with a mutual understanding of their meaning. Common use of the recommended terminology will be helpful in reducing questions and confusion regarding date information reported for components. Use of terminologies other than those discussed below is discouraged, as the terms may be ill-defined and have different meanings for the component supplier and user. Examples of ambiguous terms that should be avoided include Shelf Life, Use-By Date, Warranty Date, and Expiration Period.

In reporting dates on COAs for components, it is important that a clear and unambiguous format be used, to prevent possible misinterpretation. To accomplish this, it is recommended that an alpha designation be used for the month (may be abbreviated), rather than a numerical representation. It is also recommended that the year include all 4-digits (i.e., Jan. 1, 2010 or 1 Jan. 2010, etc.).

6.2 Date of Manufacture

The Date of Manufacture should be included on the COA for each component lot and should be assigned by the supplier based on its established policies and procedures. It is recognized that components may be manufactured using a variety of processes (e.g., continuous or batch) which may require a period of several days or more to complete. In addition, some components may be extracts, mixtures or blends of other components, and production may include reprocessing steps. Because of this diversity, the Date of Manufacture should be clearly defined by the supplier and consistently applied for the particular component and process. In reporting the Date of Manufacture, the component supplier should indicate the date of completion of the final manufacturing process (as defined by the supplier).

It is important to note that re-packaging alone is not considered a processing step to be used in determining the Date of Manufacture. To provide traceability for a specific component lot, other dates may be required, in addition to the Date of Manufacture, to reflect additional steps, such as re-packaging.

6.3 Expiration Date and Recommended Re-Evaluation Date

The stability of components may be an important factor in the stability of the finished dietary supplements that contain them. Many components are very stable and may not require extensive testing to demonstrate continued conformance to appropriate specifications. Other components may undergo chemical, physical, and/or microbiological changes over time that may cause the material to fall outside established specifications.

Appropriate Expiration and/or Recommended Re-Evaluation Dates for components should be established from the results of a documented stability-testing program, or from historical data (e.g., appropriate evaluation of retained samples). The testing program should include defined and controlled storage conditions (e.g., temperature and humidity), a consideration of different packaging types that may be used as market containers, and meaningful, specific test methods to adequately assess the stability characteristics of the component. Stability testing should determine whether possible changes, such as degradation, moisture gain or loss, viscosity changes, or other possible changes, occur that may render the component unacceptable for use (e.g., unstable or hygroscopic materials).

The Expiration Date for a component is defined as the date after which the supplier recommends that the material should not be used. Prior to the assigned Expiration Date, the component is expected to remain within established specifications, if stored according to the supplier's recommended conditions. A component user may extend the expiration date of a component based on its own studies, taking into account the component's specific intended use.

The Recommended Re-Evaluation Date for a component is the date suggested by the supplier when the material should be re-evaluated to ensure continued compliance with specifications. Re-evaluation of the component may include physical inspection and/or appropriate chemical, physical, organoleptic and microbiological testing. Prior to the Re-Evaluation Date, the component is expected to remain within established specifications, provided it has been stored according to the supplier's recommended conditions. Beyond the Recommended Re-Evaluation Date, the component should not be used without adequate evaluation, at appropriate intervals, to determine whether the component continues to be acceptable for use. The Recommended Re-Evaluation Date differs from the Expiration Date in that the component supplier may re-evaluate the component to extend the length of time it may be used, if supported by the results of the evaluation and appropriate stability data.

In reporting Expiration and Recommended Re-Evaluation Dates, the component supplier is providing important information to the user about the stability of the component. It is acceptable to report both an Expiration Date and a Recommended Re-Evaluation Date on the COA for a component if applicable, but both dates may not always be necessary. Expiration and Recommended Re-Evaluation Dates should not be reported by a supplier without sufficient stability data or product history to support the assigned dates.

For components determined to be very stable (greater than two years), either the specific Expiration and/or Recommended Re-Evaluation Dates should be reported on the COA for the component, or a general stability statement may be included (e.g., stability greater than two years). If available data indicate that a component has limited stability (two years or less) under anticipated storage conditions, then specific Expiration and/or Recommended Re-Evaluation Dates should be reported on the COA for the component.

If long-term stability data is not available for a component, then an appropriate Stability Statement should be included on the COA to indicate what is known about the stability of the component, and/or whether stability studies are in progress.

6.4 Date Retested

If retesting is performed by a component supplier and the results are used to extend the length of time that the component may be used, then the Date Retested should also be reported on the COA. The specific tests that were subject to retesting should be clearly identified and the results obtained upon retesting should be reported. After retesting, a new Recommended Re-Evaluation Date may be reported on the COA as appropriate.

6.5 Additional Dates

Other dates may appear on a COA, if desired by the component supplier or requested by the user. Examples include the release date, shipping date, date of testing, and

date the COA was printed or approved. Any additional dates that appear on a COA for components should include a clear indication of what the date represents or means.

7. COMPONENT TESTING FREQUENCY

7.1 General Guidance

Dietary supplement component specifications are set by the supplier to ensure that the quality of the component is maintained until the Expiration Date or Recommended Re-Evaluation Date, and reflect both the component manufacturing process and inherent properties of the component. The analytical methods used to evaluate the characteristics of components should be scientifically valid and should be demonstrated to provide accurate, reproducible and consistent results for the characteristics being tested.

While analysis of components by suppliers for all specification parameters may not be necessary for each lot of component, sufficient analysis and process verification data should exist for components to assure that a lot meets all specifications before it is released. Periodic testing of all parameters should be performed to re-validate the control system. The frequency of these periodic tests should be determined by the supplier based on its understanding of the component's manufacturing control system. At a minimum, the parameters should be checked once a year.

7.2 Reduced Frequency Testing by the Component Supplier

When analysis by the supplier of some parameters is carried out at a reduced frequency, (e.g., every tenth lot) the supplier should clearly state that information on the COA. Each specific test subject to reduced frequency testing should be indicated, and the frequency with which these tests are done should be disclosed. Any reduced testing should be agreed to by the component supplier and user. It is recommended that a formal process (i.e., report, subject to user approval) be issued to the component user to justify reduced testing of a specific attribute. It should be noted that when reduced-frequency testing is employed by the supplier, the user may not be able to rely on the supplier's certificate of analysis for lots not tested by the supplier. In addition, the user may be required to conduct testing for such lots to confirm that the user's specifications are met for any such parameters not tested by the supplier.

Reduced frequency testing should only be used for components made using a consistent and stable process and with documentation and history of no or low variance of a given parameter(s). There should be a sound technical basis and sufficient documentation to support testing any parameter at a reduced frequency. This would normally include the following points:

- Appropriate verification of the manufacturing process

- Process controls – attribute charting (when appropriate)
- GMP controls
- Historical compliance with specification(s)

As part of the justification for reduced testing, it is important that there be assurances in place showing that the component manufacturer's process complies with applicable component GMPs.

Some tests, due to their significance, should always be tested on each lot, whereas others may be candidates for reduced frequency testing i.e., attribute testing. Attribute testing results in qualitative data which are represented by pass/fail results or less than or greater than a specified value. The result merely establishes compliance with a specification parameter and there are no data to indicate how well the component complies, which would be obtained from variable or quantitative test results.

Reduced frequency testing of an attribute may necessitate the component supplier to demonstrate that the qualitative parameter is in a state of statistical control. This necessitates tabulating the test results for consecutive lots produced.

Skip-Lot testing may be applied to a component that is made by either a batch or continuous process. Various commonly accepted statistical sampling plans may be used to demonstrate appropriate process control. Examples of each are listed below:

Example 1: For an Average Outgoing Quality Level (AOQL) of 1% and a test frequency of 1 in 10, the supplier must find 100 consecutive lots in conformance. At a 2% AOQL and a test frequency of 1 in 10, the supplier would test 50 consecutive lots. For a 1% AOQL and a 1 in 5 test frequency, the supplier must test 70 consecutive lots. Nomographs are available to determine the test requirements.

Example 2: When the component is manufactured by a continuous process, no discrete lot is produced. The sampling plan again is based upon the risk of approving a lot that is nonconforming. By testing 140 consecutive lots before going to a test frequency of 1 in 10, the plan establishes a low risk of approving a lot that is non-compliant.

Once the requirement is met in the examples above, the supplier can monitor conformance to the specification parameter by testing according to the indicated test frequency requirement (e.g., 1 in 10 lots). Should any lot fail the analysis, the supplier must return to 100% testing until the results once again meet the specification as above.

Since components vary greatly in chemical and physical properties, the supplier of the component should determine which tests should be routinely performed and which tests may be appropriate for reduced testing. This determination should be

justified and documented based on the adequacy of the supplier's control system. Documentation should be kept detailing the assumptions and the data supporting the Skip-Lot testing plan.

Only certain types of tests are appropriate for reduced frequency testing. Type A defines those tests that may not be easily controlled through standard process control techniques or may change with time. These tests should normally be performed on each lot. Type B defines those tests that normally can be controlled utilizing standard process control techniques and are not expected to change with time. These tests are candidates for reduced frequency testing. Examples of both types of tests are listed below (not an exhaustive or definitive list):

Type A - Examples of tests that should <u>not be</u> candidates for reduced frequency testing:

- Assay – critical quality parameter (if specified)
- Viscosity – usually indicates grade
- Loss on drying (or moisture determination) – indication of stability and appropriate process controls
- Color - indication of stability and appropriate process controls
- pH - indication of stability and appropriate process controls
- Heavy Metals (Lead, Arsenic, Cadmium, Mercury) (if applicable, e.g., botanicals)
- Microbiological testing (if applicable, e.g. botanicals)
  - TPC, Yeast & Mold, E. coli, Salmonella, Staph, Pseudomonas, Total Coliforms/numerical results/method
- Marker Compound/Assay/numerical result/method (if applicable, e.g., botanicals)

Type B - Examples of tests that may be candidates for reduced frequency testing:

- Identification
- Manufacturing impurities based on starting materials and process.
- Heavy Metals (Lead, Arsenic, Cadmium, Mercury) (non-botanical)
- Microbiological testing (if applicable; non-botanical)
- Residue on Ignition
- Residual Solvents
- Pesticide residues (if applicable)
- Aflatoxins (if applicable)
- Bulk density
- Particle size distribution

This is not meant to be an exhaustive list of tests. It simply provides some direction on how a supplier can assess the importance of each test to the overall control of the

process. Tests listed as possible candidates for reduced frequency testing (Type B) may need to be routinely tested (Type A), depending on the component and process. Determinations can also be made for some Type A tests to become Type B tests. In a dedicated facility, identification testing by the supplier may not be necessary.

7.3 Documentation

The supplier of a dietary supplement component should develop and maintain documentation which outlines the process control systems and verification data which justify the use of reduced frequency testing.

The minimum number of lots to be fully tested for all specification parameters after a change has been made depends on the process and the significance of the change and should be based on sound statistical considerations.

Additionally, the documentation should contain procedures for re-evaluating the reduced frequency testing program when a testing failure occurs. Decisions regarding the continuance of reduced frequency testing should be justified based on the reasons for the failure and the supplier's ability to provide assurances that the reduced frequency testing program or other in-process parameters would identify these types of failures in the future.

7.4 Examples

The following are examples of situations where reduced frequency testing might be justified. These are not the only situations where a sound technical basis can be demonstrated.

- The Process Capability Index (Cp) on the relevant parameter is high and based on a stable process. Statistical analysis of the reduced frequency data should show that the property remains stable and within specifications. A process is considered stable when the output of the process, regardless of the nature of the processing (batch or continuous), can be demonstrated, by appropriate means, to show a level of variability which consistently meets all aspects of the stated specification, (supplier, pharmacopeial or customer-specific) and is thus acceptable for its intended use. For continuous processing, it is also important to demonstrate that the component has been produced under conditions where the process has achieved a form of 'steady state,' i.e., minimal operator intervention and the in-process parameters have been stabilized. (See **Appendix 1** for further definition of this concept and for determining levels of control).

- For a continuous process, the in-process analyses show that the property which is determined at reduced frequency is stable and within specification. Repeating the test on each lot would be redundant.

- An analysis that is determined on every lot has been shown to strongly correlate with an analysis that is run at a reduced frequency. The correlation shows that if a lot is within specification on the first analysis, it will be within specification on the second analysis.

8. USE OF ELECTRONIC SIGNATURES

With the need to accommodate paperless record systems, an electronic alternative to handwritten records and signatures is required. Most dietary supplement component suppliers have adopted computer information systems to enhance productivity.

The primary issue with transfer of COAs without a handwritten signature is the verification of data. There are several considerations that should be taken into account before an electronic signature or name attachment to a COA is deemed acceptable.

- Computer systems access must be limited to authorized individuals. Access is gained only after inputting a user name and a password. The system should require frequent changes of each individual password.

- A confirmation of the integrity and accuracy of the information stored in the system must be completed.

- The operation of the system must be checked routinely to ensure the correct information is transferred from the database to the printed record.

- Data entered into a database from which information is extracted for a COA must be accompanied by time- and date-stamped audit trails.

With these criteria met, the issuance of a COA with an electronic signature or the responsible person's name attached to the document, in lieu of a handwritten signature, is acceptable.

Note: Computer systems are currently regulated by 21 CFR Part 11. Users should monitor the FDA's approach to judging compliance in this area.

9. DISTRIBUTOR INFORMATION

9.1 General Guidance

The presentation of a COA issued by a distributor presents some challenges. Since COAs are important documents characterizing the dietary supplement components and the state of their quality, the source of that information becomes very important to the end user(s). Because distributors take on different roles in fulfilling the

services for which they are contracted, it is necessary to assure that procedures and methods are appropriate for the functions performed.

Distributors function in a number of capacities for the movement of components and services. Some are simply pass-through locations in which nothing is done to the component with the exception of storage and handling. Others serve as extensions of the component manufacturer's process, taking bulk quantities and re-packaging for the manufacturer. Still, others purchase components and re-package them under a different label for sale and distribution. These scenarios need to be understood and properly documented with programs that will protect the integrity and safety of the components as they move through the distribution process.

9.2 Original Manufacturer and Manufacturing Site

The identity of the original manufacturer and the manufacturing site should be included on the COA for dietary supplement components. This information is important for providing traceability for specific component lots and in assuring the component users that they are consistently obtaining material from the same qualified manufacturer and site.

It is recognized that reporting the identity and location of the manufacturer may represent an issue when the original manufacturer is not the direct supplier of the component, as this information may be considered proprietary by a component distributor. To adequately address this issue, component distributors should list the specific information identifying the original manufacturer and location, and a non-disclosure or confidentiality agreement may be executed to reveal confidential or proprietary information.

9.3 Certificate of Analysis Data

When a distributor is primarily used as a "pass through" of the component and makes no changes to the component and packaging, the COA that accompanies the component from the manufacturer can be passed on in the original form. If the data are extracted, translated or rewritten on other letterhead, a system should be in place to verify the rewritten information, and justification and/or original data should be demonstrated upon request. Alternatively, the source of the data should be indicated on the document.

For a distributor that accepts bulk quantities of a component from a supplier and introduces that component into a process e.g., blending with other components, analysis of the new blend should be performed to verify the uniformity of the blended component and assure that established specifications are met. Appropriate analytical data should be included on the COA to verify the quality. The distributor should use equivalent methodology and equipment for the analytical evaluation.

In all scenarios, it is expected that the distributor will have the appropriate level of good manufacturing practices in place.

10. REFERENCES

21 CFR Part 111 Current Good Manufacturing Practice in Manufacturing, Packaging, Labeling, or Holding Operations for Dietary supplements

Volume 2: How to Perform Continuous Sampling (CSP) and Volume 4: How to Perform Skip-Lot and Chain Sampling by Kenneth Stephens, ASQ, 1979 and 1982.

United States Pharmacopeia (USP)

European Pharmacopoeia (EP)

Food Chemicals Codex (FCC)

Japanese Pharmacopoeia/Japanese Dietary supplement Components (JP/JPE)

Joint FAO/WHO Expert Committee on Food Additives (JECFA)

Glossary and Tables for Statistical Quality Control, 3rd Edition, ASQC Statistics Division, ASQC Quality Press, Milwaukee, WI

ANSI/ASQC A1-1978, Definitions, Symbols, Formulas and Tables for Control Charts, ASQC, (1978), Milwaukee, WI

Quality Assurance for the Chemical and Process Industries: A Manual of Good Practices, Chemical Interest Committee, Chemical and Process Industries Division, American Society for Quality Control, (1987), ASQC Quality Press, Milwaukee, WI

21 CFR Part 11 Electronic Records; Electronic Signatures

11. GLOSSARY

Acceptance Criteria: The specifications and acceptance/rejection limits, such as acceptable quality level and unacceptable quality level, with an associated sampling plan that are necessary for making a decision to accept or reject a lot or batch of raw material, intermediate, packaging material, or component.

Batch: A defined quantity of component processed so that it could be expected to be homogeneous. In a continuous process, a batch corresponds to a defined portion of the production, based on time or quantity (e.g. vessel's volume, one day's production, etc.).

Batch Number: A unique and distinctive combination of numbers and/or letters from which the complete history of the manufacture, processing, packaging, coding and distribution of a batch can be determined.

Batch Process: A manufacturing process that produces the component from a discrete supply of the raw materials that are present before the completion of the reaction.

Certificate of Analysis (COA): A document relating specifically to the results of testing a representative sample drawn from the batch of material to be delivered.

Chemical Property: A quality parameter that is measured by chemical or physiochemical test methods.

Continuous Process: A manufacturing process that continually produces the component from a continuous supply of raw material.

Contract Facility: An internal or external facility that provides services to the manufacturer and/or distributor of a component. These can include, but are not limited to: manufacturing facilities, laboratories, repackaging facilities (including labeling), warehouses, etc.

Date of Manufacture: A date indicating the completion of the final manufacturing process (as defined by the supplier for the particular component and process).

Date Retested: The date when retesting is performed by a component supplier to extend the length of time that the material may be used.

Distributor: A party other than the manufacturer who sells the component.

Dietary ingredient: A vitamin, mineral, herb or other botanical, amino acid, a dietary substance for use by man to supplement the diet by increasing the total dietary intake (e.g., enzymes or tissues from organs or glands), or a concentrate, metabolite, constituent or extract http://www.fda.gov/Food/DietarySupplements/ConsumerInformation/ucm110417.htm.

Dietary Supplement Component: Any substance intended for use in the manufacture of a dietary supplement, including those that may not appear in the finished batch of the dietary supplement. Components include dietary ingredients and other ingredients (such as excipients, preservatives and colorants) which may be included in a dietary supplement.

Expiration Date: The date after which the supplier recommends that the material should not be used.

Impurity: Any portion of a component that is not the intended chemical entity but is present as a consequence of either the raw materials used or the manufacturing process.

Lot: See “Batch.”

Lot Number: See “Batch Number.”

Manufacturer: The party who performs the final processing step.

Packaging: The container and its components that hold the component for storage and transport to the customer.

Periodic Testing Program: See "Skip-Lot Testing."

Physical Property: A quality parameter that can be measured solely with mechanical equipment.

Process: The set of operating instructions describing how the component is to be synthesized, isolated, purified, etc.

Process Capability Index (Cp): A statistical measurement that can be used to assess whether or not the process is adequate to meet specifications. A “State of Statistical Control” can be said to exist if the random variation in test results for a process parameter is such that the calculated process capability is greater than 1.33. (See **Appendix 1** for further explanation).

Process Step: An instruction to the component manufacturing personnel directing that an operation be done.

Recommended Re-Evaluation Date: Date suggested by the supplier when the material should be re-evaluated to ensure continued compliance with specifications. Differs from the Expiration Date in that the component may be re-evaluated to extend the length of time the material may be used, if supported by the results of the evaluation and appropriate stability data.

Reduced Frequency Testing Program: See "Skip-Lot Testing."

Re-packaging: Transfer of a component from one container to another.

Reprocessing: Introducing previously processed material that did not conform to standards or specifications back into the process and repeating steps that are already part of the normal manufacturing process and are part of the same batch.

Site: A location where the component is manufactured. This may be within the facility but in a different operational area or at a remote facility including a contract manufacturer.

Skip-Lot Testing Program: Periodic or intermittent testing performed for a particular test parameter, which is justified by historical data demonstrating a state of statistical process control.

Specification: The quality parameters to which the component or component intermediate must conform and that serve as a basis for quality evaluation.

Stable Process: A process is considered stable when the output of the process, regardless of the nature of the processing (batch or continuous), can be demonstrated, by appropriate means, to show a level of variability which consistently meets all aspects of the stated specification, (both pharmacopeia and customer specific) and is thus acceptable for its intended use.

Stability Statement: A statement that describes the known stability characteristics of a component when an expiration or re-evaluation date is not applicable

Supplier: A manufacturer or distributor who directly provides the component to the user.

User: A party who utilizes a component in the manufacture of a dietary supplement or another component.

APPENDIX 1

State of Statistical Control
Process Capability Parameters for Determining Levels of Control

A process is considered to be in a 'state of statistical control' if variations among the observed sampling results from the process can be attributed to a constant system of chance causes. Process Capability Index (Cp) or Capability Index Adjusted for the Process Average (Cpk) or Performance Index (Pp) or Performance Index Adjusted for the Process Average (Ppk) can be used to assess whether or not the process is adequate to meet specifications. Values of these parameters exceeding 1.33 show the process is adequate to meet specifications. Values between 1.00 and 1.33 indicate the process, while adequate to meet specifications, will require close control. Values below 1.00 indicate the process is not adequate to meet specifications and that the process and/or specifications must be changed. Pp/Ppk will always be less than or equal to Cp/Cpk respectively. The essential difference between the Capability and Performance Indices is the data used. Capability indices require the calculation of σ, the population standard deviation, whereas the Performance indices require the calculation of s, the sample standard deviation. Thus for dietary supplement components a "State of Statistical Control" can be said to exist if the random variation in test results for a process parameter is such that the calculated process capability or performance index is greater than 1.33.

APPENDIX 2

Dietary Supplement Industry Trade Associations:

American Herbal Products Association (AHPA), Silver Spring, MD

Consumer Healthcare Products Association (CHPA), Washington, DC

Council for Responsible Nutrition (CRN), Washington, DC

Natural Products Association (NPA), Washington, DC

United Natural Products Alliance (UNPA), Salt Lake City, UT