DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration

21 CFR Ch. I

[Docket No. 96N–0417]

RIN 0910–AA59

Current Good Manufacturing Practice in Manufacturing, Packing, or Holding Dietary Supplements

AGENCY: Food and Drug Administration, HHS.

ACTION: Advance notice of proposed rulemaking.

SUMMARY: The Food and Drug Administration (FDA) is announcing that it is considering whether to institute rulemaking to develop current good manufacturing practice (CGMP) regulations for dietary supplements and dietary supplement ingredients. FDA solicits comments on whether it should do so, and if it should, what constitutes CGMP for these products. In issuing this notice, FDA is responding to the section of the Federal Food, Drug, and Cosmetic Act (the act) that provides that the Secretary of Health and Human Services (the Secretary) may, by regulation, prescribe good manufacturing practice for dietary supplements and to a submission from representatives of the dietary supplement industry asking FDA to consider a framework that the industry had developed as a basis for CGMP regulations. FDA is publishing the industry submission and is asking for public comment on the framework that the submission presents. In addition, FDA is requesting comment on a number of other related issues.

DATES: Written comments by May 7, 1997.

ADDRESSES: Submit written comments to the Dockets Management Branch (HFA–305), Food and Drug Administration, 12420 Parklawn Dr., rm. 1–23, Rockville, MD 20857.

FOR FURTHER INFORMATION CONTACT: Robert J. Moore, Center for Food Safety and Applied Nutrition (HFS–456), Food and Drug Administration, 200 C St. SW., Washington, DC 20204, 202–205–4605.

SUPPLEMENTARY INFORMATION:

I. Background

On October 25, 1994, the Dietary Supplement Health and Education Act (the DSHEA) (Pub. L. 103–417) was signed into law. The DSHEA, among other things, amended the act by adding section 402(g) (21 U.S.C. 342(g)), which provides, in part, that:

> The Secretary may by regulation prescribe good manufacturing practices for dietary supplements. Such regulations shall be modeled after current good manufacturing practice regulations for food and may not impose standards for which there is no current and generally available analytical methodology. No standard of current good manufacturing practice may be imposed unless such standard is included in a regulation promulgated after notice and opportunity for comment in accordance with chapter 5 of title 5, United States Code.

While section 402(g) of the act does not require that the Secretary (and by delegation, FDA) adopt regulations that prescribe CGMP, a significant segment of the dietary supplement industry has told the agency that such regulations would be helpful for ensuring that dietary supplements are safe for their intended use.

On November 20, 1995, representatives of the dietary supplement industry submitted to FDA a suggested outline for the development of CGMP regulations for dietary supplements. FDA evaluated the outline and determined that it provided an extremely useful starting point should FDA decide to proceed to rulemaking to adopt such regulations. However, the agency recognizes that the first question that must be addressed is whether there is a need for such regulations or whether part 110 (21 CFR part 110) continues to be adequate. The agency also recognizes that if it decides that there is a need for CGMP regulations, certain issues were not addressed in the submission, and that other interested parties, such as consumers, segments of the industry not represented by the manufacturers and trade associations who submitted the outline, and the health care community, should have an opportunity to provide comment before the agency developed a proposal. Therefore, the agency is issuing this notice to solicit comments and other information on whether it should propose new CGMP regulations for dietary supplements and, if it should, what those regulations should include. Based on the submission and the comments that the agency receives in response to this notice, FDA will consider whether to develop a proposed rule that is designed to establish CGMP that will ensure that dietary supplements are produced under conditions that will result in a safe and properly labeled product but that does not impose any unnecessary burden on the industry.

II. The Industry Submission

A. Introduction

On November 30, 1995, FDA met with representatives of the dietary supplement industry at their request (Ref. 1). At that meeting, the industry representatives submitted a document that outlined suggested CGMP for dietary supplements (Ref. 2). The objectives of the CGMP, as stated by the industry representatives, are to ensure that consumers are provided with dietary supplement products that: (1) Are safe and not adulterated or misbranded; (2) have the identity and provide the quantity of dietary ingredients declared in labeling; and (3) meet the quality specifications that the supplement is represented to meet. The industry submission was patterned after the CGMP for food regulation contained in part 110, but also contained requirements beyond those in part 110 that the industry representatives stated that they ''consider essential to the manufacture of safe and properly labeled dietary supplements.'' FDA is publishing the industry suggested dietary supplements CGMP and soliciting comments from industry, consumers, and other interested parties on the need for dietary supplement CGMP regulations and on the requirements that should be included in such regulations.

B. The Industry Draft

The text of the industry suggested dietary supplements CGMP follows:

Good Manufacturing Practices (GMP's) for Dietary Supplements: Statement of Purpose

This document describes Good Manufacturing Practices to be followed in the manufacturing and control operations for dietary supplements and dietary ingredients. The objective of these Good Manufacturing Practices is to assure that consumers are provided with safe dietary supplement products which are not adulterated or misbranded, which have the identity and provide the quantity of dietary ingredients declared in labeling, and which meet the quality specifications that the supplement is represented to meet.

The Food, Drug, and Cosmetic Act defines dietary supplements in section 201(ff). Dietary supplements include a broad spectrum of product forms and a broad spectrum of dietary ingredients. Dietary ingredients may include vitamins; minerals; herbs or other botanicals; amino acids; other dietary substances used to supplement the diet; and concentrates, metabolites, constituents, extracts, or combinations of these. Product forms include tablets, capsules, softgels, gelcaps, liquids, and other forms including—under some conditions—conventional food forms. These Good Manufacturing Practices are intended to encompass all of these types of products. In some cases, judgment may be required in determining the applicability of a specific provision to a particular product or class of products.

Dietary supplements in the physical form of conventional food shall comply with these

Good Manufacturing Practices and with applicable food GMP's. For example, if they are thermally processed low-acid products packaged in hermetically sealed containers, they shall also comply with the applicable GMP's covering that product category.

These Good Manufacturing Practices are modeled after good manufacturing practices for foods. Provisions have been adopted, modified, or expanded as appropriate, considering the special requirements applicable to the manufacture of dietary supplements and dietary ingredients. There is no desire or intent to impose on dietary supplements the type of documentation and validation currently required in the manufacture of pharmaceutical products, where it would be inappropriate or unnecessary to ensure safe and unadulterated products. Dietary supplements are classified as foods, and the Good Manufacturing Practices applicable to them are similar to those generally applicable to other foods.

Proposed Supplement GMP

Definitions

The definitions and interpretations of terms in section 201 of the Federal Food, Drug, and Cosmetic Act (the act) are applicable to such terms when used in this part. The following definitions shall also apply:

(a) ''Adequate'' means that which is needed to accomplish the intended purpose in keeping with good public health practice.

(b) ''Batch or Lot'' means 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.

(c) ''Blanching'' means a prepackaging heat treatment of a dietary product for a sufficient time and at a sufficient temperature to partially or completely inactivate the naturally occurring enzymes and to effect other physical or biochemical changes in the product.

(d) ''Composition'' means, as appropriate:

(1) the identity of a dietary ingredient or dietary supplement, and

(2) the concentration of a dietary ingredient (e.g., weight or other unit of use/weight or volume), or the potency or activity of one or more dietary ingredients, as indicated by appropriate procedures.

(e) ''Dietary ingredient'' means an ingredient intended for use or used in a dietary supplement that is:

(1) a vitamin,

(2) a mineral,

(3) an herb or other botanical,

(4) an amino acid,

(5) a dietary substance for use by man to supplement the diet by increasing the total dietary intake, or

(6) a concentrate, metabolite, constituent, extract, or combination of any of the foregoing ingredients.

(f) ''Dietary product'' means either a dietary ingredient or dietary supplement as defined in this Part.

(g) ''Dietary supplement'' means dietary supplement as defined in section 201(ff) of the act.

(h) ''In-process material'' means any material fabricated, compounded, blended, ground, extracted, sifted, sterilized, derived by chemical reaction or processed in any other way that is produced for, and used in, the preparation of a dietary product.

(i) ''Lot'' means ''batch'' as defined in this part.

(j) ''Lot number'' means 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 a finished dietary ingredient, dietary supplement or other material can be determined.

(k) ''Manufacture'' or ''manufacturing'' includes all operations associated with the production of dietary products, including packaging and labeling operations, testing, and quality control of a dietary ingredient or dietary supplement.

(l) ''Microorganisms'' means yeasts, molds, bacteria, and viruses and includes, but is not limited to, species having public health significance. The term ''undesirable microorganisms'' includes those microorganisms that are of public health significance, that subject food to decomposition, that indicate that a dietary ingredient or dietary supplement is contaminated with filth, or that otherwise may cause a dietary product to be adulterated within the meaning of the act. Occasionally in these regulations, the adjective ''microbial'' is used instead of using an adjectival phrase containing the word microorganism.

(m) ''Pest'' refers to any objectionable animals or insects including, but not limited to, bird, rodents, flies, and larvae.

(n) ''Plant'' means the building or facility or parts thereof, used for or in connection with the manufacturing, packaging, labeling, or holding of a dietary product.

(o) ''Quality control operation'' means a planned and systematic procedure for taking all actions necessary to prevent a dietary product from being adulterated within the meaning of the act.

(p) ''Quality control unit'' means any person or organizational element designated by the firm to be responsible for the duties relating to quality control operations.

(q) ''Raw material'' means any ingredient intended for use in the manufacture of a dietary ingredient or dietary supplement, including those that may not appear in such finished product.

(r) ''Representable sample'' means 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.

(s) ''Rework'' means clean, unadulterated material that has been removed from processing for reasons other than insanitary conditions or that has been successfully reconditioned by reprocessing and that is suitable for use in the manufacture of a dietary product.

(t) ''Sanitize'' means to adequately treat equipment, containers, or utensils by a process that is effective in destroying vegetative cells of microorganisms of public health significance, and in substantially reducing numbers of other undesirable microorganisms, but without adversely affecting the product or its safety for the consumer.

(u) ''Shall'' is used to state mandatory requirements.

(v) ''Should'' is used to state recommended or advisory procedures or identify recommended equipment.

(w) ''Water activity (a_w)'' is a measure of the free moisture in a dietary ingredient or dietary supplement and is the quotient of the water vapor pressure of the substance divided by the vapor pressure of pure water at the same temperature.

Personnel

The plant management shall take all reasonable measures and precautions to assure the following:

(a) Disease control. Any person who, by medical examination or supervisory observation, is shown to have, or appears to have, an illness, open lesion, including boils, sores, or infected wounds, or any other abnormal source of microbial contamination by which there is a reasonable possibility of an in-process or finished dietary product becoming adulterated, or processing equipment, utensils or packaging materials becoming contaminated, shall be excluded from any operations which may be expected to result in such adulteration or contamination until the condition is corrected. Personnel shall be instructed to report such health conditions to their supervisors.

(b) Cleanliness. All persons working in direct contact with raw materials, in-process or finished dietary products, processing equipment, utensils or packaging materials shall conform to hygienic practices while on duty to the extent necessary to protect against adulteration or contamination of such materials. The methods for maintaining cleanliness include, but are not limited to:

(1) Wearing outer garments suitable to the operation in a manner that protects against the adulteration of in-process or finished dietary products, or contamination of processing equipment, utensils or packaging materials.

(2) Maintaining adequate personal cleanliness.

(3) Washing hands thoroughly (and sanitizing if necessary to protect against contamination with undesirable microorganisms) in an adequate hand-washing facility before starting work, after each absence from the work station, and at any other time when the hands may have become soiled or contaminated.

(4) Removing all unsecured jewelry and other objects that might fall into raw materials, in-process or finished dietary product, equipment, or containers, and removing hand jewelry that cannot be adequately sanitized during periods in which in-process or finished product is manipulated by hand. If such hand jewelry cannot be removed, it may be covered by material which can be maintained in an intact, clean, and sanitary condition and which effectively

protects against the adulteration of dietary products or contamination of processing equipment, utensils or packaging materials.

(5) Maintaining gloves, if they are used in-process or finished product handling, in an intact, clean, and sanitary condition. The gloves should be of a material that adequately protects the product from contamination.

(6) Wearing, where appropriate, in an effective manner, hair nets, caps, beard covers, or other effective hair restraints.

(7) Storing clothing or other personal belongings in areas other than where in-process or finished product is exposed or where processing equipment or utensils are washed.

(8) Confining the following to areas other than where in-process or finished product may be stored or exposed, or where processing equipment or utensils are washed: eating food, chewing gum, drinking beverages, or using tobacco.

(9) Taking any other necessary precautions to protect against adulteration of raw materials, in-process or finished product, or contamination of processing equipment, utensils or packaging materials with micro-organisms or foreign substances including, but not limited to, perspiration, hair, cosmetics, tobacco, chemicals, and medicines applied to the skin.

(c) Education and training. Each person engaged in the manufacture of a dietary 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 as they relate to the employee's functions. Appropriate documentation of training shall be retained by the manufacturer.

(d) Supervision. Responsibility for assuring compliance by all personnel with all requirements of this part shall be clearly assigned to qualified personnel with proper education, training and experience (or any combination thereof).

Exclusions

The following operations are not subject to this part: Establishments engaged solely in the harvesting, storage, or distribution of one or more ''raw agricultural commodities,'' as defined in section 201(r) of the act, which are ordinarily cleaned, prepared, treated, or otherwise processed before being marketed to the consuming public.

Plant and Grounds

(a) Grounds. The grounds about a dietary product manufacturing plant under the control of the operator shall be kept in a condition that will protect against the adulteration of dietary products. The methods for adequate maintenance of grounds include, but are not limited to:

(1) Properly storing equipment, removing litter and waste, and cutting weeds or grass within the immediate vicinity of the plant buildings or structures that may constitute an attractant, breeding place, or harborage for pests.

(2) Maintaining roads, yards, and parking lots so that they do not constitute a source of adulteration in areas where product is exposed.

(3) Adequately draining areas that may contribute to product adulteration by seepage, foot-borne filth, or providing a breeding place for pests.

(4) Operating systems for waste treatment and disposal in an adequate manner so that they do not constitute a source of adulteration in areas where product is exposed. If the plant grounds are bordered by grounds not under the operator's control and not maintained in the manner described in paragraph (a)(1) through (3) of this section, care shall be exercised in the plant by inspection, extermination, or other means to exclude pests, dirt, and filth that may be a source of product adulteration.

(b) Plant construction and design. Plant buildings and structures shall be suitable in size, construction. and design to facilitate maintenance, cleaning and sanitary operations for dietary product manufacturing purposes and to prevent mixups between different raw materials and products. The plant and facilities shall:

(1) Provide sufficient space for such placement of equipment and storage of materials as is necessary for the prevention of mixups, maintenance of sanitary operations and the production of safe dietary products.

(2) Permit the taking of proper precautions to reduce the potential for mixups or adulteration of in-process or finished dietary product, or contamination of processing equipment, utensils or packaging materials with microorganisms, chemicals, filth, or other extraneous material. The potential for mixups and product adulteration may be reduced by adequate product safety controls and operating practices or effective design, including the separation of operations in which contamination is likely to occur, by one or more of the following means: Location, time, partition, air flow, enclosed systems, or other effective means.

(3) Permit the taking of proper precautions to protect dietary ingredients or dietary supplements in outdoor bulk fermentation vessels by any effective means, including:

(i) Using protective coverings.

(ii) Controlling areas over and around the vessels to eliminate harborages for pests.

(iii) Checking on a regular basis for pests and pest infestation.

(iv) Skimming the fermentation vessels, as necessary.

(4) Be constructed in such a manner that floors, walls, and ceilings may be adequately cleaned and kept clean and kept in good repair; that drip or condensate from fixtures, ducts and pipes does not adulterate raw materials, in-process or finished dietary products, or contaminate product containers, utensils or packaging materials; and that aisles or working spaces are provided between equipment and walls and are adequately unobstructed and of adequate width to permit employees to perform their duties and to protect against adulterating in-process or finished product, or contaminating processing equipment with clothing or personal contact.

(5) Provide adequate lighting in hand-washing areas, dressing and locker rooms, and toilet rooms and in all areas where product is examined, processed, or stored and where equipment or utensils are cleaned; and provide safety-type light bulbs, fixtures, sky-lights, or other glass suspended over exposed product in any step of preparation or otherwise protect against product adulteration in case of glass breakage.

(6) Provide adequate ventilation or control equipment to maintain adequate control over microorganisms, dust, humidity, and temperature, when appropriate, for the manufacture of dietary products; to minimize odors and vapors (including steam and noxious fumes) in areas where they may adulterate dietary products; and locate and operate fans and other air-blowing equipment in a manner that minimizes the potential for adulterating raw materials, in-process or finished dietary products, or contaminating processing equipment, utensils or packaging materials.

(7) Provide, where necessary, adequate screening or other protection against pests.

Sanitation of Buildings and Facilities

(a) General maintenance. Buildings, fixtures, and other physical facilities of the plant shall be maintained in a sanitary condition and shall be kept in repair sufficient to prevent raw materials, in-process or finished dietary products from becoming adulterated within the meaning of the act.

(b) Cleaning and sanitizing materials.

(1) Cleaning compounds and sanitizing agents used in cleaning and sanitizing procedures shall be free from undesirable microorganisms and shall be safe and adequate under the conditions of use. Compliance with this requirement may be verified by any effective means including purchase of these substances under a supplier's guarantee or certification, or examination of these substances for contamination. Only the following toxic materials may be used or stored in a plant where product is processed or exposed:

(i) Those required to maintain clean and sanitary conditions;

(ii) Those necessary for use in laboratory testing procedures;

(iii) Those necessary for plant and equipment maintenance and operation; and

(iv) Those necessary for use in the plant's operations.

(2) Toxic cleaning compounds, sanitizing agents, and pesticide chemicals shall be identified, used, held, and stored in a manner that protects against adulteration of raw materials, in-process or finished product, or contamination of processing equipment or packaging materials. All

relevant regulations promulgated by other Federal, State, and local government agencies for the application, use or holding of these products should be followed. Rodenticides, insecticides, and fungicides should be registered and used in accordance with the Federal Insecticide, Fungicide, and Rodenticide Act.

(c) Pest control. No pests shall be allowed in any area of a dietary product manufacturing plant. Effective measures shall be taken to exclude pests from the processing areas and to protect against the adulteration of product on the premises by pests. The use of insecticides or rodenticides is permitted only under precautions and restrictions that will protect against the adulteration of raw materials, in-process or finished product, or contamination of processing equipment, utensils or packaging materials.

(d) Water supply. Potable water at a suitable temperature, and under pressure as needed, shall be provided in all areas where required for the processing of dietary products, for the cleaning of processing equipment, utensils, and packaging materials, or for employee sanitary facilities. Any water that contacts in-process or finished dietary products, utensils or processing equipment shall meet the standards prescribed in the Environmental Protection Agency's Primary Drinking Water Regulations (40 CFR part 141).

(e) Plumbing. Plumbing shall be of adequate size and design and adequately installed and maintained to:

(1) Carry sufficient quantities of water to required locations throughout the plant.

(2) Properly convey sewage and liquid disposable waste from the plant.

(3) Avoid constituting a source of adulteration to product, or contamination of water supplies, processing equipment, or utensils or creating an unsanitary condition.

(4) Provide adequate floor drainage or other appropriate means of water removal in all areas where floors are subject to flooding-type cleaning or where normal operations release or discharge water or other liquid waste on the floor.

(5) Provide that there is not backflow from, or crossconnection between, piping systems that discharge waste water or sewage and piping systems that carry water used for the manufacture of dietary products.

(f) Sewage disposal. Sewage disposal shall be made into an adequate sewerage system or disposed of through other adequate means.

(g) Toilet facilities. Each plant shall provide its employees with adequate, readily accessible toilet facilities. Compliance with this requirement may be accomplished by:

(1) Maintaining the facilities in a sanitary condition.

(2) Keeping the facilities in good repair at all times.

(3) Providing self-closing doors.

(4) Providing doors that do not open into areas where dietary product is exposed to airborne contamination, except where alternate means have been taken to protect against such contamination (such as double doors or positive air-flow systems).

(h) Hand-washing facilities. Hand-washing facilities shall be adequate and convenient and be furnished with running water at a suitable temperature. Compliance with this requirement may be accomplished by providing:

(1) Hand-washing and, where appropriate, hand-sanitizing facilities at each location in the plant where good sanitary practices require employees to wash and/or sanitize their hands.

(2) Effective hand-cleaning and sanitizing preparations.

(3) Air driers, sanitary towel service or suitable drying devices.

(4) Devices or fixtures, such as water control valves, so designed and constructed to protect against recontamination of clean, sanitized hands.

(5) Readily understandable signs directing employees handling unprotected product, packaging materials, utensils or processing equipment to wash and, where appropriate, sanitize their hands before they start work, after each absence from post of duty, and when their hands may have become soiled or contaminated. These signs may be posted in the processing room(s) and in all other areas where employees may handle such products, materials, utensils or equipment.

(6) Refuse receptacles that are constructed and maintained in a manner that protects against adulteration of dietary products.

(i) Rubbish disposal. Rubbish shall be so conveyed, stored, and disposed of as to minimize the development of odor, minimize the potential for the waste becoming an attractant and harborage or breeding place for pests, and protect against adulteration of raw materials, in-process or finished dietary products, or contamination of utensils, processing equipment, water supplies, and ground surfaces.

(j) Supervision. Overall sanitation of the plant shall be under the supervision of one or more individuals qualified by education, experience and training (or any combination thereof) assigned responsibility for assuring that sanitation procedures are accomplished.

Equipment and Utensils

(a) Design and construction.

(1) All plant equipment and utensils shall be so designed and of such material and workmanship as to be adequately cleanable, and shall be properly maintained.

(2) The design, construction and use of equipment and utensils shall preclude the adulteration of raw materials, packaging materials, in-process materials or finished product with lubricants, fuel, metal fragments, contaminated water, or any other contaminants.

(3) All equipment should be so installed and maintained as to facilitate the cleaning of the equipment and of all adjacent spaces. Processing equipment and utensils shall be corrosion-resistant when in contact with raw materials, in-process or finished dietary product. They shall be made of nontoxic materials and designed to withstand the environment of their intended use and the action of dietary products, and, if applicable, cleaning compounds and sanitizing agents. Processing equipment and utensils shall be maintained to protect dietary products from being adulterated by any source.

(4) Seams on utensils and processing equipment shall be smoothly bonded or maintained so as to minimize accumulation of product, dirt, and organic matter and thus minimize the opportunity for growth of microorganisms.

(5) Equipment that is in the manufacturing or product handling area and that does not come into contact with a dietary product shall be so constructed that it can be kept in a clean condition.

(6) Holding, conveying, and manufacturing systems, including gravimetric, pneumatic, closed, and automated systems, shall be of a design and construction that enables them to be maintained in an appropriate clean condition.

(7) Each freezer and cold storage compartment used to store and hold a dietary product capable of supporting growth of microorganisms shall be fitted with an indicating thermometer, temperature-measuring device, or temperature-recording device so installed as to show the temperature accurately within the compartment, and should be fitted with an automatic control for regulating temperature or with an automatic alarm system to indicate a significant temperature change in a manual operation.

(8) Instruments and controls used in the manufacture, processing, packing or holding dietary products, including instruments and controls used for measuring, regulating, or recording temperatures, pH, acidity, water activity, or other conditions that control or prevent the growth of undesirable microorganisms in such products shall be accurate and adequately maintained, and adequate in number for their designated uses.

(9) Compressed air or other gases mechanically introduced into a dietary product or used to clean equipment or utensils shall be treated in such a way that dietary ingredients or dietary supplements are not adulterated.

(b) Sanitation of equipment and utensils.

(1) Cleaning and sanitizing of utensils and equipment shall be conducted in a manner that protects against adulteration of raw materials, in-process or finished dietary product, processing equipment, utensils or packaging materials.

(2) All utensils and processing equipment shall be cleaned as frequently as necessary to protect against product adulteration.

(3) Utensils and processing equipment used for manufacturing or holding of dry dietary products shall be in a dry, sanitary condition at the time of use. When the surfaces are wet-cleaned, they shall, when necessary, be sanitized and thoroughly dried before subsequent use.

(4) In wet processing, when cleaning is necessary to protect against the introduction of microorganisms into a dietary product, all utensils and processing equipment shall be cleaned and sanitized as appropriate before use and after any interruption during which the utensils or processing equipment may have become contaminated. Where equipment and utensils are used in a continuous production operation or in back-to-back operations involving different batches of the same products, the utensils and product-contact surfaces of the equipment shall be cleaned and sanitized as appropriate.

(5) Nonproduct-contact surfaces of equipment should be cleaned as frequently as necessary to protect against product adulteration.

(6) Single-service articles (such as utensils intended for one-time use, paper cups, and paper towels) should be stored in appropriate containers and shall be handled, dispensed, used, and disposed of in a manner that protects against adulteration of dietary products, and contamination of utensils and processing equipment.

(7) Sanitizing agents shall be adequate and safe under conditions of use. Any facility, procedure, or machine is acceptable for cleaning and sanitizing equipment and utensils if it is established that the facility, procedure, or machine will routinely render equipment and utensils clean and provide adequate cleaning and sanitizing treatment.

(8) Cleaned and sanitized portable equipment with product-contact surfaces and utensils should be stored in a location and manner that protects product-contact surfaces from contamination.

(9) Equipment and utensils and finished product containers shall be maintained in an acceptable condition through appropriate cleaning and sanitizing, as necessary. Insofar as necessary, equipment shall be taken apart for thorough cleaning.

(10) Written procedures shall be established and followed for cleaning and maintaining equipment and utensils used in the manufacture of dietary products.

(11) A written record of major equipment cleaning and use shall be maintained in individual equipment logs that show the date, product and lot number of each batch processed. The persons performing the cleaning shall record in the log that the work was performed. Entries in the log should be in chronological order.

(12) Equipment, containers, and utensils used to convey, hold, or store raw materials, in-process material, rework, or finished product shall be constructed, handled, and maintained during manufacturing or storage in a manner that protects against contamination.

Quality Control and Laboratory Operations

Appropriate quality control operations shall be employed to assure that dietary products conform to appropriate standards of purity, quality and composition, and that packaging materials are safe and suitable for their intended purpose.

(a) Quality control unit.

(1) There shall be a quality control unit that has the responsibility and authority to:

(i) Approve or reject all procedures, specifications, controls, tests and examinations, or deviations from them, that impact the purity, quality and composition of a dietary ingredient or dietary supplement;

(ii) Approve or reject all raw materials, packaging materials labeling, and finished dietary products, including products manufactured. processed, packed, or held under contract by another company, based on adequate determination of conformance to established specifications; and

(iii) Assure that completed production records are reviewed as appropriate. Quality control shall be responsible for evaluation of errors committed in the manufacture of a product and shall have the final authority to determine if the error may be corrected in such manner that the product can be approved for distribution or must be destroyed. Such evaluations and their resolution must be documented and maintained with and/or cross referenced in the batch production record.

(2) Adequate laboratory facilities should be available, as needed, to the quality control unit.

(3) The responsibilities and procedures applicable to the quality control unit shall be established in writing and followed.

(b) Laboratory records. Laboratory records shall be maintained and shall include complete data derived from all specified tests.

(c) Expiration dating.

(1) Whenever a dietary ingredient or dietary supplement bears an expiration date, such date shall be supported by data and rationale to reasonably assure that the product meets established specifications at the expiration date.

(2) Appropriate accelerated stability studies or data from similar product formulations may be used for an initial determination of shelf life. Product shelf life shall be confirmed and may be extended on the basis of real time studies on product stored under labeled storage conditions.

Production and Process Controls

(a) Master production and control records.

(1) To assure uniformity from batch to batch, a master production and control record shall be prepared for the manufacture of each dietary ingredient and dietary supplement, and shall be reviewed and approved by the quality control unit.

(2) Master production and control records shall include, as appropriate.

(i) A complete list of raw materials used in the manufacture of a dietary product, designated by names or codes sufficiently specific to indicate any special quality characteristic(s).

(ii) An accurate statement of the weight or measure of each raw material used in the manufacture of a dietary product. Each batch shall be formulated with the intent to provide not less than 100 percent of each claimed dietary ingredient.

(iii) For dietary supplements, the name and weight or measure of each dietary ingredient per unit or portion or per unit of weight or measure of the supplement.

(iv) A statement concerning any calculated excess of dietary ingredient contained in a dietary supplement.

(v) A statement of the total weight or measure of any dietary supplement unit.

(vi) A statement of theoretical weight or measure of a dietary ingredient or dietary supplement expected at the conclusion of manufacture, including the maximum and minimum percentages of theoretical yield beyond which investigation is required.

(vii) A description of the product container(s), closure(s), and other packaging materials, including positive identification of all labeling used.

(viii) Manufacturing and control instructions, designed to assure that the dietary product has the purity, composition, and quality it is represented to possess.

(b) Batch production and control records.

(1) Individual batch production and control records shall be prepared and followed for each batch of dietary product produced and shall include complete information relating to the production and control of each batch.

(2) These records shall be an accurate reproduction of the appropriate master production and control record and shall include documentation that each significant step in the manufacture, processing, packing, or holding of the batch was accomplished, including:

(i) Dates;

(ii) Identity of individual major equipment and lines used;

(iii) Specific identification, including lot number, of each raw material or in-process material used;

(iv) Weight or measure of each raw material used in the course of processing;

(v) Quality control results;

(vi) Inspection of the packaging and labeling area;

(vii) A statement of the actual yield at the conclusion of manufacture and a statement of the percentage of theoretical yield, as appropriate;

(viii) Label control records, including specimens, copies, or records of all labels used;

(ix) Description of product containers and closures used; and

(x) Any special notes of investigations or deviations from the described process.

(3) Any deviation from written, approved specifications, standards, test procedures, or other laboratory control mechanisms shall be recorded and justified.

(c) Handling and storage of raw materials, in-process materials and rework.

(1) Raw materials, in-process materials and rework shall be inspected and segregated or otherwise handled as necessary to ascertain that they are clean and suitable for processing into dietary products and shall be stored under conditions that will protect against adulteration and minimize deterioration.

Containers of raw materials should be inspected on receipt to assure that their condition has not contributed to the adulteration or deterioration of the contents.

Liquid or dry raw materials and other ingredients received and stored in bulk form shall be held in a manner that protects against contamination.

(2) Raw agricultural materials that contain soil or other contaminants shall be washed or cleaned as necessary. Water used for washing, rinsing, or conveying raw agricultural materials shall be safe and of adequate sanitary quality. Notwithstanding the general requirement for potable water, water may be reused for washing, rinsing, or conveying raw agricultural materials, if it does not increase the level of contamination of the such materials.

(3) Raw materials, in-process materials, and rework shall be held in bulk, or in containers designed and constructed so as to protect against adulteration and shall be held at such temperature and relative humidity and in such a manner as to prevent a dietary ingredient or dietary supplement from becoming adulterated within the meaning of the act. Material scheduled for rework shall be identified as such.

(4) Frozen raw materials and other ingredients shall be kept frozen. If thawing is required prior to use, it shall be done in a manner that prevents the raw materials and other ingredients from becoming adulterated within the meaning of the act.

(5) Written procedures shall be established and followed describing the receipt, identification, examination, handling, sampling, testing and approval or rejection of raw materials.

(6) Each lot of raw material shall be identified with a distinctive lot number and shall be appropriately controlled according to its status (e.g., quarantined, approved, rejected).

(7) Raw material samples shall be examined and tested as follows:

(i) Each lot of raw material, in-process material, and rework that is liable to adulteration with filth, insect infestation, or other visually evident extraneous material shall be examined against established specifications for such adulteration, and shall comply with any applicable Food and Drug Administration regulations and guidelines. In lieu of such examination by the manufacturer, a guarantee or certification of examination may be accepted from the supplier of a component provided that the manufacturer establishes the reliability of the supplier's examination.

(ii) Each lot of a raw material that is liable to microbiological contamination that is objectionable in view of its intended use shall be subjected to microbiological tests before use. Raw materials shall either not contain levels of microorganisms that may produce food poisoning or other disease in humans, or they shall be otherwise treated during manufacturing operations so that they no longer contain levels that would cause the product to be adulterated within the meaning of the act. In lieu of such testing by the manufacturer, a guarantee or certification of analysis may be accepted from the supplier of a component provided that the manufacturer establishes the reliability of the supplier's analyses.

(iii) Raw materials and other ingredients susceptible to adulteration with aflatoxin or other natural toxins shall comply with current Food and Drug Administration regulations, guidelines, and action levels for poisonous or deleterious substances before these materials or ingredients are incorporated into a finished dietary ingredient or dietary supplement. Compliance with this requirement may be accomplished by analyzing these materials and ingredients for aflatoxins and other natural toxins or, in lieu of such testing by the manufacturer, a guarantee or certification of analysis may be accepted from the supplier of a component provided that the manufacturer establishes the reliability of the supplier's analyses.

(iv) Each lot of raw material shall undergo at least one test by the manufacturer to verify its identity. Such tests may include any appropriate test with sufficient specificity to determine identity, including chemical and laboratory tests, gross organoleptic analysis, microscopic identification, or analysis of constituent markers.

(v) Each lot of raw material shall be tested for conformity with all other established specifications. In lieu of such testing by the manufacturer, a guarantee or certification of analysis may be accepted from the supplier of a component provided that the manufacturer establishes the reliability of the supplier's analyses.

(8) Approved raw materials shall be rotated so that the oldest approved stock is used first. Deviation from this requirement is permitted if such deviation is temporary and appropriate.

(9) Raw materials shall be retested or reexamined and approved or rejected by the quality control after a specified time in storage or after exposure to air, heat, or other conditions that are likely to adversely affect the purity, quality, or composition of the raw material.

(10) Rejected raw materials, shall be identified and controlled under a system that prevents their use in manufacturing or processing operations for which they are unsuitable.

(d) Manufacturing operations.

(1) All operations in the receiving, inspecting, transporting, segregating, preparing, manufacturing, packaging, and storing of dietary products shall be conducted in accordance with adequate sanitation principles.

(2) All reasonable precautions shall be taken to assure that production procedures do not contribute adulteration from any source. Chemical, microbial, or extraneous-material testing procedures shall be used where necessary to identify sanitation failures or possible product adulteration.

(3) All product that has become contaminated to the extent that it is adulterated within the meaning of the act shall be rejected, or if permissible, treated or processed to eliminate the contamination.

(4) All product manufacturing, including packaging and storage, shall be conducted under such conditions and controls as are necessary to minimize the potential for the growth of microorganisms, or for the adulteration of raw materials, in-process materials and finished product.

(5) Measures such as sterilizing, irradiating, pasteurizing, freezing, refrigerating, controlling pH or controlling water activity (a_w) that are taken to destroy or prevent the growth of undesirable microorganisms, particularly those of public health significance, shall be adequate under the conditions of manufacture, handling, and distribution to prevent dietary products from being adulterated within the meaning of the act.

(6) Work-in-process shall be handled in a manner that protects against adulteration.

(7) Effective measures shall be taken to protect finished dietary ingredients and dietary supplements from adulteration by raw materials, in-process materials or refuse. When raw materials, in-process materials or refuse are unprotected, they shall not be handled simultaneously in a receiving, loading, or shipping area if that handling could result in adulterated dietary products. Dietary ingredients and dietary supplements transported by conveyor shall be protected against adulteration as necessary.

(8) All raw material containers, compounding and storage containers, processing lines and major equipment used during the production of a batch shall be properly identified at all times to indicate their contents and when necessary, the phase of processing of the batch.

(9) Effective measures shall be taken as necessary to protect against the inclusion of metal or other extraneous material in product. Compliance with this requirement may be accomplished by using sieves, traps, magnets, electronic metal detectors, or other suitable effective means.

(10) Dietary products, raw materials, and in-process materials that are rejected or adulterated within the meaning of the act shall be identified, stored and disposed of in a manner that protects against the adulteration of other products.

(11) Written procedures shall be established and followed that describe

appropriate tests, and/or examinations to be conducted that may be necessary to assure the purity, composition, and quality of the finished product.

(12) Written procedures shall be established and followed prescribing the method for reprocessing batches or operational start-up materials that do not conform to finished goods standards or specifications. Finished goods manufactured using such materials shall meet all established purity, composition, and quality standards.

(13) Mechanical manufacturing steps such as cutting, sorting, inspecting, shredding, drying, grinding, blending, and sifting shall be performed so as to protect dietary ingredients and dietary supplements against adulteration. Compliance with this requirement may be accomplished by providing adequate physical protection of dietary products from contact with adulterants. Protection may be provided by adequate cleaning and sanitizing of all processing equipment between each manufacturing step.

(14) Heat blanching, when required in the preparation of a dietary product, should be effected by heating the product to the required temperature, holding it at this temperature for the required time, and then either rapidly cooling the material or passing it to subsequent manufacturing without delay. Thermophilic growth and contamination in blanchers should be minimized by the use of adequate operating temperatures and by periodic cleaning. Where the blanched product is washed prior to filling, potable water shall be used.

(15) Intermediate or dehydrated dietary products that rely on the control of water activity (a_w) for preventing the growth of undesirable microorganisms shall be processed to and maintained at a safe moisture level. Compliance with this requirement may be accomplished by any effective means, including employment of one or more of the following practices:

(i) Monitoring the water activity (a_w) of the material.

(ii) Controlling the soluble solids-water ratio in finished product.

(iii) Protecting finished product from moisture pickup, by use of a moisture barrier or by other means, so that the water activity (a_w) of the product does not increase to an unsafe level.

(16) Dietary ingredients and dietary supplements that rely principally on the control of pH for preventing the growth of undesirable microorganisms shall be monitored and maintained at an appropriate pH. Compliance with this requirement may be accomplished by any effective means, including employment of one or more of the following practices:

(i) Monitoring the pH of raw materials, in process material, and finished product.

(ii) Controlling the amount of acid added to the product.

(17) When ice is used in contact with dietary products, it shall be made from potable water, and shall be used only if it has been manufactured in accordance with current good manufacturing practice as outlined in 21 CFR part 110.

(e) Packaging and labeling operations.

(1) Filling, assembling, packaging, and other operations shall be performed in such a way that dietary products are protected against adulteration. Compliance with this requirement may be accomplished by any effective means, including:

(i) Adequate cleaning and sanitizing of all filling and packaging equipment, utensils, and product containers, as appropriate.

(ii) Using materials for product containers and packaging materials that are safe and suitable.

(iii) Providing physical protection from adulteration, particularly airborne contamination.

(iv) Using sanitary handling procedures.

(2) Written procedures shall be established and followed describing in sufficient detail the control procedures employed for the receipt, storage, handling, sampling, examination, and/or testing that may be necessary to assure the identity of labeling and the appropriate identity, cleanliness and quality characteristics of packaging materials for dietary products.

(3) For dietary supplements, labels and other labeling materials for each different product type, strength, or quantity of contents shall be stored separately with suitable identification.

(4) Obsolete labels, labeling, and other packaging materials for dietary products shall be destroyed.

(5) Written procedures shall be established and followed to assure that correct labels, labeling, and packaging materials are issued and used for dietary products.

(6) Dietary ingredient and dietary supplement packages shall be identified with a lot number that permits determination of the history of the manufacture and control of the batch.

(7) Packaged and labeled dietary supplements shall be examined to provide assurance that containers and packages in the lot have the correct label and lot number. Products not meeting specifications shall be rejected by the quality control unit.

Warehousing, Distribution and Post-Distribution Procedures

(a) Storage and distribution.

(1) Storage and transportation of finished product shall be under conditions that will protect product against physical, chemical, and microbial adulteration as well as against deterioration of the product and the container.

(2) Adequate distribution records shall be maintained and retained by the manufacturer at least 1 year beyond expected product shelf life, whereby an effective product recall can be achieved should one become necessary.

(b) Reserve samples. An appropriately identified reserve sample that is representative of each batch of a dietary product should be retained and stored under conditions consistent with the product labeling until at least 1 year after the expiration date, or if no expiration date is identified on the product, for at least 3 years after the date of manufacture. The reserve sample should be stored in the same immediate container-closure system in which the finished product is marketed or in one that provides similar protection. The reserve sample shall consist of at least twice the quantity necessary to perform all the required tests.

(c) Records retention.

(1) Any laboratory, production, control or distribution record specifically associated with a batch of product shall be retained for at least 1 year after the expiration date of the batch, or if no expiration date is identified on the product, for at least 3 years after the date of manufacture.

(2) Raw material records shall be maintained for at least 1 year after the expiration date of the last batch of product incorporating the raw material, or if no expiration date is identified on the product, for at least 3 years after the date of manufacture of the finished product.

(d) Complaint files.

(1) Written procedures describing the handling of all written and oral complaints regarding a dietary product shall be established and followed. Such procedures shall 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, for such products, a determination as to the need for an investigation.

(2) A written record of each complaint shall be maintained, until at least 1 year after the expiration date of the product, or 1 year after the date that the complaint was received, whichever is longer.

(3) The written record shall include, where known: The name and description of the product, lot number, name of complainant, nature of complaint, and reply to complainant, if any.

(4) Where an investigation is conducted, the written record shall include the findings of the investigation and followup action taken.

(e) Returned products. Returned dietary products shall be identified as such and held. If the conditions under which returned dietary 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 purity, composition or quality of the product, the returned product shall be destroyed unless examination, testing, or other investigations prove the product meets appropriate standards of purity, composition, and quality. A product may be reprocessed provided the subsequent product meets appropriate specifications. Records pertaining to returned products that are subsequently reprocessed and/or redistributed shall be maintained and shall include the name and description of the

product, lot number, reason for the return, quantity returned, date of disposition, and ultimate disposition of the returned product.

(f) Product salvaging. Dietary 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 shall 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: (1) Evidence from laboratory tests that the products meet all applicable standards of purity, quality, and composition; and (2) evidence from inspection of the premises that the products and their associated packaging were not subjected to improper storage conditions as a result of the disaster or accident. Records including name, lot number, and disposition shall be maintained for products subject to this section.

(g) Defect action levels.

(1) Some dietary ingredients and dietary supplements, even when produced under current good manufacturing practice, contain natural or unavoidable defects that at low levels are not hazardous to health. The Food and Drug Administration establishes maximum levels for these defects in dietary products produced under current good manufacturing practice and uses these levels in deciding whether to recommend regulatory action.

(2) Defect action levels are established for dietary products whenever it is necessary and feasible to do so. These levels are subject to change upon the development of new technology or the availability of new information.

(3) Compliance with defect action levels does not excuse violation of the requirement in section 402(a)(4) of the act that dietary products not be prepared, packed, or held under unsanitary conditions or the requirements in this part that dietary product manufacturers, distributors, and holders shall observe current good manufacturing practice. Evidence indicating that such a violation exists causes a dietary product to be adulterated within the meaning of the act, even though the amounts of natural or unavoidable defects are lower than the currently established defect action levels. The manufacturer, distributor, and holder of a dietary product shall at all times utilize quality control operations that reduce natural or unavoidable defects to the lowest level currently feasible.

(4) The mixing of a dietary ingredient or dietary supplement containing defects above the current defect action level with another lot of dietary ingredient or dietary supplement is not permitted and renders the final product adulterated within the meaning of the act, regardless of the defect level of the final product.

(5) A compilation of the current defect action levels for natural or unavoidable defects in dietary products that present no health hazard may be obtained upon request from the Industry Programs Branch (HFF–326), Center for Food Safety and Applied Nutrition, Food and Drug Administration, 200 C St. SW., Washington, DC 20204.

III. Economic Issues

FDA requests comment on and descriptions of CGMP in the dietary supplement industry. The agency seeks information on how closely the current practices of firms manufacturing dietary supplements conform to the industry submission, and on how costly it would be to bring those practices into conformity. The agency asks for comments on whether there should be new CGMP regulations, whether the regulations should be mandatory or voluntary, and, if mandatory, how long it would take establishments to come into compliance. Because FDA would like to determine how current manufacturing practices differ with plant size, the agency particularly requests comments from both small businesses and large businesses.

The establishment of CGMP could have effects on small businesses in the dietary supplement industry. There are several possible definitions of ''small'' that can be applied to dietary supplements. Although the Small Business Administration (SBA) does not define small for the dietary supplement industry, the industry's products are generally closest to foods and botanicals. The SBA size standards for small businesses are 500 or fewer employees for food preparations, 750 or fewer employees for botanical products, and annual sales revenue less than $5 million for businesses that cannot be classified into a specific industry. The *Nutrition Business Journal* (August 1996) divides firms into large (annual sales over $100 million), medium (annual sales between $20 and $100 million), and small (annual sales under $20 million). Under any of the possible definitions, instituting CGMP's for the industry has the potential to affect a significant number of small businesses. FDA asks for comments on this matter.

IV. Summary and Request for Comments

FDA asks for comments on the regulatory framework presented in the industry submission in section II. of this document and the economic issues discussed above. In addition, the agency requests comments on the following issues:

1. Is there a need to develop specific defect action levels (DAL's) for dietary ingredients? While FDA has established DAL's for many food ingredients, including botanical food ingredients, these DAL's reflect their use for specific purposes, for example, the use of many botanicals as spices, flavorings, or other trace ingredients in foods. The DAL's are designed to provide reasonable assurance of the safety and wholesomeness of the ingredient when it is present in the food supply in small quantities. However, the use of a botanical in a dietary supplement may result in a much greater exposure to the botanical ingredient for consumers because the dietary supplement will be consumed in greater amounts than if the ingredient was in a food as a spice or flavoring agent. Therefore, FDA tentatively concludes that it would not be appropriate to apply the current DAL's to dietary supplements, and the agency requests comments that would assist in developing DAL's for dietary supplements.

2. FDA requests comments on appropriate testing requirements to provide positive identification of dietary ingredients, particularly plant materials, used in dietary supplements. The misidentification of dietary ingredients, particularly plant materials, used in dietary supplements may present a significant public health and economic concern. However, the analytical methodology available for identifying many dietary ingredients is limited. Furthermore, section 402(g)(2) of the act states that CGMP regulations may not impose standards for which there is no current and generally available analytical methodology. FDA is asking for comments on the technical and scientific feasibility for the identification of different types of dietary ingredients. The agency also solicits information on what constitutes ''adequate testing'' for identity of different types of ingredients, and, in the absence of testing, what types of practices would be effective alternatives to testing to ensure the identity of different types of dietary ingredients.

3. FDA requests comments on standards that should be met in certifying that a dietary ingredient or dietary supplement is not contaminated with filth; that it is free of harmful contaminants, pesticide residues, or other impurities; that it is microbiologically safe; and that it meets specified quality and identity standards. For food (§ 110.80), it is CGMP for a manufacturer to accept certification from a supplier that products do not contain microorganisms or filth or other foreign material that would adulterate the product in lieu of direct testing or evaluation of the raw materials or final product. However, many ingredients used in dietary supplements do not have a history of food use in the United

States, and thus the potential for contamination with microorganisms or filth is unknown. The agency does not have information that provides a basis for it to determine whether certification by a supplier provides adequate assurance that a dietary ingredient is what it purports to be and is not adulterated. Therefore, the agency asks for comments on whether a certification will provide assurance that dietary ingredients are not contaminated, or whether specific testing requirements are necessary and would effectively ensure the safety and wholesomeness of these products.

4. CGMP is intended to ensure that a firm follows quality control and other procedures necessary to ensure that a food is safe for its intended use. It is possible that a firm will develop adequate standard operating procedures and other mechanisms to achieve this end, but that such procedures will not be followed. The agency asks for comments on whether there is a need for CGMP to include requirements for manufacturers to establish procedures to document that the procedures prescribed for the manufacture of a dietary supplement are followed on a continuing or day-to-day basis.

FDA is aware that no provision of part 110 deals with the establishment of documentation that a manufacturer is following established procedures prescribed for the manufacture of a dietary supplement, and that section 402(g) of the act states that any CGMP regulations for dietary supplements are to be modeled after the CGMP regulations for food. However, FDA's tentative judgment is that section 402(g) of the act does not preclude FDA from adopting CGMP regulations for dietary supplements that have no counterpart in part 110 if there is an appropriate basis for so doing. FDA requests comments on this issue.

5. The agency asks for comments on whether dietary supplement CGMP should require that reports of injuries or illnesses to a firm be evaluated by competent medical authorities to determine whether followup action is necessary to protect the public health. Many dietary supplements contain pharmacologically active substances, and some may contain potential allergens that result in adverse events in certain consumers. The presence of pharmacologically active substances in these products distinguishes them from most other foods. Because of the potential for serious injury or illness in some persons from the consumption of such substances, it may be necessary that trained medical professionals, rather than quality control or nonmedical scientific/regulatory personnel, evaluate all reported adverse events associated with the use of a specific substance and advise responsible management of their findings. FDA also asks for comments on whether CGMP for dietary supplements should contain a requirement that a firm establish procedures for determining whether a reported injury constitutes a serious problem, and what actions are to be taken when serious problems are identified.

FDA is aware that no provision of part 110 deals with followup to reports of illness or injury, and that section 402(g) of the act states that any CGMP regulations for dietary supplements are to be modeled after the CGMP regulations for food. However, as stated above, FDA's tentative judgment is that section 402(g) of the act does not preclude FDA from adopting CGMP regulations for dietary supplements that have no counterpart in part 110 if there is an appropriate basis for so doing.

6. FDA asks for comments on whether CGMP for dietary supplements should require that manufacturers establish procedures to identify, evaluate, and respond to potential safety concerns with dietary ingredients. As discussed above, many dietary ingredients have little history of use in food in the United States or of use in the amounts that would be used in a dietary supplement. Moreover, dietary ingredients are excepted from the definition of ''food additive'' in section 201(s)(6) of the act (21 U.S.C. 321(s)(6)). In these circumstances, it may be appropriate to provide that CGMP requires that a manufacturer critically evaluate the available scientific information on the safety of the dietary ingredients that it intends to use in its products to assure itself that those products will be safe. FDA asks for comments on whether such an evaluation is necessary, and, if so, what elements need to be included in such an evaluation and their relative importance (e.g., the presence and potency of pharmacologically active substances, the presence of different microorganisms, the presence of different contaminants and impurities). In addition, the agency asks for comments on whether it should require that such an evaluation be documented in a firm's records, and, if so, what type of records would be adequate to document that such an evaluation had occurred.

7. The agency asks for comments on whether specific controls are necessary for computer controlled or assisted operations. Many modern manufacturing operations rely on computers to ensure that proper procedures are followed in the handling and processing of ingredients and the manufacture of food products. If such equipment is used in the production of dietary supplements, FDA requests comment on how best to ensure that the software programs and equipment used to direct and monitor the manufacturing process are properly designed, tested, validated, and monitored.

8. The agency asks for comments on whether certain, or all, of the requirements for manufacturing and handling dietary ingredients and dietary supplements may be more effectively addressed by a regulation based on the principles of Hazard Analysis and Critical Control Points (HACCP), rather than the system outlined in the industry submission. FDA has issued regulations based on HACCP to ensure the safety of other foods (i.e., seafood) (Ref. 3) and has issued an advance notice of proposed rulemaking on the appropriateness of extending the HACCP concept to other segments of the food industry (Ref. 4). HACCP-based requirements enable manufacturers to develop and implement processes and controls that are tailored to their specific products and manufacturing operations. Because of the wide variety of dietary ingredients and dietary supplements and because of the heterogenous composition of the dietary supplement industry, CGMP based on the principles of HACCP may provide a more flexible and less burdensome regulatory framework for manufacturers and distributors than the approach set out in the industry submission.

9. The dietary supplement industry includes a broad spectrum of firms that conduct one or more distinct operations, such as the manufacture or distribution of raw dietary ingredients, the manufacture of finished products, or solely the distribution and sale of finished products (manufactured by a separate firm) at the wholesale or retail level. Consequently, the dietary supplement CGMP regulations may need to address the distinctive requirements of each of these segments of the industry in order to effectively ensure that dietary supplements are what they are represented to be and are safe for their intended use. The agency asks for comments on whether broad CGMP regulations will be adequate, or whether it will be necessary to address the operations of particular segments of the dietary supplement industry.

VII. Comments

Interested persons may, on or before May 7, 1997, submit to the Dockets Management Branch (address above)

written comments regarding this proposal. Two copies of any comments are to be submitted, except that individuals may submit one copy. Comments are to be identified with the docket number found in brackets in the heading of this document. Received comments may be seen in the office above between 9 a.m. and 4 p.m., Monday through Friday.

VIII. References

The following references have been placed on display in the Dockets Management Branch (address above) and may be seen by interested persons between 9 a.m. and 4 p.m., Monday through Friday.

1. Memorandum of Meeting, Center for Food Safety and Applied Nutrition, Food and Drug Administration, Washington, DC, November 30, 1995.

2. Discussion Draft of GMP's for Dietary Supplements, submitted to the Food and Drug Administration, November 21, 1995.

3. Food and Drug Administration, ''Procedures for the Safe and Sanitary Processing and Importing of Fish and Fishery Products,'' final rule, 60 FR 65096, December 18, 1995.

4. Food and Drug Administration, Food and Safety Assurance Program; ''Development of Hazard Analysis Critical Control Points for the Food Industry,'' proposed rule, 59 FR 39888, August 4, 1994.

Dated: December 11, 1996.

William B. Schultz,

Deputy Commissioner for Policy.

[FR Doc. 97–3014 Filed 2–5–97; 8:45 am]

BILLING CODE 4160–01–F