# Quality control and documentation in Supplements & Nutraceuticals

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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

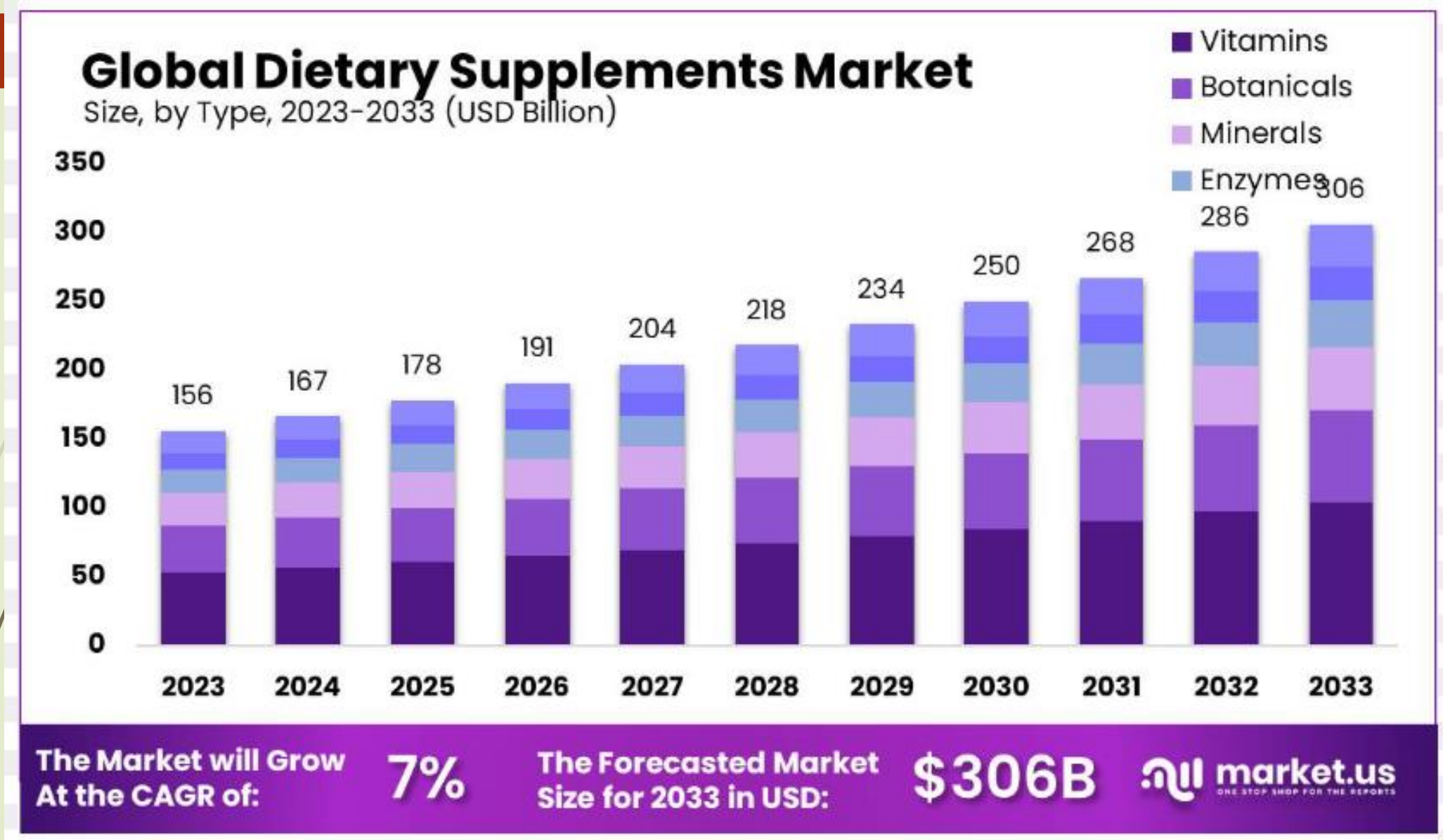
- Bone& joint health
- Cancer risk reduction
- Cardivascular health and diabetes
- Cognitive and mental function
- Energy & endurance
- Eye health
- Immune system
- Maternal & infant health
- Respiratory health
- Skin health
- Weight management

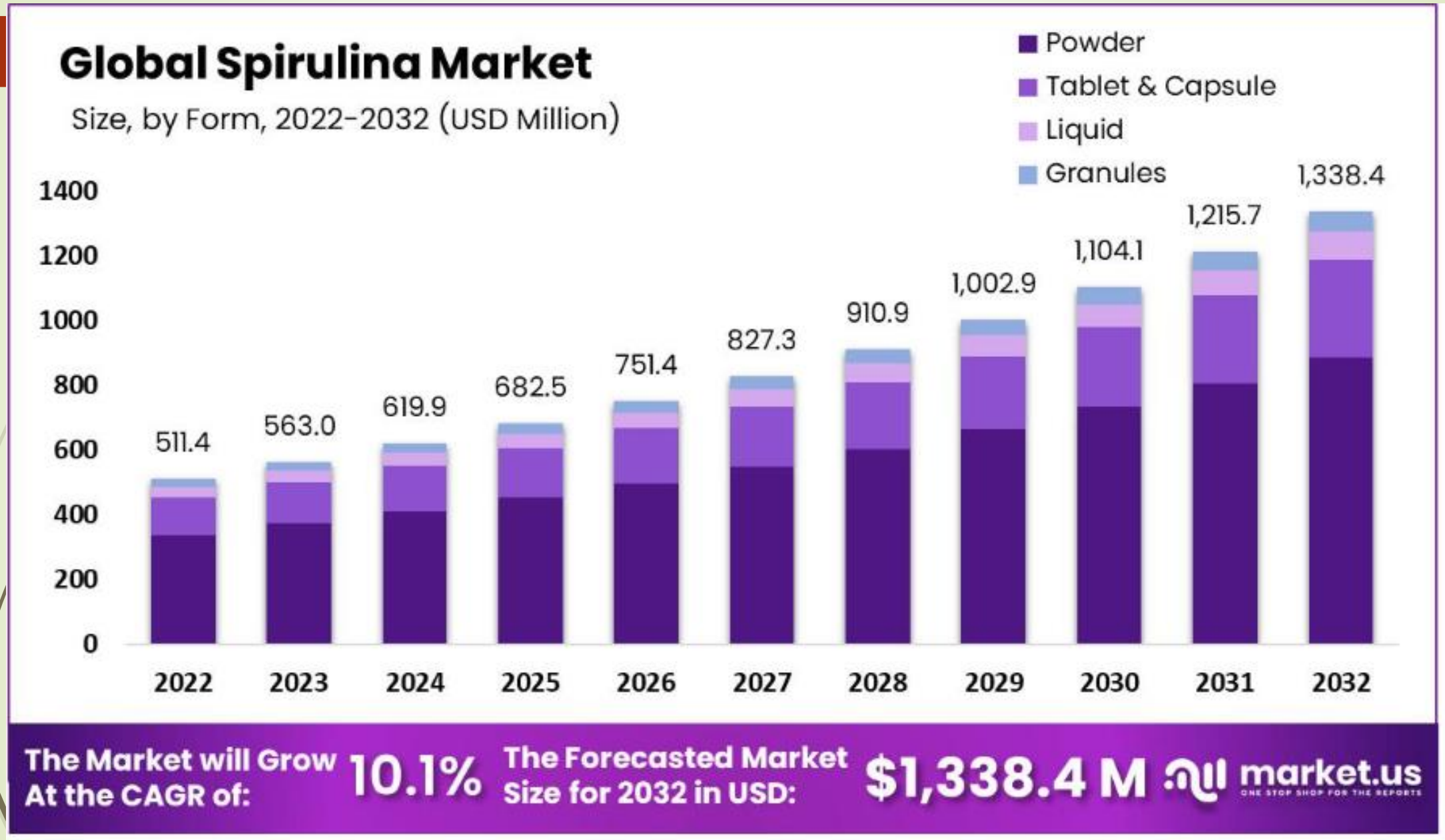
# Why rising popularity

- 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


Global Dietary Supplements Market
Size, by Type, 2023-2033 (USD Billion)
Vitamins
Botanicals
Minerals
Enzymes
350
300
250
200
150
100
50
0
156
167
178
191
204
218
234
250
268
286
306
2023
2024
2025
2026
2027
2028
2029
2030
2031
2032
2033
The Market will Grow At the CAGR of:
7%
The Forecasted Market Size for 2033 in USD:
$306B
market.us


Global Spirulina Market
Size, by Form, 2022-2032 (USD Million)
Powder
Tablet & Capsule
Liquid
Granules
1400
1200
1000
800
600
400
200
0
511.4
563.0
619.9
682.5
751.4
827.3
910.9
1,002.9
1,104.1
1,215.7
1,338.4
2022
2023
2024
2025
2026
2027
2028
2029
2030
2031
2032
The Market will Grow At the CAGR of:
10.1%
The Forecasted Market Size for 2032 in USD:
$1,338.4 M
market.us
ONE STOP SHOP FOR THE REPORTS

# Dietray supplements

- Orally ingested products that contain an ingredient that is intended to supplement the diet
- Not controlled by FDA untillfor many years
- Now every manufacturer or distributer of dietray supplements has to be in compliance with GMP requirements
- 21CFR(210,211),21CFR(110,117)

- **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

*Add the following:*

**•⟨2251⟩ ADULTERATION OF DIETARY SUPPLEMENTS WITH DRUGS AND DRUG ANALOGS**

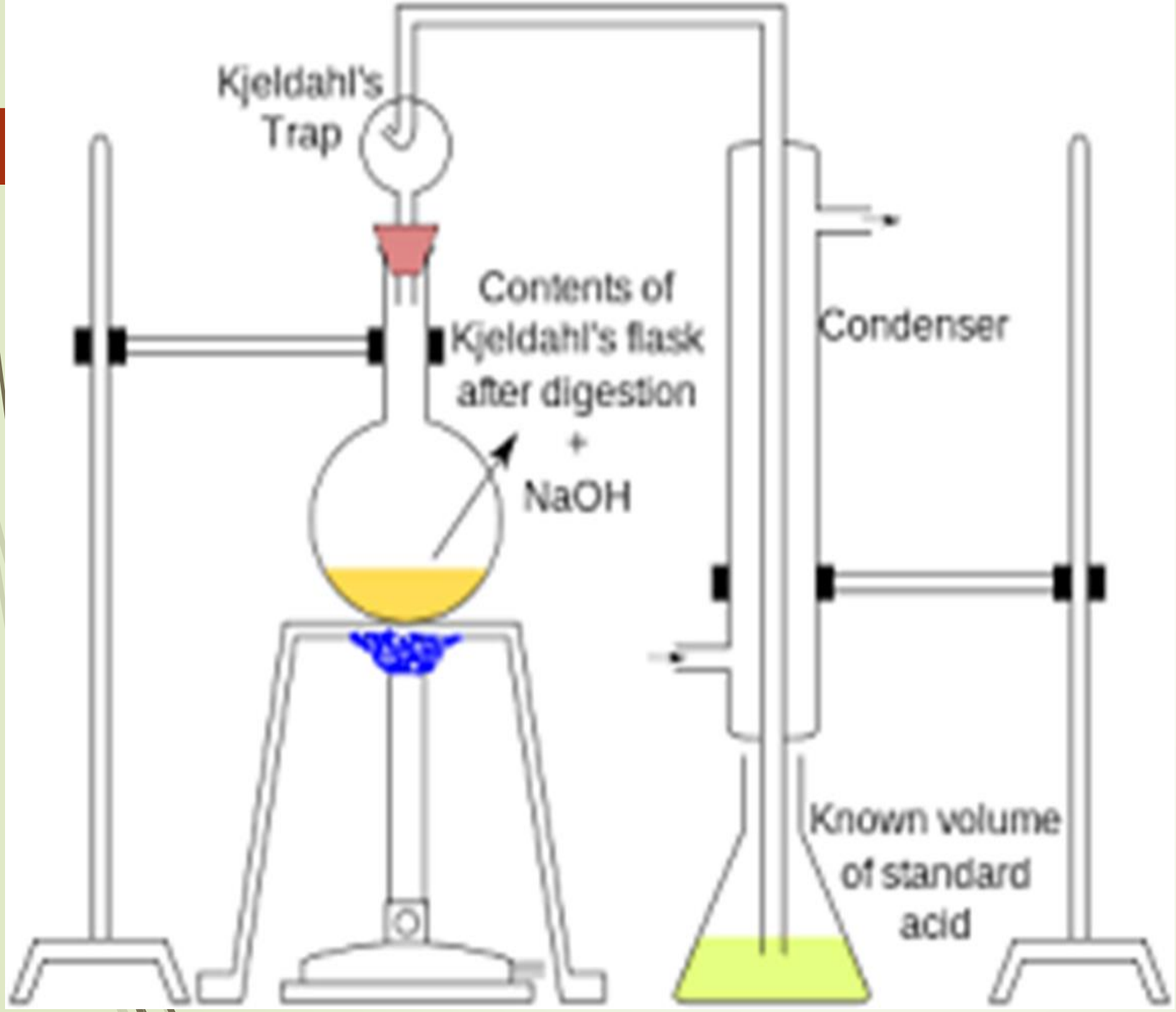
## DIETARY SUPPLEMENT ADULTERATION CATEGORIES

The following major categories of adulterated DS are recognized:

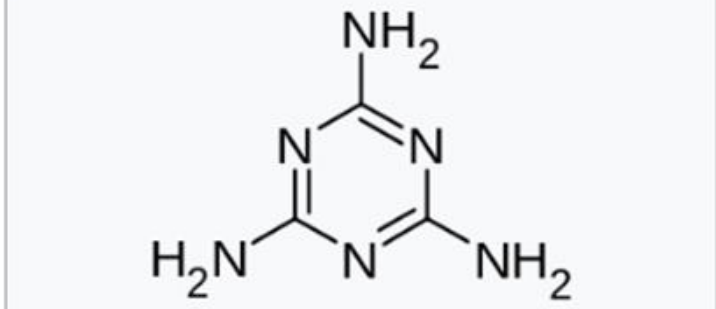
- **Sexual Enhancement:** This category is also referred to as the Erectile Dysfunction (ED) category. It encompasses a functionally coherent group of adulterants, including several approved drugs, their numerous approved and unapproved analogs, synthetic intermediates, and derivatives. Their functionality is manifested by selective inhibition of phosphodiesterase type 5 enzyme (PDE5), which hydrolyzes cyclic guanosine 3,5-monophosphate (cGMP); this group of drugs is frequently identified as PDE5 inhibitors. Screening methods for DS adulterated with ED drugs are presented in *Appendix A*.
- **Weight Loss (WL):** This category comprises a functionally and chemically diverse collection of compounds that include stimulants, laxatives, diuretics, anorexiants, and psychoactive drugs. Although stimulants constitute an important segment of WL adulterants, the oral anorexiant sibutramine dominates this category, frequently in combination with phenolphthalein, a laxative. Methods for analysis of DS adulterated with WL drugs will be addressed in Appendix B (to come).
- **Sports Performance Enhancement (SPE):** These compounds constitute the third major category of adulteration. Professional and amateur athletes are targeted with designer anabolic steroids and stimulants, which are systematically banned by the World Anti-Doping Agency. Functional and structural diversity, synthetic proclivity of the adulterators, and the generally small amounts of the infringing substances required to elicit a therapeutic effect make this category especially challenging to address. These supplements are customarily formulated in protein- and fat-rich matrices, thereby further complicating detection. For these reasons, GC- and LC-$MS^n$ techniques constitute primary analytical methodologies within this category. Analysis of DS adulterated with SPE drugs will be addressed in Appendix C (to come).

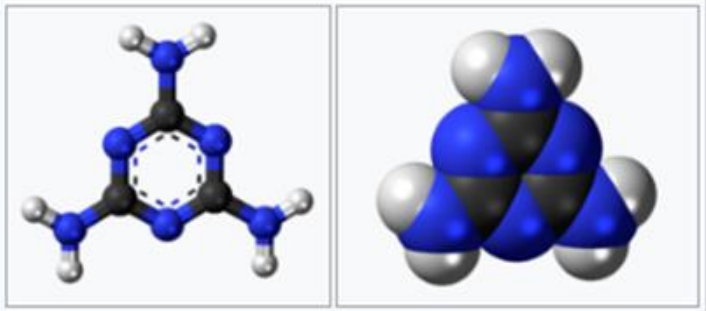
## Table 4. Mass Spectral Data for Select PDE5 Inhibitors[a]

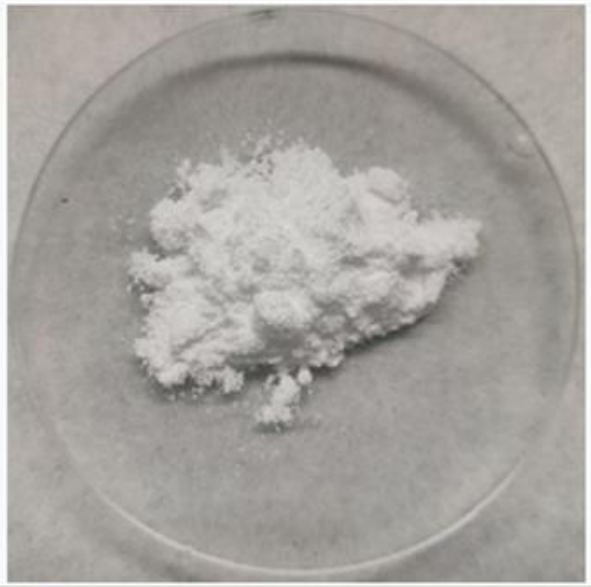
| # | Name | CAS Number | Chemical Formula | Exact Mass | $[M+H]^+$ | $[M-H]^-$ | Fragments |
|---|---|---|---|---|---|---|---|
| 1 | (−)-*trans*-Tadalafil (ent-Tadalafil) | 629652-72-8 | $C_{22}H_{19}N_3O_4$ | 389.1376 | 390 | — | 779 $[2M+H]^+$, 262, 250, 135 |
| 2 | Acetaminotadalafil | 1446144-71-3 | $C_{23}H_{20}N_4O_5$ | 432.1434 | 433 | — | 455 $[M+Na]^+$, 391, 311, 269, 250 |
| 3 | Acetil acid | — | $C_{18}H_{20}N_4O_4$ | 356.1485 | 357 | — | 329, 300, 285, 268, 256, 242, 166, 131 |
| 4 | Acetildenafil (Hongdenafil) | 831217-01-7 | $C_{25}H_{34}N_6O_3$ | 466.26924 | 467.28 | — | 449, 439, 420, 404, 396, 381, 355, 353, 339, 325, 324, 311, 297, 285, 166, 127, 111, 99, 97 |
| 5 | Acetylvardenafil | 1261351-28-3 | $C_{25}H_{34}N_6O_3$ | 466.2692 | 467 | — | 439, 396, 341, 317, 270 |
| 6 | Aildenafil (Dimethylsildenafil, Methisosildenafil) | 496835-35-9 | $C_{23}H_{32}N_6O_4S$ | 488.22057 | 489.23 | — | 432, 377, 313, 311, 283, 113, 99 |
| | | | | | — | 487.40 | 460, 310, 282 |
| 7 | Aminotadalafil | 385769-84-6 | $C_{21}H_{18}N_4O_4$ | 390.1328 | 391.14 | — | 269, 262, 241, 239, 224, 197, 169 |
| | | | | | — | 389.1248 | 362, 298, 262, 234, 233, 232 |
| 8 | Avanafil | 330784-47-9 | $C_{23}H_{26}N_7O_3Cl$ | 483.1786 | 484.186 | — | 375, 349, 221 |
| 9 | Benzylsildenafil | — | $C_{28}H_{34}N_6O_4S$ | 550.2362 | 551 | — | 377, 283 |
| 10 | Carbodenafil (Fondenafil) | 944241-52-5 | $C_{24}H_{32}N_6O_3$ | 452.2536 | 453 | — | 283 |


Kjeldahl's Trap
Contents of Kjeldahl's flask after digestion
+
NaOH
Condenser
Known volume of standard acid

**Melamine**


NH2
N
N
H2N
N
NH2





# 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

# 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

Tom Brody, Ph.D.

**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<br>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." |

Department of Health and Human Services

Public Health Service
Food and Drug Administration
5100 Paint Branch Parkway
College Park, MD 20740

February 28, 2003

WARNING LETTER
VIA OVERNIGHT DELIVERY

Mr. Ross Blechman, Chairman, President, CEO
Twinlab
150 Motor Parkway, Suite 210
Hauppauge, NY 11788

Dear Mr. Blechman:

The Food and Drug Administration (FDA) has reviewed your web site at the address: http://www.twinlab.com. This review shows what we believe to be violations of the Federal Food, Drug, and Cosmetic Act (the Act) in the labeling of your products, Diet Fuel, Ultimate Diet Fuel, and Energy Fuel. You can find the Act and the dietary supplement labeling regulations through links on FDA's Inter

Under the Act, dietary supplement labeling may include claims about the supplement's effect on the structure or a function of the human body. To be permissible under the Act, these "structure/function" claims must be truthful and may not be misleading.

The labeling of Diet Fuel, Ultimate Diet Fuel, and Energy Fuel bears structure/injunction claims that include the following:

- Energy Fuel: "provides maximum sustaining power.. ."
- Ultimate Diet Fuel: "promoting lean muscle mass," and "helps preserve lean muscle mass."
- Diet Fuel: "help tone muscle. .," and "helps preserve lean muscle mass."

Based on the scientific data available to us, we do not believe that these claims are substantiated. If these claims do not have an adequate scientific basis, they are false or misleading and cause your products to be misbranded within the meaning of Sections 403(a)(1) and 403(r)(6)(B) of the Act. Section 301(a) of the Act prohibits the introduction or delivery for introduction into interstate commerce prohibits the doing of any act with respect to a food, including a dietary supplement, if such act is done while such article is held for sale (whether or not the first sale) after shipment in interstate commerce and results in such article being misbranded. If you have data which you believe substantiates your claims, please share it with us within fifteen (15) working days of your receipt of this letter.

In addition, except for health claims authorized by FDA, claims that a dietary supplement is intended to prevent, diagnose, mitigate, treat, or cure a disease (disease claims), may cause the supplement to be an unapproved new drug. The Act prohibits the introduction of unapproved new drugs into interstate commerce. If you are making disease claims about Diet Fuel, Ultimate Diet Fuel, or Energy I to regulatory action without further notice.

This letter is not an all-inclusive review of your web site and the products that your firm markets. It is your responsibility to ensure that all products marketed by your firm comply with the Act and its implementing regulations.

The Act authorizes the seizure of illegal products and injunctions against the manufacturers and distributors of those products. You should take prompt action to correct any violations identified in this letter. Failure to do so may result in enforcement action without further notice.

Please advise this office, in writing and within fifteen working days of receipt of this letter, as to the specific steps that you have taken to correct any violations and to assure that similar violations do not occur. If corrective action cannot be completed with fifteen working days, state the reason for the delay and the time within which the corrections will be made.

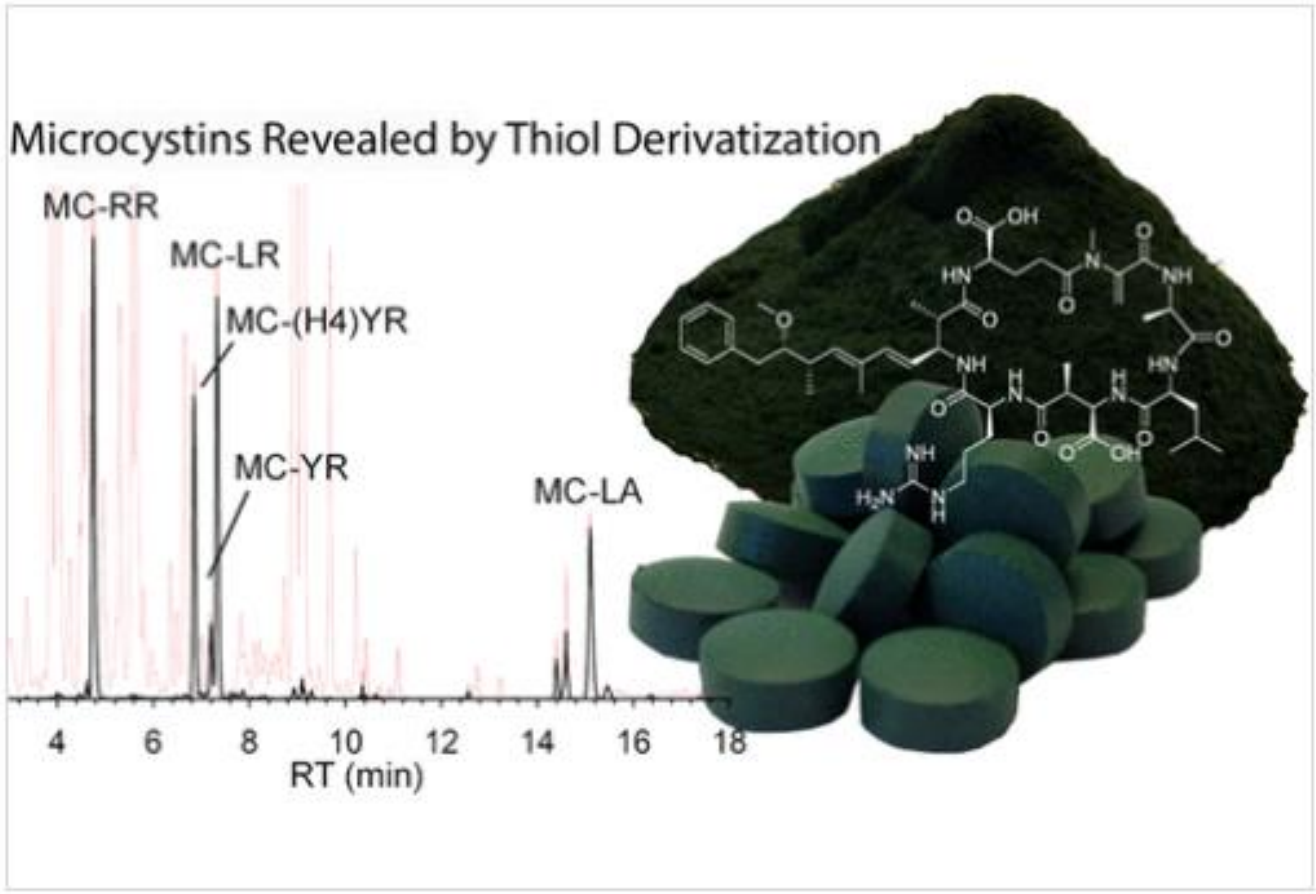
Any reply should be sent to the attention of Compliance Officer Quyen Tien at the above address.

Sincerely your,

/s/

Joseph R. Baca
Director
Office of Compliance
Center for Food Safety and Applied Nutrition

This page was posted on July 2, 2003.


Microcystins Revealed by Thiol Derivatization
MC-RR
MC-LR
MC-(H4)YR
MC-YR
MC-LA
4
6
8
10
12
14
16
18
RT (min)

# What the FDA Does About Microcystins in Dietary Supplements and Other Foods

As part of our mission to protect the public health, the FDA works to prevent dietary supplements and other foods with unsafe levels of microcystins from entering the food supply and removes them from the market when unsafe levels are detected.

**Determining the health and safety risk.** We assess the public health and safety risk of microcystins in dietary supplements and other food products on a case-by-case basis. The World Health Organization (WHO) and the U.S. Environmental Protection Agency (EPA) have established provisional guidelines for the amount of microcystins a person can be safely exposed to daily. We use this information, along with information on the amount of microcystins we find in a product and how much of the product people typically consume, to determine if the product is a potential health concern and whether it should be recalled.

**Product Description:**

Genestra brand AFA-gen capsule 15 mg Niacin/ capsule 300 mg Blue Green Algae / capsule 2 capsules, twice daily Dietary supplement 90 capsules, White 150cc HDPE Bottle with Desiccant and white cap, packed as 12 bottles / shipper case

**Product Quantity:**

4,226 bottles (1691 Canada and 2535 USA)

**Code Information:**

Lot # 6E436-0; Product Code # 07596; Expiry Date: 09/2018

**Reason for Recall:**

Microcystins level found to be above the specification limit of NMT1 ppm as per Raw Material Specification.

**Product Quantity:**

4,226 bottles (1691 Canada and 2535 USA)

**Recall Number:**

F-1756-2018

# 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
  - 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.**

General lab Equip.
Major instrument
Optional items

# 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

**Category I**—Analytical procedures for quantitation of major components of bulk drug substances or active ingredients (including preservatives) in finished pharmaceutical products.

**Category II**—Analytical procedures for determination of impurities in bulk drug substances or degradation compounds in finished pharmaceutical products. These procedures include quantitative assays and limit tests.

**Category III**—Analytical procedures for determination of performance characteristics (e.g., dissolution, drug release, etc.).

**Category IV**—Identification tests.

**Table 2. Data Elements Required for Validation**

| Analytical Performance Characteristics | Category I | Category II | | Category III | Category IV |
|---|---|---|---|---|---|
| | | Quantitative | Limit Tests | | |
| Accuracy | Yes | Yes | * | * | No |
| Precision | Yes | Yes | No | Yes | No |
| Specificity | Yes | Yes | Yes | * | Yes |
| Detection Limit | No | No | Yes | * | No |
| Quantitation Limit | No | Yes | No | * | No |
| Linearity | Yes | Yes | No | * | No |
| Range | Yes | Yes | * | * | No |

* May be required, depending on the nature of the specific test.

# 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 work sheet

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;(USP,BP,In house) ⟶

# 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.

Release
Recovery
Reprocessing
Reworking
Reject

# 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.

Raw mat
Packaging Mat.
Intermediates
Finished product

# 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.

# *USP–NF* Dietary Supplement Monographs

This section contains official monographs that are provided as a consolidated source of specifications for those articles with potential use as dietary supplements, dietary ingredients or as other components of dietary supplements found in the U.S. market. The monographs in this section are derived from monographs contained in the *USP*, including monographs found in the Dietary Supplements section of the *USP*. The presence of a monograph for an article in this compendium does not represent endorsement by USP that the article is in fact a dietary ingredient or a dietary supplement. Dietary supplements and dietary ingredients marketed in the United States must comply with current U.S. laws and regulations, some of which are provided in the Dietary Supplements Regulatory Framework section.

ess than 98.5 percent and not more than 101.5 percent of $C_6H_{14}N_4O_2$, as L-arginine, calculated on the dried basis.

reserve in well-closed containers.

11 〉— USP *L*-Arginine RS. USP *L*-Lysine Hydrochloride RS.

ption 〈 197K 〉.

between +26.3° and +27.7°.

n 6 N hydrochloric acid.

ry it at 105° for 3 hours: it loses not more than 0.5% of its weight.

: not more than 0.3%.

ortion shows no more chloride than corresponds to 0.70 mL of 0.020 N hydrochloric acid (0.05%).

rtion shows no more sulfate than corresponds to 0.30 mL of 0.020 N sulfuric acid (0.03%).

1 〉: 0.0015%.

chromatographic silica gel mixture.

ccurately weighed quantity of Arginine in 2 N hydrochloric acid to obtain a solution having a concentration of 10 mg per mL. Apply 5 µL.

an accurately weighed quantity of USP L-Arginine RS in 0.1 N hydrochloric acid to obtain a solution having a known concentration of about 0.05 mg per mL. Apply 5 µL. [NOTE—This solution has a concentration equivalent to about 0.5% of that of the *Test solution*.]

Prepare a solution in 0.1 N hydrochloric acid containing 0.4 mg each of USP *L-Arginine RS* and USP *L-Lysine Hydrochloride RS* per mL. Apply 5 µL.

g of ninhydrin in 100 mL of a mixture of butyl alcohol and 2 N acetic acid (95:5).

Prepare a mixture of isopropyl alcohol and ammonium hydroxide (70:30).

cted for *Thin-Layer Chromatography* under *Chromatography* 〈 621 〉. Dry the plate between 100° and 105° until the ammonia disappears completely. Spray with *Spray reagent*, and heat between 100° and 105° for about 15 minutes. Examine the plate under white light. The chromatogram obtaine
l spots. Any secondary spot in the chromatogram obtained from the *Test solution* is not larger or more intense than the principal spot in the chromatogram obtained from the *Standard solution*: not more than 0.5% of any individual impurity is found; and not more than 2.0% of total impurities is found.

*Method I* 〈 467 〉: meets the requirements.

meets the requirements.

g of Arginine, accurately weighed, to a 125-mL flask, dissolve in a mixture of 3 mL of formic acid and 50 mL of glacial acetic acid, and titrate with 0.1 N perchloric acid VS, determining the endpoint potentiometrically. Perform a blank determination, and make any necessary correction. Each mL of 0.

*f Liaison* : Lawrence Evans, III, Ph.D., Scientist

» Arginine Tablets contain not less than 90.0 percent and not more than 110.0 percent of the labeled amount of arginine or arginine hydrochloride in an amount equivalent to $C_6H_{14}N_4O_2$.

**Packaging and storage**— Preserve in tight, light-resistant containers.

**Labeling**— The label states the form of the arginine that is used and the equivalent amount of $C_6H_{14}N_4O_2$.

**USP Reference standards** ⟨ 11 ⟩ — *USP L-Arginine RS*. *USP Arginine Hydrochloride RS*.

**Identification—**

**A**: *Thin-Layer Chromatographic Identification Test* ⟨ 201 ⟩ —

*Test solution*— Transfer a portion of finely powdered Tablets, equivalent to about 150 mg of arginine, to a 100-mL volumetric flask. Dissolve in water, and then sonicate for 15 minutes. Dilute with water to volume, mix, and filter.

*Standard solution*— Dissolve an accurately weighed quantity of *USP L-Arginine RS* or *USP Arginine Hydrochloride RS* in water to obtain a solution having a known concentration of about 1.5 mg per mL.

*Application volume*: 5 µL.

*Developing solvent system*— Prepare a mixture of isopropyl alcohol and ammonium hydroxide (70:30).

*Spray reagent*— Dissolve 0.2 g of ninhydrin in 100 mL of a mixture of butyl alcohol and 2 N acetic acid (95:5).

*Procedure*— Proceed as directed for *Thin-Layer Chromatography* under *Chromatography* ⟨ 621 ⟩. Dry the plate between 100° and 105° until the ammonia disappears completely. Spray with *Spray reagent*, and heat between 100° and 105° for about 15 minutes. Examine the plate under white light. The principal spot from the *Test solution* corresponds in appearance and $R_F$ value to that of the *Standard Solution*.

**B**: The retention time of the major peak in the chromatogram of the *Assay preparation* corresponds to that in the chromatogram of the *Standard preparation*, as obtained in the *Assay*.

**Dissolution** ⟨ 2040 ⟩ —

*Medium*: 0.1 N hydrochloric acid; 900 mL.

*Apparatus 2*: 75 rpm.

*Time*: 60 minutes.

*Procedure*— Determine the amount of $C_6H_{14}N_4O_2$ dissolved by employing the procedure set forth in the *Assay*, making any necessary modifications.

*Tolerances*— Not less than 75% of the labeled amount of $C_6H_{14}N_4O_2$ is dissolved in 60 minutes.

**Weight variation** ⟨ 2091 ⟩ : meet the requirements.

**Assay—**

*Phosphate buffer, 2.3 mM 1-Octanesulfonic acid sodium salt solution, Mobile phase, Standard preparation*, and *Chromatographic system*— Proceed as directed in the *Assay* under *Arginine Capsules*.

*Assay preparation*— Weigh and finely powder not fewer than 20 Tablets. Transfer an accurately weighed portion of the powder, equivalent to about 150 mg of arginine, into a 100-mL volumetric flask. Add about 80 mL of *Phosphate buffer*, and then sonicate for 15 minutes. Dilute with *Phosphate buffer* to volume, and mix.

*Procedure*— Separately inject equal volumes (about 10 µL) of the *Standard preparation* and the *Assay preparation* into the chromatograph, record the chromatograms, and measure the responses for the major peaks. Calculate the quantity, in mg, of arginine ($C_6H_{14}N_4O_2$) in the portion of Tablets taken by the

| | | | |
|---|---|---|---|
| **Material:** PE Plastic bags | **Reference:** USP 33 & IH | **Code No.:** | **Precautions:** |
| **Sampling Method:** SOP … | **Supplier:** | **Storage conditions:** | **Retest date:** |

| **Test** | **Specifications** | **Results** | **Method (SOP)** |
|---|---|---|---|
| **Dimensions** | | | In house |
| **Heavy Metals** | 1 ppm in extract | LT 1 ppm | USP 33 |
| **Nonvolatile Residue** | NMT 15 mg | 12.1 mg | USP 33 |
| **Residue on Ignition** | NMT 5 mg | 3.2 mg | USP 33 |
| **Buffering Capacity** | NMT 10.0 mL | 6.3 mL | USP 33 |

| Name:<br>Code No:<br>Pharmacopoeia:<br>Sampling Method: | Packaging size & materials:<br>Manufacturer/Supplier:<br>Shelf life:<br>Storage condition & Precaution: Below ---°C | |
|---|---|---|
| Tests | Methods | Specifications/ Limits |
| Description | USP xx | |
| - Color | " | |
| - Odor | " | |
| - Solubility | In-house | |
| - Clarity of solution | USP xx | |
| Identification | " | |
| Water content | " | |
| Residue on ignition | " | |
| pH (1 in 20) | " | |
| Specific Rotation | " | |
| Heavy Metals | " | |
| Chloride | " | |
| Crystallinity | In-house | |
| Particle size distribution | In-house | |
| Tapped density | In-house | |
| Assay | USP xx | |

## Quality control requirements for oral solid dosage forms (Tablets, Capsules Powders)

1.Evaluation for visual appearance, labelling, odour, taste, texture, hardness and friability.

**2.Moisture content:** Limits are given in official compendia.

**3.Standards and tests of identity:** designed to demonstrate clearly that the specimens examined contain the active ingredient(s) they purport to contain.

**4.Standards and tests of homogeneity:** Apply test for uniformity of weight.

**5.Standards and test for purity:** for potentially harmful degradation compounds that may be generated during production and storage of dosage forms and for contaminants whose presence may indicate deviation from GMP.

**6-Standards and assays for the active ingredient(s) and for degradation products:** It provides quantitatively permitted range per tablet or capsule of average weight.

**7-Uniformity of content:** It involves individual analysis of for a given number of dosage forms to assess possible variation. This test is particularly more important where the declared quantity of active ingredient in a single tablet is less than 5 mg and in case of sugar-coated tablets 10 mg or less.

**8-Standards and tests of performance:** Designed to provide some assurance that the dosage form will release its active ingredient as intended. Dissolution rate tests for poorly soluble drugs, potent drugs and cases with dissolution problems; disintegration test to supplement dissolution rate tests.

**9-Stability indicating tests:** This is to take into account the deterioration in activity or strength of the drug product that may occur because of degradation of the active ingredient in the dosage form as well as aspects of physical instability of the product e.g. development of undue colour or colour instability. Storage conditions**.**

**Liquid Dosage Forms Evaluation**

General Evaluation Tests

**1. Organoleptic properties**

The color, odor, taste, clarity and other physical characters of the product are noted by visual examination.

**2. Specific gravity**

It can be determined with a hydrometer.

**3. Rheological studies**

The viscosity can be determined with a viscometer.

**4. pH determination**

The pH of the liquid dosage form can be determined with a pH meter.

**5. Uniformity of content**

Assays of the active ingredients must be carried out to ensure that the dose contains the labeled amount of drug. It is determined by chemical or spectrophotometric analysis.

# Special Tests for Suspensions

1. Sedimentation volume (F)
2. Redispersibility
3. Particle size changes

## Special Tests for Emulsions

1. Dilution test This test is used to identify the emulsion type.
2. Creaming, sedimentation and coalescence In creaming, the dispersed globules move upward and form a thick layer
3. Stability to freeze-thaw cycling The emulsion is exposed to freeze-thaw cycling and visually examined for any creaming or coalescence. In freeze-thaw cycling, the emulsion is stored in an incubator at 500 C for 48 hours and then transferred to a freezer at -5 0 C for 48 hours.

Special tests for Semi-Solid

a. Drug contents determination.
b. Assay of active ingredients.
c. Uniformity and homogeneity test.
d. Viscosity and specific gravity test.

# 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: 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

# Spirulina

## DEFINITION

Spirulina consists of the dried, whole, blue-green microalgae *Arthrospira platensis* (Nordstedt) Gomont, synonym *Spirulina platensis* (Nordstedt) Geitler; *Arthrospira maxima* Setchell & Gardner, synonym *Spirulina maxima* (Setchell & Gardner) Geitler in Rabenhorst (illegitimate); or *Arthrospira fusiformis* (Voronichin) J. Komarek & J.W.G. Lund, synonym *Spirulina*

# 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.