Quality control and documentation in Supplements & Nutraceuticals

Nutraceuticals are classified on the basis of their ingredients or therapeutic use

Nutraceuicals refers to **extracts of foods having a medicinal effect** on human health.it comprises of foods, dietary supplements, and medical foods meant for **prevention or treatment of disease**

Traditionally, nutraceuticals came in a **medicinal format** Such as a capsule, tablet or powder in a prescribed dose

Modern Nutraceuticals are available as forms of **food, or included in foods** or as whole food itself such as **probiotic drinks and yogurt**

Nutaceuticals can be classified on the basis of the beneficial ingredient and/or therapeutic benefit claimed

Ingredients

- Antioxidants, carotenoids
- Dairy-based ingredients
- Fibres and carbohydrates
- Minerals
- Nutritional lipids and oils
- Phytochemicals, plant extracts
- Probiotics and prebiotics
- Proteins, peptides, amino acids
- Soy-based ingredients
- Vitamins & premixes

Therapeutic Use

- Bone& joint health
- Cancer risk reduction
- Cardivascular health and diabetes
- Cognitive and mental function
- Energy & endurance
- Eye health
- Immune system
- Maternal & infant health
- Respiratory health
- Skin health
- Weight management

Why rising popularity

- The increased interest in healthy living
- Growing desire for natural cures
- Consumer demands are changing to preventive therapies for chronic disease

Concerns

- Medical experts and regulatroy authorities are concerned that certified nutraceuticals are still rare in the market
- Most raw materials used for the manufacture of nutraceuticals are imported and therefore offer no quality control
- Not much data available on how the herbal and botanical ingredients-that go into the manufacture of nutraceuticals-are produced
- Nutraceuticals clearly affect physiology but they are not submitted to testing process as rigorously as pharmaceutical drugs

Dietray supplements

- Orally ingested products that contain an ingredient that is intended to supplement the diet
- Not controlled by FDA untill 2007
- Now every manufacturer or distributer of dietray supplements has to be in compliance with GMP requirements

GMP for dietary supplements

- FDA requires compliance in manufacturing, packaging, labeling, or holding operations
- Packaging and labeling has to be done per **master manufacturing record**
- Products must meet specifications for **identification, purity, strength, and composition and limits on contaminants**
- Demonstrate that product has been manufactured, packaged, labeled, and held under conditions to prevent adulteration

- **On February 11, 2004, FDA** published in the Federal Register a final rule that established a regulation declaring dietary **supplements containing ephedrine** alkaloids adulterated under the Federal Food, Drug, and Cosmetic Act because they present an unreasonable risk of illness or injury under the conditions of use

- All requirements for GMP compliance are in the FDA's "final rule" on dietary supplements

Comprehensive REVIEWS in Food Science and Food Safety

Food and Dietary Supplement Package Labeling—Guidance from FDA's Warning Letters and Title 21 of the Code of Federal Regulations

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Abstract: Package labels for foods and dietary supplements must conform with Title 21 of the Code of Federal Regulations. This review provides guidance for the content and format of labels, including for the Nutrient Facts panel and Supplement Facts panel, and for drafting structure/function claims, health claims, and nutrient content claims. Also provided is guidance on how to refrain from drafting disease claims. Inappropriate disease claims on a food or dietary supplement compels FDA to review the product as a drug. Disease claims is the most common source of complaint in FDA's warning letters. This review makes use of all of FDA's warning letters that were published over a 14-y span (2002to 2015). This is the first comprehensive review on package labels to make use of FDA's warning letters as a source document.

Keywords: dietary supplements, FDA, food, package labels

Name of product	Incorrect name on the package label	Common or usual name suggested by FDA reviewer	Warning Letter number
Jalapeno Cheese Bagel	Natural bagel base	Bagel base	MIN 11-05. Nov. 5, 2010
Red Skin Potato Salad	Corn sweetener	Fructose corn syrup	CIN-12-214994-05
Red Skin Potato Salad	EDTA	Disodium calcium EDTA	CIN-12-214994-05
Red Skin Potato Salad	Sugar	Fructose	CIN-12-214994-05
Three Bean Salad	Soybean oil	Partially hydrogenated soybean oil	CIN-12-214994-05
Jamaican Choice Flavor Enhancer	MSG	Monosodium glutamate[a]	FLA-12-27. March 19, 2012. See also, FLA-13-06. Nov. 20, 2012
Lifesoy Natural Soymilk Unsweetened	Soy milk Note: The product did not contain any cow's milk	Soy drink or soy beverage	W/L 20-08. Aug. 8, 2008. See also, Fong Kee Tofu Co. (March 7, 2012)
Organic Alfalfa Sprouts	Organic alfalfa seeds	Alfalfa sprouts	NWE-13-11W. March 24, 2011
Calcium Orange Juice Beverage	Orange juice	Orange juice from concentrate.	SJN-06-11. Aug. 31, 2006
Waterthins Cheese Twists Classic Cheddar	Cheddar	Natural cheddar cheese flavored	396837. July 26, 2013
Rebuild!	Inositol hexaniacinate	Niacin	DEN-13-06-WL. Feb. 4, 2012
Krier Foods, Inc. product	MSM	Methylsulfonylmethane	MIN 14-03. Dec. 13, 2013.
Krier Foods, Inc. product	5-HTP	5-hydroxytryptophan	MIN 14-03. Dec. 13, 2013.
Annalisa White Beans	Beans	Borlotti beans, butter beans, or cannellini beans	391860. March 7, 2013.

[a] 21 CFR §101.22(h)(5) requires that, "Any monosodium glutamate used as an ingredient in food shall be declared by its common or usual name "monosodium glutamate."".

Table 2–Structure/function claims on dietary supplement labels.

Warning letter	Product	Structure/function claim
Genesis Nutrition. March 26, 2004.	Super Chitosan	"dramatically reduce fat absorption in the body"
MuscleShoppe.com. Feb. 28, 2003.	Ripped Force	"for a ripped, well defined physique"
Natures Hand. Dec. 9, 2003.	Coral Calcium Supreme	"neutralize harmful acids"
W/L 31-04. March 4, 2004.	Coral Calcium	"when your pH is slightly alkaline, your body has the most ability to maintain good health. Only when you have enough calcium in the body will your pH be able to reach an alkaline state"
Natural Balance. Feb. 28, 2003.	Turbo Charge	"maximum sports performance"
SEA 05–14. Feb. 8, 2005.	Stabilized Vitamin O	"[i]n double blind clinical studies involving blood gas analysis, Vitamin O has been shown to significantly increase blood oxygen levels … those taking Vitamin O showed a 17% to 32% increase in arterial blood oxygen! In oral interviews conducted during this study, research participants reported greater youthfulness, improved mobility, better circulation, sharper mental clarity, enhanced lung and heart function, and increased physical energy"
Twinlab. Feb. 28, 2003.	Energy Fuel	"helps preserve lean muscle mass."

Top 10 critical deficiencies

Documentation - quality system elements/procedures
Documentation - manufacturing
Documentation - specification and testing
In-process controls - control and monitoring of production operations
Starting material and packaging component testing
Batch release procedures
Analytical validation
Finished product testing
Intermediate and bulk product testing
reference materials and reagents

Good Laboratory Practices, GLP

Good Quality Control Laboratory Practice

Good Practices in Quality Control

PART 211—Current Good Manufacturing Practice for Finished Pharmaceuticals

1. Subpart A—General Provisions
2. Subpart B—Organization and Personnel
3. Subpart C—Buildings and Facilities
4. Subpart D—Equipment
5. Subpart E—Control of Components and Drug Product Containers and Closures
6. Subpart F—Production and Process Controls
7. Subpart G—Packaging and Labeling Control
8. Subpart H—Holding and Distribution
9. Subpart I—Laboratory Controls
10. Subpart J—Records and Reports
11. Subpart K—Returned and Salvaged Drug Products

GMP PIC/S

- Chapter 1. Quality Management
- Chapter 2. Personnel
- Chapter 3. Premises and Equipment
- Chapter 4. Documentation
- Chapter 5. Production
- Chapter 6. Quality Control
- Chapter 7. Contract Manufacture and Analysis
- Chapter 8. Complaints and Product Recall
- Chapter 9. Self Inspection

GMP-PIC/S

Chapter 6

Good Quality Control Laboratory Practice

Principle

- Quality Control is concerned with
  - sampling,
  - specifications and
  - testing
  - release procedures

General

- 6.1. Each holder of a manufacturing authorisation should have a Quality Control Department.
- This department should be independent from other departments, and **under the authority of a person** with appropriate qualifications and experience, who has *one or several control laboratories* at his disposal.
- Adequate resources *must* be available to ensure that all the Quality Control arrangements are effectively and reliably carried out.

General

6.2. The principal duties of the head of Quality Control are summarised in **Chapter 2.**

- The QC Department as a whole will also have other duties, such as
- to establish, validate and implement all **quality control procedures**,

General

- ensure the correct labelling of containers of *materials* and *products*,
- ensure the monitoring of the stability of the products,
- participate in the investigation of complaints related to the quality of the product, etc.
- All these operations should be carried **out in ccordance with** written procedures and, where necessary, recorded.
- keep the reference samples of materials and products,

Good Practices for QC Laboratories

6.3. **Finished product assessment** should embrace all relevant factors, including

- production conditions,
- results of in-process testing,
- a review of manufacturing (including packaging) documentation,
- compliance with Finished Product Specification and
- examination of the final finished pack.

Good Practices for QC Laboratories

- 6.4. Quality Control personnel should have access to production areas for sampling and investigation as appropriate.

Good Practices for QC Laboratories

- 6.5. Control Laboratory premises and equipment should meet the general and specific requirements for Quality Control areas given in **Chapter 3.**

Good Practices for QC Laboratories

- 6.6. The personnel, premises, and equipment in the laboratories should be appropriate to the tasks imposed by the nature and the scale of the manufacturing operations.
- The use of outside laboratories, in conformity with the principles detailed in Chapter 7, Contract Analysis, can be accepted for particular reasons, but this **should be stated in the Quality Control records.**

GLP Documentation

6.7. Laboratory documentation should follow the principles given in **Chapter 4**.

- An important part of this documentation deals with QC and the following details should be readily available to the Quality Control Department:
- specifications;
- sampling procedures;

GLP Documentation

- testing procedures and records (including analytical worksheets and/or laboratory notebooks);
- analytical reports and/or certificates;
- data from environmental monitoring, where required;
- validation records of test methods, where applicable;
- procedures for and records of the calibration of instruments and maintenance of equipment.

GLP Documentation

- 6.8. Any Quality Control documentation relating to a batch record should be retained for one year after the expiry date of the batch.

- 6.9. For some kinds of data (e.g.
  - analytical tests results,
  - yields,
  - environmental controls, ...)
- it is recommended that records in a manner permitting trend evaluation be *kept*.

GLP Documentation

- 6.10. In addition to the information which is part of the batch record, other **original data** such as laboratory notebooks and/or records should be retained and readily available.

Sampling

6.11. The sample taking should be done in accordance with approved written procedures that describe:

- the method of sampling;
- the equipment to be used;
- the amount of the sample to be taken;

sampling

- 6.12. Reference samples should be representative of the batch of materials or products from which they are taken.
- 6.13. Sample **containers** should bear a label indicating the contents, with the batch number, the date of sampling and the containers from which samples have been drawn.
- 6.14. Reference samples from each batch of finished products should be retained till one year after the expiry date.
- Finished products should usually be kept in their final packaging and stored under the recommended conditions.

Testing

- 6.15. Analytical methods should be validated.
- All testing operations described in the marketing authorisation should be carried out according to the approved methods.

Testing

VALIDATION OF ANALYTICAL PROCEDURES

Validated test methods should be applied.

- The validation of test methods includes verification of:
  - 1. Specificity,
  - 2. Linearity,
  - 3. Range,
  - 4. Accuracy,
  - 5. Precision
  - 6. LOD
  - 7. LOQ
  - 8. Robustness
  - 9. SYSTEM SUITABILITY TESTING

Testing

- 6.16. The results obtained should be recorded and checked to make sure that they are consistent with each other.
- Any calculations should be critically examined.

Testing

6.17. The tests performed should be recorded and the records should include at least the following data:

- **a**) name of the material or product and, where applicable, dosage form;
- **b**) batch number and, where appropriate, the manufacturer and/or supplier;
- **c**) references to the relevant specifications and testing procedures;

Testing

- **d**) test results, including observations and calculations, and reference to any certificates of analysis;
- **e**) dates of testing;
- **f)** initials of the persons who performed the testing;

Testing

- **g**) initials of the persons who verified the testing and the calculations, where appropriate;
- **h**) a clear statement of release or rejection (or other status decision) and the dated signature of the designated responsible person.

Testing

- 6.18. All the in-process controls, including those made in the production area by production personnel, should be performed according to methods approved by Quality Control and the results recorded.

Testing

- 6.19. Special attention should be given to the quality of laboratory reagents, volumetric glassware and solutions, reference standards and culture media.
- They should be prepared in accordance with written procedures.

Testing

- 6.20. Laboratory reagents intended for prolonged use should be marked with the preparation date and the signature of the person who prepared them.
- The expiry date of unstable reagents and culture media should be indicated on the label, together with specific storage conditions.
- In addition, for volumetric solutions, the last date of standardisation and the last current factor should be indicated.

Testing

- 6.21. Where necessary, the date of receipt of any substance used for testing operations (e.g. reagents and reference standards) should be indicated on the container.
- Instructions for use and storage should be followed.
- In certain **cases it may be necessary** to carry out an identification test and/or other testing of reagent materials upon receipt or before use.

Testing

- 6.22. Animals used for testing components, materials or products, should, where appropriate, be quarantined before use.
- They should be maintained and controlled in a manner that assures their suitability for the intended use.
- They should be identified, and adequate records should be maintained, showing the history of their use.

Chapter 4

GMP-PIC/S

Documentation

Principle

- *Good documentation* constitutes an essential part of the quality assurance system.
- Clearly written documentation prevents *errors from spoken communication* and permits tracing of batch history.
- Specifications, Manufacturing Formulae and instructions, procedures, and records must be free from errors and available in writing.
- The legibility of documents is of paramount importance.

General

- 4.1. Specifications describe in detail the requirements with which the products or materials used or obtained during manufacture have to conform.
- They serve as a basis for quality evaluation.

General

- 4.2. Documents should be designed, prepared, reviewed and distributed with care.
- They should comply with the relevant parts of the manufacturing and marketing authorisation dossiers.

General

- 4.3. Documents should be **approved, signed and dated** by appropriate and authorised persons.

General

- 4.4. Documents should have unambiguous contents; title, nature and purpose should be clearly stated.
- They should be laid out in an orderly fashion and be easy to check.
- Reproduced documents should be clear and legible.
- The reproduction of working documents from master documents must not allow any error to be introduced through the reproduction process.

General

- 4.5. Documents should be
  - ✓ regularly reviewed and kept
  - ✓ up-to-date.
- When a document has been revised, systems should be operated to *prevent* inadvertent use of superseded documents.

General

- 4.6. Documents should not be hand-written;
- although, where documents require the entry of data, these entries may be made in
  - ✓ clear, legible, indelible handwriting.
- Sufficient space should be provided for such entries.

General

- 4.7. Any alteration made to the entry on a document should be signed and dated;
- the alteration should permit the reading of the original information.
- Where appropriate, the reason for the alteration should be recorded.

General

- 4.8. The records should be made or completed at the time each action is taken and in such a way that all significant activities concerning the manufacture of medicinal products are traceable.
- They should be retained for at least one year after the expiry date of the finished product.

Documentation
General

- 4.9. Data may be recorded by electronic data processing systems, photographic or other reliable means,
- but detailed procedures relating to the system in use should be available and the accuracy of the records should be checked.

GMP
Documents Required

- Specifications

- 4.10 There should be appropriately authorised and dated specifications for:
  - starting and packaging materials, and
  - finished products; where appropriate,
  - they should be also available for intermediate or bulk products.

Specifications for starting and packaging materials

- 4.11. Specifications for starting and primary or printed packaging materials should include, if applicable:
- a) a description of the materials, including:
  - the designated name and the internal code reference;
  - the reference, if any, to a pharmacopoeial monograph;
  - the approved suppliers and, if possible, the original producer of the products;
  - a specimen of printed materials;

Specifications for starting and packaging materials

- b) directions for sampling and testing or reference to procedures;
- c) qualitative and quantitative requirements with acceptance limits;
- d) storage conditions and precautions;
- e) the maximum period of storage before re-examination.

Specifications for intermediate and bulk products

- 4.12. Specifications for intermediate and bulk products should be available if these are purchased or dispatched, or if data obtained from intermediate products are used for the evaluation of the finished product.
- The specifications should be similar to specifications for starting materials or for finished products, as appropriate.

Specifications for finished products

- 4.13. Specifications for finished products should include:
- a) the designated name of the product and the code reference where applicable;
- b) the formula or a reference to;
- c) a description of the pharmaceutical form and package details;
- d) directions for sampling and testing or a reference to procedures;
- e) the qualitative and quantitative requirements, with the acceptance limits;
- f) the storage conditions and any special handling precautions, where applicable;
- g) the shelf-life.

Specifications: Components

Specifications needed for each component used in manufacturing

- Vitamins or minerals might include:
- Identification
- assay
- appearance
- odor
- solubility
- melting point
- loss on drying or residue on ignition
- heavy metals
- organic volatile impurities

Specifications: Components

Specifications needed for each component used in manufacturing

Botanicals might include:

- Identification such as visual comparison to standard or picture
- Part of the plant such as root or leaves
- Color
- Odor
- Characteristics that differentiate the desired species from related species

Specifications: Not required

- Dissolution
- Bioavailability

Manufacturing Formula(a-d)

- 4.14. The Manufacturing Formula should include:
- a) the name of the product, with a product reference code relating to its specification;
- b) a description of the pharmaceutical form, strength of the product and batch size;

Manufacturing Formula

- c) a list of all starting materials to be used, with the amount of each, described using the designated name and a reference which is unique to that material; mention should be made of any substance that may disappear in the course of processing;
- d) a statement of the expected final yield with the *acceptable limits*, and of relevant intermediate yields, where applicable.

Processing Instructions(a-f)

- 4.15. The Processing Instructions should include:
- a) a statement of the *processing location* and the *principal equipment* to be used;
- b) the methods, or reference to the methods, to be used for preparing the critical equipment (e.g. cleaning, assembling, calibrating, sterilising);

Processing Instructions

- c) detailed stepwise processing instructions (e.g. checks on materials, pretreatments, sequence for adding materials, mixing times, temperatures);
- d) the instructions for any in-process controls with their limits;
- e) where necessary, requirements for bulk storage of the products; including the container, labelling & special storage conditions where applicable;
- f) any special precautions to be observed.

Packaging Instructions

- 4.16. There should be formally authorised Packaging Instructions for each product for pack size and type.
- These should normally include, or have a reference to, the following:
- a) name of the product;
- b) description of its pharmaceutical form, and strength where applicable;

Packaging Instructions(a-h)

- c) the pack size expressed in terms of the number, weight or volume of the product in the final container;
- d) a complete list of all the packaging materials required for a standard batch size, including quantities, sizes and types, with the code or reference number relating to the specifications of each packaging material;

Packaging Instructions

- e) where appropriate, an example or reproduction of the relevant printed packaging materials, and specimens indicating where to apply batch number references, and shelf-life of the product;

Packaging Instructions

- f) special precautions to be observed, including a careful examination of the area and equipment in order to ascertain the line clearance before operations begin;
- g) a description of the packaging operation, including any significant subsidiary operations, and equipment to be used;
- h) details of in-process controls with instructions for sampling and acceptance limits.

Batch Manufacturing Records, BMR

Batch Processing Records, BPR

- 4.17. A Batch Processing Record should be kept for each batch processed.
- It should be based on the relevant parts of the *currently approved Manufacturing Formula and Processing Instructions*.
- The method of preparation of such records should be designed to avoid transcription errors.
- The record should carry the number of the batch being manufactured.

Batch Processing Records, BPR

- Before any processing begins, there should be recorded checks that the equipment and work station are clear of previous products, documents or materials not required for the planned process,
- and that equipment is clean and suitable for use.

Batch Processing Records, BPR(a-i)

- During processing, the following information should be recorded at the *time each action is taken*
- and, after completion, the record should be dated and signed in agreement by the person responsible for the processing operations:
- a) the name of the product;
- b) dates and times of commencement, of significant intermediate stages and of completion of production;

Batch Processing Records, BPR

- c) *name of the person responsible* for each stage of production;
- d) *initials of the operator* of different significant steps of production and, where appropriate, of the person who checked each of these operations (e.g. weighing);
- e) the batch number and/or analytical control number as well as the quantities of each starting material actually weighed (including the batch number and amount of any recovered or reprocessed material added);

Batch Processing Records, BPR

- f) any relevant processing operation or event and major equipment used;
- g) a record of the in-process coontrls and the initials of the person(s) carrying them out, and the results obtained;
- h) the amount of product yield obtained at different and pertinent stages of manufacture;
- i) notes on special problems including details, with signed authorisation for any deviation from the Manufacturing Formula and Processing Instructions.

Batch Packaging Records, BPR

Batch Packaging Records

- 4.18. A Batch Packaging Record should be kept for each batch or part batch processed.
- It should be based on the relevant parts of the Packaging Instructions and the method of preparation of such records should be designed to avoid transcription errors.

Batch Packaging Records

- The record should carry the batch number and the quantity of bulk product to be packed, as well as the batch number and the planned quantity of finished product that will be obtained.

Batch Packaging Records

- Before any packaging operation begins, there should be recorded checks that the *equipment* and *work station* are clear of previous products, documents or materials not required for the planned packaging operations, and that equipment is clean and suitable for use.

Batch Packaging Records

- The following information should be entered at the time each action is taken and, after completion, the record should be dated and signed in agreement by the person(s) responsible for the packaging operations:
- a) the name of the product;
- b) the date(s) and times of the packaging operations;
- c) the name of the responsible person carrying out the packaging operation;

Batch Packaging Records

- d) the initials of the operators of the different significant steps;
- e) records of checks for identity and conformity with the Packaging Instructions including the results of in-process controls;
- f) details of the packaging operations carried out, including references to equipment and the packaging lines used;

Batch Packaging Records

- g) whenever possible, samples of printed packaging materials used, including specimens of the batch coding, expiry dating and any additional overprinting;
- h) notes on any special problems or unusual events including details with signed authorisation for any deviation from the Manufacturing Formula and Processing Instructions;

Batch Packaging Records

- i) the quantities and reference number or identification of all printed packaging materials and bulk product:
  - issued,
  - used,
  - destroyed or
  - returned to stock and
  - the quantities of obtained product,
- in order to provide for an adequate reconciliation.

Procedures and Records

- 4.19. There should be written procedures and records for the receipt of each delivery of each starting and primary and printed packaging material.

- 4.20. The records of the receipts should include:
- a) the name of the material on the delivery note and the containers;
- b) the "in-house" name and/or code of material (if different from a);
- c) date of receipt;
- d) supplier's name and, if possible, manufacturer's name;

- e) manufacturer's batch or reference number;
- f) total quantity, and number of containers received;
- g) the batch number assigned after receipt;
- h) any relevant comment (e.g. state of the containers).

Internal labeling

- 4.21. There should be written procedures for the
  - internal labelling,
  - quarantine and
  - storage of starting materials,
  - packaging materials and
  - other materials, as appropriate.

Sampling

- 4.22. There should be written procedures for sampling, which include the person(s) authorised to take samples, the methods and equipment to be used, the amounts to be taken and any precautions to be observed to avoid contamination of the material or any deterioration in its quality (see Chapter 6, Item 13).

Testing

- 4.23. There should be written procedures for testing materials and products at different stages of manufacture, describing the methods and equipment to be used.
- The tests performed should be recorded (see Chapter 6, Item 17).

Release records

- 4.24 Written release and rejection procedures should be available for materials and products, and in particular for the release for sale of the finished product by the authorised person(s) designated for the purpose.

Distribution Records

- 4.25. *Records* should be maintained of the distribution of each batch of a product in order to facilitate the recall of the batch if necessary (see Chapter 8).

- 4.26. There should be written procedures and the associated records of actions taken or conclusions reached, where appropriate, for:
- SOP Validation:
- SOP Environmental monitoring :
- SOP container control:
- SOP Recalls

- 4.27. Clear operating procedures should be available for major items of *manufacturing* and *test* equipment.

- 4.28. Log books should be kept for major or critical equipment recording, as appropriate,
  - any validations,
  - calibrations,
  - maintenance,
  - cleaning or
  - repair operations,
- including the dates and identity of people who carried these operations out.

- 4.29. Log books should also record in chronological order the use of major or critical equipment and *the areas where* the products have been processed.