Private and Confidential Training Webinar -- eBook

SPECIFICATIONS, TESTING & SAMPLES

FDA Dietary Supplement
Good Manufacturing Practices (GMPs)
Part IX

Ver 1.0a © 02 April2019 / 38 Slides

This Webinar eBook includes a comprehensive 6 slide "new product development" checklist appendix .

PRESENTED BY RALPH FUCETOLA JD

- President of the Institute of Health Research
- During 36 Years Legal Practice (1971 – 2006) Known as *The Vitamin Lawyer*
- Certifications in Human BioAcoustics, Homeopathy & Hololinguistics

Please Note: the information on the webinar slides is reproduced in this Webinar eBook

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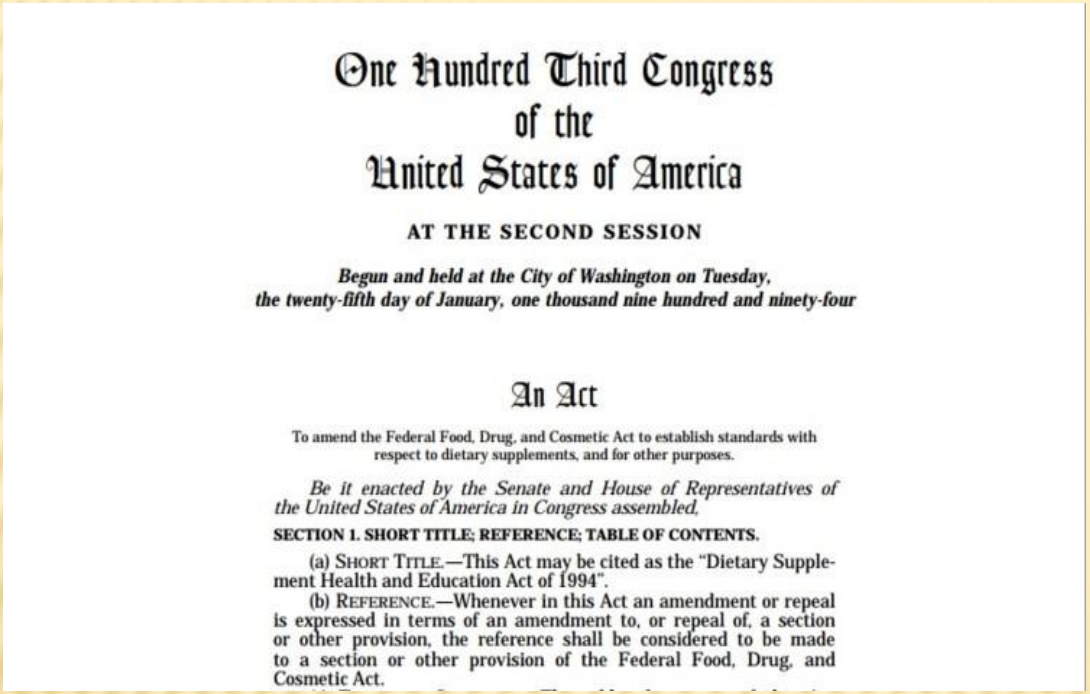
MY PROMISE TO YOU



One Hundred Third Congress
of the
United States of America

AT THE SECOND SESSION

Begun and held at the City of Washington on Tuesday,
the twenty-fifth day of January, one thousand nine hundred and ninety-four

An Act

To amend the Federal Food, Drug, and Cosmetic Act to establish standards with respect to dietary supplements, and for other purposes.

Be it enacted by the Senate and House of Representatives of the United States of America in Congress assembled,

SECTION 1. SHORT TITLE; REFERENCE; TABLE OF CONTENTS.

(a) SHORT TITLE.—This Act may be cited as the "Dietary Supplement Health and Education Act of 1994".

(b) REFERENCE.—Whenever in this Act an amendment or repeal is expressed in terms of an amendment to, or repeal of, a section or other provision, the reference shall be considered to be made to a section or other provision of the Federal Food, Drug, and Cosmetic Act.

"The purpose of this webinar is to provide Dietary Supplement Label Owners with a basic understanding of Section IX of the Food and Drug Administration's Good Manufacturing Practices for DSHEA* products."

Ralph Fucetola JD

* Dietary Supplements Health and Education Act of 1994

BATCH TESTING

- Here is a Practice Question I often receive from my Vitamin Consultancy clients.

Does FDA require that the Label Owner of a DSHEA Dietary Supplement have finished product batch-tested [in addition to verifying the ingredients]?

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SUBPART C BATCH TESTING

Yes. Here are the batch testing concerns from Subpart C of Part IX of the GMP regulations:

- **1. That the product meets the specifications for the product** in 6 specific areas - 21 CFR 111.75(a) through (g)
- **2. That an expiration date, if any, is scientifically valid** [Such a date is not required by FDA, so I do not recommend expiration dates]
- **3. Specific types of tests required** - 21 CFR 111.75(h)(2)
- **4. Must test for: identity, purity, strength, composition**, and the limits on types of contamination that may adulterate - 21 CFR 111.75(c) & (d)
- **5. Every finished batch must be tested** - 21 CFR 111.75(c)
- **6. There are certain exemptions** - 21 CFR 111.75(d)

Details as we continue…

PART IX REQUIREMENTS 1

- In addition to testing concerns, Part IX also addresses Specifications and Samples.
- You have to determine what your Specifications are for 7 specific areas set forth in Subpart B, and,
- Under Subpart C, you have to determine whether your product meets the specifications in 6 specific areas listed there.

PART IX REQUIREMENTS 2

- Subpart A - "General Requirements“
- Subpart B - Requirements to Establish Specifications
- Subpart C - Testing.
- Subpart D* - Specifications & verification of dietary ingredients
- Subpart E - Representative and reserve samples.

* "The DS CGMP rule requires you to conduct at least one appropriate test or examination to verify the identity of any dietary ingredient..."

COMPARISON OF SUBPART B AND C SPECIFICATION & TEST REQUIREMENTS

B. Required to *Establish* Product Specs:

1. control point specifications
2. components
3. in-process
4. labels and packaging
5. finished batch
6. received for packaging and labeling
7. finished product packaging and labeling

C. Required to *Determine* Product Meets:

1. components
2. in-process
3. finished batch
4. received for packaging and labeling
5. labels and packaging
6. finished product packaging and labeling

SPECIFICATIONS - 1

- Before you can test your product to determine if it meets the specifications for the product, you need to have Specifications.
- There are 7 specification areas, of which 3 are the Label Owner's primary responsibility and the rest are typically the Manufacturer's [Note: however, FDA says the *Label Owner* "**must be in a state of control**" so it is up to the Label Owner to *audit* Manufacturer compliance.]
- The Label Owner primary concerns are:

1. Specifications for final product (ingredients)
2. Specifications for label
3. Specification for finished labeling and packaging

SPECIFICATIONS 2 – SEVEN REQUIREMENTS

- 1. A specification for any point, step, or stage in the manufacturing process where control is necessary to ensure the quality of the dietary supplement and that the dietary supplement is packaged and labeled as specified in the master manufacturing record (21 CFR 111.70(a)); *
- 2. Specifications for components you use in the manufacture of a dietary supplement (21 CFR 111.70(b));
- 3. Specifications for the in-process production (21 CFR 111.70(c));
- 4. Specifications for dietary supplement labels and packaging (21 CFR 111.70(d));
- 5. Product specifications for the finished batch of the dietary supplement (21 CFR 111.70(e));
- 6. Specifications for product you receive from a supplier for packaging or labeling as a dietary supplement (21 CFR 111.70(f)); and
- 7. Specifications for the packaging and labeling of the finished packaged and labeled dietary supplements (21 CFR 111.70g)).

* - See the Vitamin Consultancy Quality Control Webinar

SPECIFICATIONS 3 – EXCLUSIONS

- [1] Does the DS CGMP rule require me to establish an “expiration date” (or a “shelf date” or “best if used by” date)?

  No. 72 FR 34752 at 34855
- But if you do, you must have substantiation for the choice of that date.
- [2] Should have data to support any specifications as established for parameters such as dissolution, disintegration, and bioavailability.
- Although the DS CGMP rule does not require you to establish specifications for parameters such as dissolution, disintegration, and bioavailability, if you establish such specifications you should have data to support that such specifications are met. 72 FR 34752 at 34851

* - See the Vitamin Consultancy Quality Control Webinar

SPECIFICATIONS 4 - SPECS MET?

The DS CGMP rule requires you to determine whether each of the following required specifications are met:

1. **Specifications for components of the product** (21 CFR 111.75(a));
2. **Specifications for the in-process production** (21 CFR 111.75(b));
3. **Specifications for the finished batch** of the dietary supplement (21 CFR 111.75(c) and (d));
4. **Specifications for product you receive** from a supplier for packaging or labeling as a dietary supplement (21 CFR 111.75(e));
5. **Specifications for dietary supplement** labels and packaging (21 CFR 111.75(f)); and
6. **Specifications for the packaging** and labeling of the finished packaged and labeled dietary supplements (21 CFR 111.75(g)).

TESTS AND EXAMINATIONS - 1

The DS CGMP rule requires, regarding the tests and examinations to determine whether specifications are met, that you ensure that the tests and examinations you use to determine whether the specifications are met are appropriate, scientifically valid methods (21 CFR 111.75(h)(1)); and

The tests and examinations you use include at least one of the following (21 CFR 111.75(h)(2)):

Gross organoleptic analysis (21 CFR 111.75(h)(2)(i));
Macroscopic analysis (21 CFR 111.75(h)(2)(ii));
Microscopic analysis (21 CFR 111.75(h)(2)(iii));
Chemical analysis (21 CFR 111.75(h)(2)(iv)); or
Other scientifically valid methods (21 CFR 111.75(h)(2)(v)).

TESTS AND EXAMINATIONS - 2

The DS CGMP rule requires verification that a finished batch of dietary supplements meets product specifications, by verifying that a subset of finished dietary supplement batches (which you identify through a sound statistical sampling plan) meets product specifications (i.e., specifications that the DS CGMP rule requires you to establish under 21 CFR 111.70(e)),

Unless you choose to verify that product specifications are met for *every* finished batch (21 CFR 111.75(c)).

To do so, the DS CGMP rule requires that: you select one or more established specifications for:

Identity
Purity
Strength
Composition, and
Limits on contamination that may adulterate or that may lead to adulteration of the dietary supplement that. --

TESTS AND EXAMINATIONS - 3

if determined to be in compliance with specifications by testing or examination of the finished batch of the dietary supplement, would verify that the production and process control system is producing a dietary supplement that meets all product specifications (with the exception of those product specifications that are exempted from this requirement) (21 CFR 111.75(c)(1) and 21 CFR 111.75(d));

You conduct appropriate tests or examinations to determine compliance with these specifications (21 CFR 111.75(c)(2));

You provide adequate documentation of your basis for determining that compliance with the selected specification(s), through the use of appropriate tests or examinations, will ensure that your finished batch of the dietary supplement meets all product specifications established under 21 CFR 111.70 (e) (21 cFR111.75(c)(3)); and

Your quality control personnel review and approve this documentation (21 CFR 111.75(c)(4)).

VERIFICATION EXEMPTION

6. Is there any exemption from the requirement of the DS CGMP rule regarding verification that a finished batch of dietary supplement meets product specifications?

Yes (21 CFR 111.75(d)). We realize that there may well be some specifications that you may not be able to test for at the finished batch stage. For example, you may determine that you could not verify, by testing for compliance with the specifications for identity and composition, that the purity specification is met, and there may be no scientifically valid method for testing or examining the finished batch to evaluate the purity in the finished batch of dietary supplement. In such a case, the DS CGMP rule provides that you can document why, for example, any component and in-process testing, examination, or monitoring, and any other information, will ensure that this product specification is met without verification through periodic testing of the finished batch, provided your quality control personnel review and approve that documentation (21 CFR 111.75(d)). For example, you could exempt the specification for purity from the requirement in 21 CFR 111.75(c)(1) through, for example, documentation that meeting component and specifications for strength is sufficient, or through documentation that in-process monitoring is sufficient, provided your quality control personnel review and approve such documentation (21 CFR 111.75(d))./ (72 FR 34752 at 34850)

VERIFICATION OF INGREDIENTS - 1

In addition to verifying that the product meets specifications the label owner must also verify the identity of each dietary ingredient.

The DS CGMP rule requires conducting at least one appropriate **test** or **examination** to verify the identity of any dietary ingredient.

It is up to the label owner to determine the appropriate test(s) or examination(s) necessary to verify the identity of a dietary ingredient.

In some cases, a single test or examination may be all that is needed to verify the identity of a dietary ingredient; in other cases, it may be necessary to conduct more than one test or examination

(72 FR 34752 at 34847).

VERIFICATION OF INGREDIENTS - 2

ALTERNATIVE TESTING

You may petition FDA for an alternative to the required 100% identity testing of components that are dietary ingredients You would submit the petition as a citizen petition in accordance with the provisions of 21 CFR 10.30 (21 CFR 111.75(a)(1)(ii)).

Your petition must set forth the scientific rationale, and be accompanied by the supporting data and information, for proposed alternative testing that will demonstrate that there is no material diminution of assurance, compared to the assurance provided by 100% identity testing, of the identity of the dietary ingredient *before use* when the dietary ingredient is obtained from one or more suppliers identified in the petition

VERIFICATION OF INGREDIENTS - 3

COMPONENTS

The DS CGMP rule requires you to confirm the identity of components, and determine whether other specifications for components (including dietary ingredients), are met, either by conducting appropriate tests or examinations or **by relying on a certificate of analysis from the supplier of the component.**

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. 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. You maintain documentation of how you qualified the supplier. You periodically re-confirm the supplier's certificate of analysis.

Your quality control personnel review and approve the documentation setting forth the basis for qualification (and re-qualification) of any supplier (21 CFR 111.75(a)(2)(ii)(E)).

REPRESENTATIVE AND RESERVE SAMPLES - 1

The Company or Manufacturer share sampling responsibilities. They should collect representative samples of the following materials:

In general, collect and hold reserve samples of each lot of packaged and labeled dietary supplements that you distribute. This would include dietary supplements that you package and label in bulk. (21 CFR 111.83(a))

[1] Company: Each unique lot of components, packaging, and labels that you use (21 CFR 111.80(a));

[2] Manufacturer: 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 dietary supplements (21 CFR 111.80(b));

REPRESENTATIVE AND RESERVE SAMPLES - 2

[3] Company: a subset of finished batches of each dietary supplement that you manufacture, which you identify through a sound statistical sampling plan (or otherwise every finished batch), before releasing for distribution (21 CFR 111.80(c));

[4] Manufacturer: Each unique shipment, and 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 (21 CFR 111.80(d)); and

[5] Each lot of packaged and labeled dietary supplements (21 CFR 111.80(e)).

REPRESENTATIVE AND RESERVE SAMPLES - 3

Why does FDA want you to collect and keep representative samples:

[1] “to determine whether applicable specifications are met.” (21 CFR 111.80)

[2] “for use in appropriate investigations, such as consumer complaint investigations.” (21 CFR 111.83(b)(3) and 21 CFR 111.465(b))

Samples must be dated, labeled and kept in a separated location (such as designated shelving with wire mesh closing it off) under lock. A Log should be kept of the Sample Locker’s contents with “with the batch, lot, or control number.” (21 CFR 111.83(b)(2))

REPRESENTATIVE AND RESERVE SAMPLES - 4

How long do you have to keep the samples?

[1] Here is the FDA *minimal* reservation periods:

One year past the shelf life date (if shelf life dating is used); or
Two years from the date of distribution of the last batch of dietary supplements associated with the reserve sample.
(21 CFR 111.83(b)(3); 72 FR 34752 at 34905)

[2] However, the Vitamin Consultancy advises keeping samples as long beyond the minimum as possible. Longer retention periods could support substantiation of longer shelf life and a sample might be useful as evidence in the event of litigation.

CONCLUSION

Thank you for participating! DSHEA GMPs are a complex set of Regulations consisting of 21 parts. This webinar was about Part IX (also known as Subpart E):

Subpart E – Requirement To Establish A Production And Process Control System

A. General Requirements of Subpart E
B. Requirements to Establish Specifications
C. Requirements to Determine Whether Specifications Are Met
D. Specific Requirements Regarding Specifications for Dietary Ingredients and Other Components
E. Representative and Reserve Samples

https://www.fda.gov/food/guidanceregulation/guidancedocumentsregulatoryinformation/dietarysupplements/ucm238182.htm#IX

More about my services regarding Process Controls here:
www.SystemsProcessingIntegration.com

INDEX OF SLIDES

APPENDIX: NEW PRODUCT CHECKLIST - 1

Checklist [From GMPs Section IX]

1. Initial specifications list of proposed ingredients and the expected ratio/amount of each in the product.

2. Research and report on availability of ingredients and pricing.

3. Working specifications:

[1] Follow DSHEA "Supplement Box" format, with:

(1) estimate of size of capsules
(2) number of capsules in bottle
(3) serving directions.

[2] List vitamins and minerals with DVs first (alphabetical order).
[3] For herbs, include the common name (may also include the scientific name).

APPENDIX: NEW PRODUCT CHECKLIST - 2

3. Working Specifications – Continued

[4] Specific ingredient purity and other detailed specifications should be included for each ingredient.
[5] "Other ingredients" to be specified.
[6] The Label Owner primary specification concerns are:

1. Specifications for final product (ingredients)
2. Specifications for label
3. Specification for finished labeling and packaging

4. Draft Label including:

[1] Central Panel with name, "Dietary Supplement" declaration and amount
[2] Right Panel with Supplement Box and contact information
[3] Left Panel with directions, disclosures and warnings

APPENDIX: NEW PRODUCT CHECKLIST - 3

5. Submit Bid Package to contract manufacturer, including:

[1] Specifications
[2] Draft Label
[3] GMP contract terms and conditions [Ten conditions binding the manufacturer to abide by GMPs – this Appendix]

6. Select manufacturer and issue Purchase Order, including:

[1] Final Specifications
[2] Final Label
[3] GMP contract terms and conditions attached to PO
[See this Appendix for the ten conditions]

APPENDIX: NEW PRODUCT CHECKLIST - 4

7. Testing:

[1] Test each ingredient before approving it for manufacturing
[2] Test each production batch to determine:

1. That the product meets the specifications for the product
   [6 specific areas - 21 CFR 111.75(a) through (g)]
2. That an expiration date, if any, is scientifically valid
   [Such a date is not required by FDA
   I do not recommend expiration dates]
3. Specific types of tests required - 21 CFR 111.75(h)(2)
4. Must test for: identity, purity, strength, composition, and the limits on types of contamination that may adulterate - 21 CFR 111.75(c) & (d)
5. Every finished batch must be tested - 21 CFR 111.75(c)

APPENDIX: NEW PRODUCT CHECKLIST - 5

7. Testing - Continued

[3] The tests and examinations you use include at least one of the following (21 CFR 111.75(h)(2)):

[1] Gross organoleptic analysis (21 CFR 111.75(h)(2)(i));
[2] Macroscopic analysis (21 CFR 111.75(h)(2)(ii));
[3] Microscopic analysis (21 CFR 111.75(h)(2)(iii));
[4] Chemical analysis (21 CFR 111.75(h)(2)(iv)); or
[5] Other scientifically valid methods (21 CFR 111.75(h)(2)(v)).

"...verify that a subset of finished dietary supplement batches (which you identify through a sound statistical sampling plan) meets product specifications..."

APPENDIX: NEW PRODUCT CHECKLIST - 6

8. Samples and Shipping

[1] Obtain written approval of Quality Control Manager to release the product for shipping.

[2] Maintain samples of each batch in a locked cabinet, with indication of when the sample was taken.

9. Post Market FDA Notice: [See this Appendix for S&F Notice format]

Prepare Structure and Function Notice setting forth:

- Claims
- Ingredients
- Label Copy
- Sworn statement that the company has “substantiation” of claims on file.

APPENDIX: MANUFACTURER P.O. TERMS 1

Terms and Conditions (GMP Quality)
Attached to and Incorporated into Purchase Order

To meet United States importation, manufacturing, packaging and delivery requirements, the following Terms and Conditions apply to this Purchase Order [_____ is "Manufacturer" and _____ is "Customer" or "Company"]:

1. PRODUCT STANDARDS: During the term of this Agreement, Manufacturer will supply product that meets all assembly, test, quality and documentation requirements at a cost provided in the Purchase Order for the product, and on a delivery schedule guided by the Purchase Order. Manufacturing & test, labeling and production records must meet all applicable FDA and internationally recognized and accepted growing and production standards. Product is manufactured, tested and labeled per Customer specifications. Customer has responsibility to ensure specifications meet applicable regulatory requirements and effectively communicate requirements to Manufacturer. Manufacturer has responsibility to ensure that product has been grown and produced in strict adherence to internationally accepted growing standards in every aspect of growth and production of the crop.

2. REPRESENTATION: Manufacturer represents that it has expertise in meeting all current Good Manufacturing Practices (GMPs) and growing and production practices, as mandated by FDA dietary supplement or medical food regulations or, internationally recognized standards. Manufacturer shall ensure compliance with GMPs as they apply to the Company's dietary supplement products, under 21 USC 342(g), and subject to the final regulations issued by the FDA June 22, 2007 - http://www.cfsan.fda.gov/~dms/dscgmps6.html

APPENDIX: MANUFACTURER P.O. TERMS 2

3. CONSISTANCY: The standards to which the Manufacturer adheres must ensure that dietary supplements are manufactured consistently as to identity, purity, quality, strength, and composition and freedom from materials which are incompatible with labeled dietary supplements.

4. PURCHASE ORDER: Manufacturer shall manufacture, test, label and deliver the Product exclusively to the Company (Customer) under the terms and conditions of the Quotation/Purchase Order.

5. LABELS / BATCH NUMBER: All Product labels shall conform to all legal requirements for dietary supplement or other Products; all labels shall carry a unique batch number which identifies the month and year of manufacture and the traceable batch records for the Product Run.

6. INGREDIENTS: All ingredients and components purchased and inventory used in the manufacture of the Product, shall be sourced from certified for Farming sources.

APPENDIX: MANUFACTURER P.O. TERMS 3

7. LABORATORY TESTING: As required by Food and Drug Administration regulation, 21 CFR 111.75 (1)(i), there shall be at least one appropriate test per source of each nutrient ingredient as to "purity, identity, composition and strength..." Manufacturer shall keep records of such tests and provide copies to the Company, which shall verify and keep copies of such records. In addition, each batch shall be tested by an independent third party laboratory for any agrochemical or residue which is incompatible with dietary supplement requirements and provide copies to the Company.

Every batch must be laboratory certified to be free of any and all Genetically Modified Organisms or material of such origin. Such certification shall be the responsibility of the Manufacturer and the laboratory result confirming such genetically modified-free status shall be presented with the other documentation prior to sale.

Every batch must be certified to be no higher in radiation levels than acceptable background radiation levels, with copy of certification to be provided to the Company. The radiation readings provided by formal test reports in a format acceptable to the Customer must be provided along with a copy of the video allowing time for inspection and approval of radiation status before each purchase can be completed. The Company shall receive and keep copies of Certificates of Analysis from duly qualified suppliers provided by the Manufacturer

APPENDIX: MANUFACTURER P.O. TERMS 4

8. GMP AND STANDARD COMPLIANCE: All manufacturing, testing and labeling shall be in strict compliance with all applicable product and GMPs, so that all dietary supplement products are manufactured, stored and shipped so that same are consistent as to identity, purity, quality, strength, and composition. The Manufacturer shall make available to the Company documentation of GMP compliance, permit a reasonable onsite audit of compliance on behalf of Company at Company's request, and the Company shall document the compliance documentation and audit. The Manufacturer shall be responsible for sourcing, meeting and carrying out all standards.

9. INDEMNITY: Manufacturer hereby undertakes to reasonably indemnify, defend and hold harmless the Customer from any willful or grossly negligent acts or omissions, which result in a judgment for damages against the indemnified party or serious loss of reputation or ability to supply product to the clients and customers of the Customer resulting from failure on the part of the Manufacturer to meet the terms of this and any other agreements, contracts and concords entered into with the Customer.

10. RECORD COPIES & GMP and AUDITS: Upon Company's periodic request, Manufacturer shall provide copies of all relevant manufacturing and quality control records and permit Company or its agent to inspect the facility and undertake a recorded GMP and/or Audit at any time without hindrance.

APPENDIX: STRUCTURE & FUNCTION NOTICE 1

SECRETARY OF HEALTH AND HUMAN SERVICES
UNITED STATES OF AMERICA

NOTICE OF STATEMENTS UNDER 21 U.S.C. 403(r)(6)
[Structure & Function Claims Notice]

To: The Division of Dietary Supplement Programs
Office of Nutritional Products, Labeling and Dietary Supplements
Center for Food Safety and Applied Nutrition
Food and Drug Administration,
5100 Paint Branch Parkway, College Park, MD 20740-3835 USA

Date: _____

Re: This Notice covers the following Brand: _____™ Dietary Supplement

PLEASE TAKE NOTICE under 21 U.S.C. 403(r) (6):

(i) The name and address of the manufacturer, packer, or distributor of the dietary supplement that bears the statement(s):
_____

(ii) The text of the statement that is being made: see attached Exhibit A.

(iii) The name of the dietary ingredient or supplement that is the subject of the statement: see attached Exhibit A.

(iv) The name of the dietary supplement (including brand name), if not provided in response to paragraph (a)(2)(iii) on whose label, or in whose labeling, the statement appears: see attached Exhibit A.

APPENDIX: STRUCTURE & FUNCTION NOTICE 2

CERTIFICATION

The undersigned, being duly authorized by the firm submitting the above Notice of Statements under 21 U.S.C. 403 (r) (6) certifies, as of the date first written above: (a) that the information contained in the Notice is complete and accurate, and (b) that the notifying firm has substantiation that the Statements to which this Notice applies are truthful and not misleading.

The undersigned certifies that the above Certification is true and is aware that the undersigned is subject to punishment as for perjury if the Certification is willfully false. This Certification is made under 18 USC 1001which makes it a crime to submit false information to the Government.

_____

[Name] [Title]

NOTICE OF STATEMENTS UNDER 21 U.S.C. 403(r)(6) - Exhibit A

[1] Brand Name(s) Included herein: _____™ – Dietary Supplement

[2] Dietary Ingredients included herein: [List]

[3] Statements made with regard to Ingredients: [List]

Copy of Label attached.

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SPECIFICATIONS, TESTING & SAMPLES

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