The United States
Pharmacopeial Convention, Inc.

June 3, 1997

Dockets Management Branch
HFA 305, Room 1-23
Food and Drug Administration
12420 Parklawn Drive
Rockville, MD 20857

Ref: **Docket No. 96N-0417** - Current Good Manufacturing Practice in Manufacturing, Packing or Holding Dietary Supplements.
Federal Register, dated February 6, 1997

Dear Sirs:

This responds to the Advance Notice of Proposed Rulemaking regarding Current Good Manufacturing Practice in Manufacturing, Packing or Holding Dietary Supplements that appeared in the *Federal Register* dated February 6,1997, Volume 62, Number 25.

The United States Pharmacopeia (USP) developed and published a General Chapter entitled, <2750> *Manufacturing Practices for Nutritional Supplements*, in 1993 (copy attached). This chapter was based on a submission from the nutritional supplements industry represented by the Council for Responsible Nutrition in addition to comments received by participants at two USP Open Conferences and through comments received via USP's public notice and comment process for standards development. Proposals were published in the January-February 1992 and May-June 1992 issues of the *Pharmacopeial Forum*. It is our understanding that provisions of the USP chapter are currently followed by the nutritional supplements industry.

After a careful review of the proposed regulations, it is our opinion that they could be strengthened by the addition of our suggested text, which is given in the attached pages. The suggested additions take into account the manufacturing technology involved in the manufacture of dietary supplements. It is our desire to harmonize USP General Chapter <2750> *Manufacturing Practices for Nutritional Supplements* with the FDA's Good Manufacturing Practices for Dietary Supplements as much as possible.

96N-0417

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Considering that the USP General Chapter <2750> was developed prior to the Dietary Supplement Health and Education Act (DSHEA) of 1994, we recognize that the USP chapter may not adequately cover the GMP requirements applicable to the botanical industry. The USP Committee of Revision is considering further review of the General Chapter to address the GMP requirements applicable to the botanical industry. As communicated earlier we are willing to work with the agency in the interest of harmonizing GMP requirements.

Sincerely yours,

Jerome A. Halperin
Executive Vice President-CEO

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Enclosures

LABORATORY CONTROLS

A quality control unit should be established that has the responsibility and authority to approve or reject all components, product containers, closures, in-process materials, packaging material, labeling, and finished nutritional products, and the authority to review production records to ensure that no errors have occurred or, if errors have occurred that they have been fully investigated. The quality control unit should be responsible for approving or rejecting products manufactured, processed, packed, or held under contract by another company.

The establishment of any specifications, standards, sampling plans, test procedures, or other laboratory control mechanisms required by this general chapter, including any change in such specifications, standards, sampling plans, test procedures, or other laboratory control mechanisms, should be drafted by the appropriate organizational unit and reviewed and approved by the quality control unit. The requirements in this section should be followed and documented at the time of performance.

Laboratory control includes the establishment of scientifically sound and appropriate specifications, standards, sampling plans, and test procedures designed to assure that components, product containers, closures, in-process materials, labeling, and finished products conform to appropriate standards of identity, strength, quality, and purity.

These controls include the following:

- Determination of conformance to appropriate **written specifications** for the acceptance of each shipment of components, product containers, closures, and labeling used in the manufacture of nutritional products. (The specifications include a description of the sampling and testing procedures used. Samples should be representative and adequately identified. Such procedures also require appropriate retesting of any component, product container, or closure that is subject to deterioration.) Based upon adequate process validation, in-process controls, and statistical confidence, a skip-lot sampling plan is an alternative to testing every batch.

- Determination of conformance to **written specifications** and a description of sampling and testing procedures for in-process materials. (Such samples should be representative and properly identified.)

- Determination of conformance to **written descriptions** of sampling procedures and appropriate specifications for finished products. (Such samples should be representative and properly identified.)

- The calibration of instruments, at suitable intervals in accordance with an established **written program** containing specific directions, schedules, limits for accuracy and precision, and provisions for remedial action in the event accuracy and/or precision limits are not met. Instruments not meeting established specifications should not be used until repaired.

Testing and Release for Distribution

There should be appropriate laboratory determination of satisfactory conformance to specifications for the finished product, including the identity and strength prior to release.

Based upon adequate process validation, in-process controls, and statistical confidence, a skip-lot or composite sampling plan is an alternative to testing every batch.

There should be appropriate laboratory testing, as necessary, of each batch of nutritional product required to be free of objectionable microorganisms. The accuracy, linearity, sensitivity, specificity, and reproducibility of test methods employed by the firm, when they differ from compendial methods, should be established and documented.

There should be a written protocol designed to assess the stability characteristics of nutritional products. The results of such testing should be used in determining appropriate storage conditions and expiration dates. This procedure should include the following:

— Sample size and test intervals based on statistical criteria for each attribute should be examined to ensure valid estimates of stability.

— Storage conditions for samples retained for testing.

— Reliable, meaningful, and specific test methods should be used.

— The nutritional product should be tested in the same type of container-closure system as that in which the nutritional product is marked.

An adequate number of batches of each nutritional product should be tested to determine an appropriate expiration date, and a record of these data should be maintained. Accelerated studies combined with basic stability information on the components, nutritional products, and container-closure systems may be used to support tentative expiration dates provided full shelf-life studies are not available. Where data from accelerated studies are used to project a tentative expiration date that is beyond a date supported by actual shelf-life studies, stability studies should be conducted, including nutritional product testing at appropriate intervals, until the tentative expiration date is verified or the appropriate expiration date is determined.

Written procedures should describe any sampling and testing plans, which should include the method of sampling and the number of units per batch to be tested.

Products failing to meet established standards or specification and any other relevant quality control criteria should be rejected.

Reprocessing may be performed. Prior to acceptance and use, reprocessed material must meet appropriate standards, specifications, and any other relevant criteria.

Laboratory Records

Laboratory records should include complete data derived from all tests necessary to ensure compliance with established specifications and standards, including examinations and assays, as follows:

A description of the sample received for testing with identification of source (that is, location from where sample was obtained), quantity, lot number or other distinctive code, and date sample was taken.

A statement of each method used in the testing of the sample.

A statement of the weight or measure of sample used for each test, where appropriate.

A complete record of all data secured in the course of each test, including all graphs, charts, and spectra from laboratory instrumentation, properly identified to show the specific component, product container, closure, in-process material, or finished product, and lot tested.

A record of all calculations performed in connection with the test, including units of measure, conversion factors, and equivalency factors.

A statement of the results of tests and how the results compare with established standards of identity, strength, quality, and purity for the component, product container, closure, in-process material, or finished product tested.

The initials or signature of the person who performs each test and the date(s) the tests were performed.

Complete records should be maintained of any modification of an established method employed in testing. Such records should include the reason for the modification and data to verify that the modification produced results that are at least as accurate and reliable for the material being tested as the established method.

Complete records should be maintained of any testing and standardization of laboratory reference standards, reagents, and standard solutions, the periodic calibration of laboratory instruments, and all stability testing performed.

Expiration Dating

Expiration dates should be related to any storage conditions stated on the labeling.

Receipt and Storage of Untested Components, Product Containers, and Closures.

Upon receipt and before acceptance, each container or grouping of containers of components, product containers, and closures should be examined visually for appropriate labeling as to contents, container damage or broken seals, and for contamination. They are then stored under quarantine until they have been tested or examined, as appropriate, and released.

Testing and Approval or Rejection

Each lot components, product containers, and closures should be sampled, tested, or examined, as appropriate, and released for use by the quality control unit.

Representative samples should be collected for testing or examination. The number of containers sampled, and the amount of material taken from each container, should be based upon appropriate criteria such as statistical criteria for component variability, confidence levels, and degree of precision desired, the past quality history of the supplier, and the quantity needed for analysis and reserve where required.

Based upon adequate process validation, in-process controls and statistical confidence, a skip-lot sampling plan is an alternative to testing every batch.

- These containers should be identified so that the following information can be determined: name of the material sampled, the lot number, the container from which the sample was taken, the date on which the sample was taken, and the name of the person who collected the sample.

- Each lot of a component, product container, or closure that is liable to microbiological contamination that is objectionable in view of its intended use should be subjected to microbiological tests before use. Skip-lot examination should apply in such cases.

- Any lot of component, product container, or closures that meets the appropriate **written specifications** of identity, strength, quality, and purity and related tests may be approved and released for use. Any lot of such material that does not meet such specifications should be rejected.

Sampling and Testing of In-Process Materials and Nutritional Products

To ensure batch uniformity and integrity of nutritional products, **written procedures** should be established and followed that describe the in-process controls and tests or examinations to be conducted on appropriate samples of in-process materials. Based upon process validation, in-process controls and statistical confidence, a skip-lot sampling plan is an alternative to testing

every batch. Control procedures should be established to monitor the output of those manufacturing processes that may be responsible for causing variability in the characteristics of in-process material and the finished product. Such control procedures may include, but are not limited to the following, where appropriate:

- Friability/hardness test
- Weight variation
- Clarity, completeness, or pH of solutions.

In-process specifications for such characteristics should be consistent with finished product specifications. Examination and testing of samples should ensure that the in-process material and nutritional product conform to the established specifications.

In-process materials should be tested for identity, strength, quality, and purity as appropriate, and approved or rejected by the quality control unit during the production process, e.g., at commencement or completion of significant phases or after storage for long periods.

LABELING AND PACKAGING

Materials Examination and Usage Criteria

Labeling and packaging materials should be representatively sampled and examined or tested upon receipt and before use in packaging or labeling of a product.

Containers and closures should be tested for conformance with all appropriate **written procedures**. However, certificate of testing may be accepted from the supplier, provided that at least a visual identification is conducted on such containers/closures by the manufacturer.

Any labeling or packaging materials meeting appropriate **written specifications** may be approved and released for use. Those that do no meet such specifications should be rejected to prevent their use in operations for which they are unsuitable.

A record should be kept of each shipment received of each different labeling and packaging material which indicates receipt, date of examination or testing, and whether accepted or rejected.

Gang printing of labeling to be used for different products or different strengths of the same product (or labeling of the same size and identical or similar format and/or color schemes) should be minimized. If gang printing is employed, packaging and labeling operations should provide for special control procedures, taking into consideration sheet layout, stacking, cutting, and handling during and after printing.

- Examination of packaging and labeling materials for suitability and correctness before packaging operations; and documentation of such examination in the batch production record.

Labeling Issuance

Strict control should be exercised over labeling issued for use in product labeling operations.

Labeling materials issued for a batch should be carefully examined for identity and conformity to the labeling specified in the master or batch production records.

- Inspection of the packaging and labeling facilities immediately before use to ensure that all products have been removed from previous operations. Inspection should also be made to ensure that packaging and labeling materials not suitable for subsequent operations have been removed. Results of the inspection should be documented in the batch production records.

Printing devices on, or associated with, manufacturing lines used to imprint labeling upon the product unit label or case should be monitored to ensure that all imprinting conforms to the print specified in the batch production record.

All excess labeling bearing lot or control numbers should be destroyed and documented.

Returned labeling should be maintained and sorted in a manner to prevent mixups and provide proper identification.

Procedures should be utilized to reconcile the quantities of labeling issued, used, and returned, and should require evaluation of discrepancies found. If discrepancies are found between the quantity of the product finished and the quantity of labeling issued and are outside preset limits based on historical operating data, such discrepancies should be investigated.

LABELING

Each retail package of a nutritional product covered by this section should bear a statement that is prominently placed so that consumers are alerted to the specific tamper-resistant feature of the package. The labeling statement should be so placed that it will be unaffected if the tamper-resistant feature of the packaging is breached or missing. If the tamper-resistant feature chosen to meet the requirement above is one that uses an identifying characteristic, that characteristic should be referred to in the labeling statement. For example, the labeling statement on a bottle with a shrink bank could say "For your protection, this bottle has an imprinted seal around the neck."

the capsules by means of a suitable clean, dry cutting instrument such as scissors or a sharp open blade, and remove the contents by washing with a suitable solvent. Allow the occluded solvent to evaporate from the shells at room temperature over a period of about 30 minutes, taking precautions to avoid uptake or loss of moisture. Weigh the individual shells, and calculate the net contents. The requirements are as stated under *Hard Capsules*.

TABLETS

Tablets conform to the weight tablets given in the accompanying table.

Weigh individually 20 whole tablets, and calculate the average weight. The requirements are met if the weights of not more than 2 of the tablets differ from the average weight by more than the percentage listed and no tablet differs in weight by more than double that percentage.

Weight Variation Tolerances for Tablets.

Average Weight of Tablet (uncoated or with coating removed), mg	Percentage Difference
130 or less	10
From 130 through 324	7.5
More than 324	5

For Coated Tablets (Other Than Film-Coated Tablets)

If the coated tablets do not meet the requirements of the test, place 20 tablets in a beaker of water at 37°, and swirl gently for not more than 5 minutes. Examine the cores for evidence of disintegration and repeat the procedure for a shorter time if disintegration has begun. Dry the cores at 50° for 30 minutes. Accurately weigh 20 individual tablet cores, and calculate the average weight.

The requirements are met if the weights of not more than 2 of the tablets differ from the average weight by more than the percentage listed in the accompanying table and no tablet differs in weight by more than double that percentage.

⟨2750⟩ MANUFACTURING PRACTICES FOR NUTRITIONAL SUPPLEMENTS

As is indicated in the *General Notices* under *Significant Figures and Tolerances*, tolerances are based upon the consideration that the article is produced under recognized principles of good manufacturing practice. Many of the principles in this general information chapter are basic in that they apply equally to various types of products and levels of technology, and that they are derived from the current good manufacturing practices for drugs. However, the practical application of these principles to nutritional products may be different.

The principles set forth in this general chapter contain recommended minimum current good manufacturing practices for the methods to be used in, and the facilities and controls to be used for, the manufacture of a nutritional supplement to assure that such a product meets the requirements of safety, and has the identity and strength and meets the quality and purity characteristics that it is represented to possess.

A glossary of terms used in this general chapter is presented at the end.

ORGANIZATION AND PERSONNEL

Responsibilities of Quality Control Unit

A quality control unit should be established that has the responsibility and authority to approve or reject all components, product containers, closures, in-process materials, packaging material, labeling, and finished nutritional products, and the authority to review production records to ensure that no errors have occurred or, if errors have occurred, that they have been fully investigated. The quality control unit should be responsible for approving or rejecting products manufactured, processed, packed, or held under contract by another company.

Adequate laboratory facilities for the testing and approval (or rejection) of components, product containers, closures, packaging materials, in-process materials, and nutritional products should be available to the quality control unit.

The quality control unit should have the responsibility for approving or rejecting all procedures or specifications that impact on the identity, strength, quality, and purity of the nutritional product. All responsibilities and procedures applicable to the quality control unit should be in writing.

Personnel Qualifications

Each person engaged in the manufacture of a nutritional product should have the proper education, training, and experience (or any combination thereof) needed to perform the assigned functions. Training should be in the particular operation(s) that the employee performs and should be based on current good manufacturing practices as they relate to the employee's functions.

Each person responsible for supervising the manufacture of a nutritional product should have the proper education, training, and experience (or any combination thereof) to perform assigned functions in such a manner as to provide assurance that the product has the safety, identity, strength, quality, and purity that it is represented to possess.

An adequate number of qualified personnel to perform and supervise the manufacture of each nutritional product should be provided.

Personnel Responsibilities

Personnel engaged in the manufacture of a nutritional product should wear clean clothing appropriate for the duties they perform. Protective apparel, such as head and hand covering, should be worn, as necessary, to protect products from contamination.

All personnel should practice good sanitation and health habits. Anyone having an apparent illness or open lesion (shown by medical examination or supervisory observation) that may adversely affect the safety or quality of products should be excluded from direct contact with components, product containers, closures, in-process materials, and finished products until the condition is corrected or determined by competent medical personnel not to jeopardize the safety or quality of these products. All personnel should report to supervisory personnel any health conditions that may have an adverse effect on such products.

Personnel working in direct contact with ingredients, in-process materials, or finished products should wash their hands thoroughly before starting work, after an absence from the work station, and at other times when the hands have become soiled or contaminated. These persons should also remove all insecure jewelry and remove from hands any jewelry that cannot be sanitized properly.

If gloves are used, personnel should maintain them in an intact, clean, and sanitary condition. Such gloves should be of an impermeable material except where their usage would be inappropriate or incompatible with the work involved.

Personnel should not store clothing or other personal belongings, eat or drink beverages, or use tobacco in any form in any manufacturing area, or in areas where products or ingredients are exposed, or in areas used for washing equipment or utensils.

All personnel should take any other necessary precaution to prevent contamination of products with microorganisms or foreign substances including, but not limited to, perspiration, hair, cosmetics, tobacco, chemicals, and medicants.

BUILDINGS AND FACILITIES

Any building or buildings used in the manufacture of a nutritional product should be of suitable size, construction, and location to facilitate cleaning, maintenance, and proper operations. It should have adequate space for the orderly placement of equipment and materials to prevent mixups between different components, product containers, closures, labeling, in-process materials, or finished products, and to prevent contamination. The flow of components, product containers, closures, labeling, in-

process materials, and products through the building or buildings should be designed to prevent contamination.

Operations should be performed within specifically defined areas of adequate size to prevent contamination or mixups. These separate or defined areas are as follows:

—An area for the receipt, identification, storage, and withholding from use of components, product containers, closures, and labeling, pending the appropriate sampling, testing, or examination by the quality control unit before release for manufacturing or packaging.
—An area for the storage of released components, product containers, closures, and labeling.
—An area for storage of in-process materials.
—An area for manufacturing and processing operations.
—An area for packaging and labeling operations.
—An area for control and laboratory operations.

Any building used in the manufacture of a nutritional product shall be maintained in a good state of repair.

Lighting

Adequate lighting should be provided in all areas and should not expose bulk or finished product to adulteration or contamination.

Ventilation, Air Filtration, Air Heating and Cooling

Adequate ventilation should be provided, as well as equipment for adequate control over microorganisms, dust, humidity, and temperature when appropriate for the manufacture of a nutritional product.

Plumbing

Potable water should be supplied in a plumbing system free of defects that could contribute contamination to any nutritional product. Potable water should meet the standards prescribed in the Environmental Protection Agency's Primary Drinking Water Regulations (40 CFR Part 141). Water not meeting such standards should not be permitted in the potable water system for *Purified Water*. If potable water is to be used as a component, it should be further purified to satisfy compendial requirements.

Drains should be of adequate size and, where connected directly to a sewer, should have an air break or other mechanical device to prevent back-siphonage.

Sewage and Refuse

Sewage, trash, and other refuse in and from the building and immediate premises should be disposed of in a safe and sanitary manner.

Washing and Toilet Facilities

Adequate washing facilities should be provided, including hot and cold water, soap or detergent, air driers or single-service towels, and clean toilet facilities easily accessible to working areas.

Sanitation

Any building used in the manufacture of a nutritional product should be maintained in a clean and sanitary condition. It should be free of infestation by rodents, birds, insects, and other vermin. Trash and organic waste matter shall be held and disposed of in a timely and sanitary manner.

Written procedures assigning responsibility for sanitation and describing in sufficient detail the cleaning schedules, methods, equipment, and materials to be used in cleaning the building and facilities are necessary.

Written procedures are also necessary for use of suitable rodenticides, insecticides, fungicides, fumigating agents, and cleaning and sanitizing agents. These procedures should be designed to prevent the contamination of equipment, components, product containers, closures, packaging, labeling materials, or products. Rodenticides, insecticides, and fungicides should be registered and used in accordance with the Federal Insecticide, Fungicide, and Rodenticide Act.

Sanitation procedures should apply to work performed by contractors or temporary employees as well as work performed by full-time employees during the ordinary course of operations.

EQUIPMENT

Equipment used in the manufacture of a nutritional product should be of appropriate design, adequate size, and suitably located to facilitate operations for its intended use and for its cleaning and maintenance.

Construction

All equipment should be constructed so that surfaces that contact components, in-process materials, or finished products are not reactive, additive, or absorptive so as to alter the safety, identity, strength, quality, or purity of the product beyond the established requirements.

Any substances required for operations such as lubricants or coolants should not come into contact with components, product containers, closures, in-process materials, or finished products that would alter the safety, identity, strength, quality, or purity of the product beyond the established requirements.

Cleaning and Maintenance

Equipment and utensils should be cleaned, maintained, and sanitized at appropriate intervals to prevent malfunctions or contamination that would alter the safety, identity, strength, quality, or purity of the product beyond the established requirements.

Written procedures for cleaning and maintaining equipment, including utensils, used in the manufacture of a product should be established and followed. These procedures should include, but are not necessarily limited to, the following:

—Assignment of responsibility for cleaning and maintaining equipment.
—Maintenance and cleaning schedules, including, where appropriate, sanitizing schedules.
—A description in sufficient detail of the methods, equipment, and materials used in cleaning and maintenance operations, and the methods of disassembling and reassembling equipment, as necessary, to assure proper cleaning and maintenance.
—Removal or obliteration of previous batch identification.
—Identification and protection of clean equipment from contamination prior to use.
—Inspection of equipment for cleanliness immediately before use.

COMPONENTS, PRODUCT CONTAINERS, AND CLOSURES

Written procedures describing in sufficient detail the receipt, identification, storage, handling, sampling, testing, and approval or rejection of components, product containers, and closures should be provided.

Components, product containers, and closures at all times should be handled and stored in a manner to prevent contamination.

Bagged or boxed components of product containers or closures should be stored off the floor and suitably spaced to permit cleaning and inspection.

Each lot should be appropriately identified as to its status (i.e., quarantined, approved, or rejected).

Receipt and Storage of Untested Components, Product Containers, and Closures

Upon receipt and before acceptance, each container or grouping of containers of components, product containers, and closures should be examined visually for appropriate labeling as to contents, container damage, or broken seals, and for contamination. They are then stored under quarantine until they have been tested or examined, as appropriate, and released.

Testing and Approval or Rejection

Each lot of components, product containers, and closures should be sampled, tested, or examined, as appropriate, and released for use by the quality control unit. Based upon adequate process validation, in-process controls and statistical confidence, a skip-lot sampling plan is an alternative to testing every batch.

Representative samples should be collected for testing or examination. The number of containers sampled, and the amount of material taken from each container, should be based upon appropriate criteria such as statistical criteria for component variability, confidence levels, and degree of precision desired, the past quality history of the supplier, and the quantity needed for analysis and reserve where required. The following procedures should be used to collect the samples:

—The containers of components selected should be cleaned, where necessary, by appropriate means.
—The containers should be opened, sampled, and resealed in a manner designed to prevent contamination of their contents and contamination of other components, product containers, or closures.
—These containers should be identified so that the following information can be determined: name of the material sampled, the lot number, the container from which the sample was taken, the date on which the sample was taken, and the name of the person who collected the sample.

Use the following procedure to examine and test the samples:

—At least one test should be conducted to verify the identity of each component of a product if skip-lot testing is used.
—Each component should be tested for conformity with all appropriate written specifications for purity, strength, and quality. However, a report of analysis may be accepted from the supplier of a component, provided that at least one identity test is conducted on such component by the manufacturer.
—Containers and closures should be tested for conformance with all appropriate written procedures. However, a certificate of testing may be accepted from the supplier, provided that at least a visual identification is conducted on such containers/closures by the manufacturer.
—Each lot of a component, product container, or closure that is liable to contamination with filth, insect infestation, or other extraneous adulterant should be examined against established specifications for such contamination. Skip-lot examination should not apply in such cases.
—Each lot of a component, product container, or closure that is liable to microbiological contamination that is objectionable in view of its intended use should be subjected to microbiological tests before use. Skip-lot examination should not apply in such cases.
—Any lot of component, product container, or closure that meets the appropriate written specifications of identity, strength, quality, and purity and related tests may be approved and released for use. Any lot of such material that does not meet such specifications should be rejected.

Use of Approved Components, Product Containers, and Closures

Components, product containers, and closures approved for use should be rotated so that the oldest approved stock is used first. Deviation from the requirement is permitted if such deviation is temporary and appropriate.

Retesting of Approved Components, Product Containers, and Closures

Components, product containers, and closures should be retested or reexamined, as appropriate, for identity, strength, quality, and purity and approved or rejected by the quality control unit as necessary, e.g., after exposure to air, heat, or other conditions that might adversely affect the component, product container, or closure and/or after storage of active and inactive ingredients and in-process materials for long periods of time.

Rejected Components, Product Containers, and Closures

Rejected components, product containers, and closures should be identified and controlled under a quarantine system that prevents their use in manufacturing or processing operations for which they are unsuitable.

PRODUCTION AND PROCESS CONTROLS

Written Procedures

Written procedures should be provided for production and process control designed to ensure that the nutritional products have the identity, strength, quality, and purity they are represented to possess. These procedures should be drafted, reviewed, and approved by the appropriate organizational units and reviewed and approved by the quality control unit. These production and process control procedures should be followed in the execution of the various production and process control functions and should be documented at the time of performance. Any deviation from the written procedures should be recorded and justified.

Charge-in of Components

Written production and control procedures should include the following, which are designed to ensure that the nutritional products have the identity, strength, quality, and purity they are represented to possess:

—The batch should be formulated with the intent to provide not less than 100 percent of the labeled or established amount of active ingredient.
—Components for product manufacturing should be weighed, measured, or subdivided as appropriate and the appropriate signatures recorded in the batch record.
—Actual yields and percentages of theoretical yield should be determined at appropriate phases of processing.

Equipment Identification

All compounding and storage containers, processing lines, and major equipment used during the production of a batch of a product should be properly identified to indicate their contents and, when necessary, the phase of processing of the batch.

Sampling and Testing of In-Process Materials and Nutritional Products

To ensure batch uniformity and integrity of nutritional products, written procedures should be established and followed that describe the in-process controls and tests or examinations to be conducted on appropriate samples of in-process materials. Based upon process validation, in-process controls and statistical confidence, a skip-lot sampling plan is an alternative to testing every batch. Control procedures should be established to monitor the output of those manufacturing processes that may be responsible for causing variability in the characteristics of in-process material and the finished product. Such control procedures may include, but are not limited to, the following, where appropriate:

—Friability
—Weight variation
—Disintegration time
—Dissolution time
—Clarity, completeness, or pH of solutions.

In-process specifications for such characteristics should be consistent with finished product specifications. Examination and testing of samples should ensure that the in-process material and nutritional product conform to the established specifications.

In-process materials should be tested for identity, strength, quality, and purity as appropriate, and approved or rejected by the quality control unit during the production process, e.g., at commencement or completion of significant phases or after storage for long periods.

Rejected in-process materials should be identified and controlled under a quarantine system designed to prevent their use in manufacturing or processing operations for which they are unsuitable.

LABELING AND PACKAGING

Materials Examination and Usage Criteria

Written procedures should be provided describing in sufficient detail the receipt, identification, storage, handling, sampling, examination, and/or testing of labeling and packaging materials. Labeling and packaging materials should be representatively sampled and examined or tested upon receipt and before use in packaging or labeling of a product.

Any labeling or packaging materials meeting appropriate written specifications may be approved and released for use. Those that do not meet such specifications should be rejected to prevent their use in operations for which they are unsuitable.

A record should be kept of each shipment received of each different labeling and packaging material, which indicates receipt, date of examination or testing, and whether accepted or rejected.

Labels and other labeling materials for each different product, strength, product type, or quantity of contents should be stored separately with suitable identification. Authorized personnel only should have access to the storage area.

Gang printing of labeling to be used for different products or different strengths of the same product (or labeling of the same size and identical or similar format and/or color schemes) should be minimized. If gang printing is employed, packaging and labeling operations should provide for special control procedures, taking into consideration sheet layout, stacking, cutting, and handling during and after printing.

Printing devices on, or associated with, manufacturing lines used to imprint labeling upon the product unit label or case should be monitored to ensure that all imprinting conforms to the print specified in the batch production record.

Obsolete and outdated labels, labeling, and other packaging materials should be destroyed and documented.

Labeling Issuance

Strict control should be exercised over labeling issued for use in product labeling operations. The control procedures employed should be in writing with sufficient detail.

Labeling materials issued for a batch should be carefully examined for identity and conformity to the labeling specified in the master or batch production records.

Procedures should be utilized to reconcile the quantities of labeling issued, used, and returned, and should require evaluation of discrepancies found. If discrepancies are found between the quantity of product finished and the quantity of labeling issued and are outside preset limits based on historical operating data, such discrepancies should be investigated.

Returned labeling should be maintained and sorted in a manner to prevent mixups and provide proper identification.

All excess labeling bearing lot or control numbers should be destroyed and documented.

Operations

Written procedures designed to ensure that correct labels, labeling, and packaging materials are used for nutritional products should incorporate the following features:

—Prevention of mixups and cross-contamination by physical or spatial separation from operations on other products.

—Identification of the product with a lot or control number.

—Examination of packaging and labeling materials for suitability and correctness before packaging operations; and documentation of such examination in the batch production record.

—Inspection of the packaging and labeling facilities immediately before use to ensure that all products have been removed from previous operations. Inspection should also be made to ensure that packaging and labeling materials not suitable for subsequent operations have been removed. Results of the inspection should be documented in the batch production records.

Tamper-Resistant Packaging

REQUIREMENTS

Each manufacturer and packer who packages a nutritional product for retail sale should package the product in a tamper-resistant package, if this product is accessible to the public while held for sale. A tamper-resistant package is one having an indicator or barrier to entry which, if breached or missing, can reasonably be expected to provide visible evidence to consumers that tampering has occurred. To reduce the likelihood of substitution of a tamper-resistant feature after tampering, the indicator or barrier to entry is required to be distinctive by design or by the use of an identifying characteristic (e.g., a pattern, name, registered trademark, logo, or picture). For purposes of this section, the term "distinctive by design" means that the packaging cannot be duplicated with commonly available materials or through commonly available processes. A tamper-resistant package may involve an immediate-container and closure system, or secondary-container or carton system, or any combination of systems intended to provide a visual indication of package integrity. The tamper-resistant feature should be designed to remain intact when handled in a reasonable manner during manufacture, distribution, and retail display.

LABELING

Each retail package of a nutritional product covered by this section should bear a statement that is prominently placed so that consumers are alerted to the specific tamper-resistant feature of the package. The labeling statement should be so placed that it will be unaffected if the tamper-resistant feature of the packaging is breached or missing. If the tamper-resistant feature chosen to meet the requirement above is one that uses an identifying characteristic, that characteristic should be referred to in the labeling statement. For example, the labeling statement on a bottle with a shrink band could say "For your protection, this bottle has an imprinted seal around the neck."

Nutritional Product Inspection

Packaged and labeled products should be examined during finishing operations to ensure that containers and packages in the lot have the correct label. A representative sample of units should be collected at the completion of finishing operations and visually examined for correct labeling. Results of these examinations should be recorded in the batch production or control records.

Expiration Dating

Nutritional products should bear an expiration date, determined by appropriate testing, to ensure that they meet applicable standards of identity, strength, quality, and purity at the time of use.

Expiration dates should be related to any storage conditions stated on the labeling.

HOLDING AND DISTRIBUTION

Warehousing Procedures

Written procedures describing the warehousing of nutritional products should be established and followed and should include:

—Quarantine of finished products before release by the quality control unit.

—Storage of finished products under appropriate conditions of temperature, humidity, and light so that the identity, strength, quality, and purity of the products are not affected.

Distribution Procedures

Written procedures describing the distribution of nutritional products should be established and followed and should include the following:

—A procedure whereby the oldest approved stock of a product is distributed first. (Deviation from this requirement is permitted if such deviation is temporary and appropriate.)

—A system by which the distribution of each lot of product can be readily determined to facilitate its recall if necessary.

LABORATORY CONTROLS

The establishment of any specifications, standards, sampling plans, test procedures, or other laboratory control mechanisms required by this general chapter, including any change in such specifications, standards, sampling plans, test procedures, or other laboratory control mechanisms, should be drafted by the appropriate organizational unit and reviewed and approved by the quality control unit. The requirements in this section should be followed and documented at the time of performance. Any deviation from the written specifications, standards, sampling plans, test procedures, or other laboratory control mechanisms should be recorded and justified.

Laboratory control includes the establishment of scientifically sound and appropriate specifications, standards, sampling plans, and test procedures designed to assure that components, product containers, closures, in-process materials, labeling, and finished products conform to appropriate standards of identity, strength, quality and purity. These controls include the following:

—Determination of conformance to appropriate written specifications for the acceptance of each lot within each shipment of components, product containers, closures, and labeling used in the manufacture of nutritional products. (The specifications include a description of the sampling and testing procedures used. Samples should be representative and adequately identified. Such procedures also require appropriate retesting of any component, product-container, or closure that is subject to deterioration.) Based upon adequate process validation, in-process controls, and statistical confidence, a skip-lot sampling plan is an alternative to testing every batch.

—Determination of conformance to written specifications and a description of sampling and testing procedures for in-process materials. (Such samples should be representative and properly identified.)

—Determination of conformance to written descriptions of sampling procedures and appropriate specifications for finished products. (Such samples should be representative and properly identified.)

—The calibration of instruments, at suitable intervals, in accordance with an established written program containing specific directions, schedules, limits for accuracy and precision, and provisions for remedial action in the event accuracy and/or precision limits are not met. Instruments not meeting established specifications should not be used until repaired.

Testing and Release for Distribution

There should be appropriate laboratory determination of satisfactory conformance to specifications for the finished product, including the identity and strength prior to release. Based upon adequate process validation, in-process controls, and statistical confidence, a skip-lot sampling plan is an alternative to testing every batch.

Written procedures should describe any sampling and testing plans, which should include the method of sampling and the number of units per batch to be tested.

Products failing to meet established standards or specifications and any other relevant quality control criteria should be rejected. Reprocessing may be performed. Prior to acceptance and use, reprocessed material must meet appropriate standards, specifications, and any other relevant criteria.

Reserve Samples

An appropriately identified reserve sample that is representative of each lot or batch of nutritional product should be retained and stored under conditions consistent with product labeling until at least one year after the expiration date of the product. The reserve sample should be stored in the same immediate container-closure system in which the finished product is marketed or in one that has essentially the same characteristics. The reserve sample consists of at least twice the quantity necessary to perform all the required tests.

RECORDS AND REPORTS

Any production, control, or distribution record that is required to be maintained and is specifically associated with a batch of a product should be retained for at least one year after the expiration date of the batch.

Records should be maintained for all components, product containers, closures, and labeling for at least one year after the expiration date of the last lot of product incorporating the component or using the container, closure, or labeling.

Master Production and Control Records

To ensure uniformity from batch to batch, master production and control records for each product should be prepared, dated, and signed by one person and independently checked, dated, and signed by a second person.

Master production and control records should include the following:

—The name and strength of the product.

—The name and weight or measure of each active ingredient per unit or portion or per unit of weight or measure of the product, and a statement of the total weight or measure of any dosage unit.

—A complete list of components designated by names or codes sufficiently specific to indicate any special quality characteristic.

—An accurate statement of the weight or measure of each component, using the same weight system (metric, avoirdupois, or apothecary) for each component.

—A statement concerning any calculated excess of component.

—A statement of theoretical weight or measure at appropriate phases of processing.

—A statement of theoretical yield, including the maximum and minimum percentages of theoretical yield beyond which investigation is required.

—A description of the product containers, closures, and packaging materials, including a specimen or copy of each label and all other labeling signed and dated by the person or persons responsible for approval of such labeling or, in lieu of specimens or copies of each label or other labeling, a positive identification of all labeling used.

—Complete manufacturing and control instructions, sampling and testing procedures, specifications, special notations, and precautions to be followed.

Batch Production and Control Records

Batch production and control records should be prepared for each batch of product produced and should include complete information relating to the production and control of each batch. These records should include accurate reproduction of the appropriate master production or control record and documentation that each significant step in the manufacture, processing, packing, or holding of the batch was accomplished, including the following:

—Dates.

—Identity of individual major equipment and lines used.

—Specific identification of each batch of component or in-process material used.

—Weights and measures of components used in the course of processing.

—In-process and laboratory control results.

—Inspection of the packaging and labeling areas before and after use.

—A statement of the actual yield and a statement of the percentage of theoretical yield at appropriate phases of processing.
—Complete labeling control records, including specimens or copies of all labeling used or identification of all labeling used.
—Any sampling performed.
—Identification of the persons performing and directly supervising or checking any step in the operation.
—Any investigation made.
—Results of examinations made.

Laboratory Records

Laboratory records should include complete data derived from all tests necessary to ensure compliance with established specifications and standards, including examinations and assays, as follows:

—A description of the sample received for testing with identification of source (that is, location from where sample was obtained), quantity, lot number or other distinctive code, and date sample was taken.
—A statement of each method used in the testing of the sample.
—A statement of the weight or measure of sample used for each test, where appropriate.
—A complete record of all data secured in the course of each test, including all graphs, charts, and spectra from laboratory instrumentation, properly identified to show the specific component, product container, closure, in-process material, or finished product, and lot tested.
—A record of all calculations performed in connection with the test, including units of measure, conversion factors, and equivalency factors.
—A statement of the results of tests and how the results compare with established standards of identity, strength, quality, and purity for the component, product container, closure, in-process material, or finished product tested.
—The initials or signature of the person who performs each test and the date(s) the tests were performed.

Complete records should be maintained of any modification of an established method employed in testing. Such records should include the reason for the modification and data to verify that the modification produced results that are at least as accurate and reliable for the material being tested as the established method.

Complete records should be maintained of any testing and standardization of laboratory reference standards, reagents, and standard solutions, the periodic calibration of laboratory instruments, and all stability testing performed.

Distribution Records

Distribution records should contain the name and strength of the product, name and address of the consignee, date and quantity shipped, and lot or control number of the finished product.

Complaint Files

Written procedures describing the handling of all written and oral complaints regarding a nutritional product should be established and followed. These procedures should include provisions for review by the quality control unit of any complaint involving the possible failure of a product to meet any of its specifications and a determination as to the need for an investigation.

Each complaint should be recorded in a file designed especially for nutritional product complaints. Written records should be maintained until at least one year after the expiration date of the product, or one year after the date that the complaint was received, whichever is longer.

The written record should include the following information, where known: the name and strength of the product, lot number, name of complainant, nature of complaint, and reply to complainant.

If an investigation is necessary, the written record should include the findings of the investigation and follow-up.

RETURNED AND SALVAGED PRODUCTS

Returned Nutritional Products

Returned products should be identified as such and held. If the conditions under which returned nutritional products have been held, stored, or shipped before or during their return, or if the condition of the product, its container, carton, or labeling, as a result of storage or shipping, casts doubt on the safety, identity, strength, quality, or purity of the product, the returned product should be destroyed unless examination, testing or other investigations prove the product meets appropriate standards of safety, identity, strength, quality, or purity. A product may be reprocessed provided the subsequent product meets appropriate standards, specifications, and characteristics. Records of returned products should be maintained and should include the name and label potency of the product, lot number (or control number or batch number), reason for the return, quantity returned, date of disposition, and ultimate disposition of the returned product. If the reason for a product being returned implicates associated batches, an appropriate investigation is necessary.

Nutritional Product Salvaging

Products that have been subjected to improper storage conditions including extremes in temperature, humidity, smoke, fumes, pressure, age, or radiation due to natural disasters, fires, accidents, or equipment failures should not be salvaged and returned to the marketplace. Whenever there is a question whether products have been subjected to such conditions, salvaging operations may be conducted only if there is (a) evidence from laboratory tests and assays that the products meet all applicable standards of identity, strength, quality, and purity, and (b) evidence that the products and their associated packaging were not subjected to improper storage conditions as a result of the disaster or accident. Organoleptic examinations should be accepted only as supplemental evidence that the nutritional product meets appropriate standards of identity, strength, quality, and purity. Records including name, lot number, and disposition should be maintained for salvaged products.

GLOSSARY OF TERMS

Batch is a specific quantity of a finished product or other material that is intended to have uniform character and quality, within specified limits, and is produced according to a single manufacturing order during the same cycle of manufacture.

Component is any ingredient intended for use in the manufacture of a product, including those that may not appear in such finished product.

Nutritional product is a finished product, for example, tablet, capsule, solution, etc., that contains an active ingredient in association with inactive ingredients. Such a product should possess nutritional value.

Active ingredient is any component that furnishes nutritional value at its prescribed potency.

Inactive ingredient is any component other than an active ingredient.

In-process material is any material fabricated, compounded, or blended that is produced for, and used in, the preparation of the finished product.

Lot is a batch, or a specific identified portion of a batch, having uniform character and quality within specified limits.

Lot number, control number, or batch number is any distinctive combination of letters, numbers, or symbols, or any combination of them from which the complete history of the manufacture, processing, packing, holding, and distribution of a batch or lot of finished nutritional product or other material can be determined.

Manufacture of a nutritional product includes processing, packaging and labeling operations, testing, quality control and holding of the product.

Quality control unit is any person or organizational element designated by the firm to be responsible for the duties relating to quality control.

Strength means the concentration of the active substance (weight/weight, weight/volume, or unit of use/volume or weight basis); and/or the potency, that is, the activity of the product as indicated by appropriate laboratory tests.

Acceptance criteria is the product specifications and acceptance/rejection criteria, such as acceptable quality level and unacceptable quality level, with an associated sampling plan, that are necessary for making a decision to accept or reject a lot or batch (or any other convenient subgroups of manufactured units).

Representative sample is a sample that consists of a number of units that are drawn based on rational criteria such as random sampling and is intended to assure that the sample accurately portrays the material being sampled.

Sanitize is the adequate treatment of surfaces by a process that is effective in destroying vegetative cells of pathogenic bacteria and in substantially reducing other microorganisms to an acceptable total plate count. Such treatment shall not adversely affect the product and shall be safe for the consumer.

Skip-lot sampling is a reduced level of sampling/testing for a particular specified parameter(s) based upon one or more of the following:

—Statistical analysis of an adequate quantity of historical test data.

—Statistical confidence in the capability of the manufacturing process as determined by suitable validation.

—Ongoing monitoring of the process using recognized statistical process control (SPC) techniques.

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Procedure for Niacin or Niacinamide, Pyridoxine, Riboflavin, and Thiamine—Determine the amount of the designated index vitamin dissolved, employing the procedure set forth in the *Assay for niacin or niacinamide, pyridoxine, riboflavin, and thiamine* under *Water-soluble Vitamins Tablets*.

Procedure for Ascorbic Acid—Determine the amount of $C_6H_8O_6$ dissolved by adding 10 mL of 1.0 *N* sulfuric acid and 3 mL of starch TS to 100.0 mL of test solution and titrating immediately with 0.01 *N* iodine VS. Perform a blank determination, and make any necessary correction.

Procedure for Iron, Calcium, Magnesium, and Zinc—Determine the amount of the designated index element dissolved employing the procedure set forth in the appropriate *Assay* under *Minerals Capsules*.■1

Change to read:

■**Tolerances**—■1 The requirements are met if not less than 75% of the assayed content of ■folic acid,■1 the index ■vitamin, or the index element■1 from the units tested is dissolved in 1 hour.

⟨2750⟩ MANUFACTURING PRACTICES FOR NUTRITIONAL SUPPLEMENTS

LABORATORY CONTROLS

The establishment of any specifications, standards, sampling plans, test procedures, or other laboratory control mechanisms required by this general chapter, including any change in such specifications, standards, sampling plans, test procedures, or other laboratory control mechanisms, should be drafted by the appropriate organizational unit and reviewed and approved by the quality control unit. The requirements in this section should be followed and documented at the time of performance. Any deviation from the written specifications, standards, sampling plans, test procedures, or other laboratory control mechanisms should be recorded and justified.

Laboratory control includes the establishment of scientifically sound and appropriate specifications, standards, sampling plans, and test procedures designed to assure that components, product containers, closures, in-process materials, labeling, and finished products conform to appropriate standards of identity, strength, quality and purity. These controls include the following:

—Determination of conformance to appropriate written specifications for the acceptance of each lot within each shipment of components, product containers, closures, and labeling used in the manufacture of nutritional products. (The specifications include a description of the sampling and testing procedures used. Samples should be representative and adequately identified. Such procedures also require appropriate retesting of any component, product container, or closure that is subject to deterioration.) Based upon adequate process validation, in-process controls, and statistical confidence, a skip-lot sampling plan is an alternative to testing every batch.

—Determination of conformance to written specifications and a description of sampling and testing procedures for in-process materials. (Such samples should be representative and properly identified.)

—Determination of conformance to written descriptions of sampling procedures and appropriate specifications for finished products. (Such samples should be representative and properly identified.)

—The calibration of instruments, at suitable intervals, in accordance with an established written program containing specific directions, schedules, limits for accuracy and precision, and provisions for remedial action in the event accuracy and/or precision limits are not met. Instruments not meeting established specifications should not be used until repaired.

Change to read:

Testing and Release for Distribution

There should be appropriate laboratory determination of satisfactory conformance to specifications for the finished product, including the identity and strength prior to release. Based upon adequate process validation, in-process controls, ■or■2 statistical confidence, a skip-lot ■or composite■2 sampling plan is an alternative to testing every batch.

■There should be appropriate laboratory testing, as necessary, of each batch of nutritional product required to be free of objectionable microorganisms. The accuracy, linearity, sensitivity, specificity, and reproducibility of test methods employed by the firm, when they differ from compendial methods, should be established and documented.■2

Written procedures should describe any sampling and testing plans, which should include the method of sampling and the number of units per batch to be tested.

Products failing to meet established standards or specifications and any other relevant quality control criteria should be rejected, ■unless the variation is documented by the quality control unit as not affecting finished product safety, identity, strength, quality, and purity.■2 Reprocessing may be performed. Prior to acceptance and use, reprocessed material must meet appropriate standards, specifications, and any other relevant criteria.

Add the following:

■Stability Testing

There should be a written protocol designed to assess the stability characteristics of nutritional products. The results of such testing should be used in determining appropriate storage conditions and expiration dates. This procedure should include the following:

—Sample size and test intervals based on statistical criteria for each attribute should be examined to ensure valid estimates of stability.

—Storage conditions for samples retained for testing.

—Reliable, meaningful, and specific test methods should be used.

—The nutritional product should be tested in the same type of container-closure system as that in which the nutritional product is marketed.

An adequate number of batches of each nutritional product should be tested to determine an appropriate expiration date, and a record of these data should be maintained. Accelerated studies combined with basic stability information on the components, nutritional products, and container-closure systems may be used to support tentative expiration dates provided full shelf-life studies are not available. Where data from accelerated studies are used to project a tentative expiration date that is beyond a date supported by actual shelf-life studies, stability studies should be conducted, including nutritional product testing at appropriate intervals, until the tentative expiration date is verified or the appropriate expiration date is determined.■2

Reserve Samples

An appropriately identified reserve sample that is representative of each lot or batch of nutritional product should be retained and stored under conditions consistent with product labeling until at least one year after the expiration date of the product. The reserve sample should be stored in the same immediate container-closure system in which the finished product is marketed or in one that has essentially the same characteristics. The reserve sample consists of at least twice the quantity necessary to perform all the required tests.