DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service
Food and Drug Administration

Memorandum

2530 '03 MAY -9 P1:49

Date: May 6, 2003

From: Chemist, Division of Dietary Supplement Programs and Compliance, Office of Nutritional Products, Labeling and Dietary Supplements, HFS-810

Subject: Submission to 96N-0417: Development of Strategy for Dietary Supplements

To: Dockets Management Branch, HFA-305

In accordance with requirements set forth at 21 Code of Federal Regulations § 10.65, the attached list of attendees and seven related information handouts including:

- "FDA Proposes Labeling and Manufacturing Standards Dietary Supplements"
- "FDA Proposes Manufacturing and Labeling Standards for all Dietary Supplements – March 7, 2003"
- "*For Immediate Release, PO3-14, March 7, 2003:* FDA Proposes Labeling and Manufacturing Standards for all Dietary Supplements"
- FEDERAL REGISTER /Vol. 68, No.49/Thursday, March 13, 2003: 21 CFR Parts 111 & 112; Current Good Manufacturing Practice in Manufacturing, Packing, or Holding Dietary Ingredients and Dietary Supplements; Proposed Rule; pp 12158-12166
- "GUIDANCE FOR SMALL BUSINESSES: Submission of Comments for CFSAN Rulemaking – U.S. Food and Drug Administration, Center for Food Safety and Applied Nutrition, October 21, 2002"
- UNITED STATES FOOD AND DRUG ADMINISTRATION, OFFICE OF REGULATORY AFFAIRS & CENTER FOR FOOD SAFETY AND APPLIED NUTRITION: Satellite Broadcast of "Current Good Manufacturing Practice in Manufacturing, Packing, or Holding Dietary Ingredients and Dietary Supplements; Proposed Rule" information sheet
- meeting agenda "FDA Proposed Regulation Current Good Manufacturing Practices (CGMPs) Dietary Ingredients and Dietary Supplements Public Stakeholder Meeting"

as provided at the April 29, 2003 meeting on Current Good Manufacturing Practices for Dietary Ingredients and Dietary Supplements should be placed on public display in docket number 96N-0417 as soon possible. Thank you for your assistance.

Kenneth M. P. Taylor, Ph.D.

Attachments

96N-0417 M 1

APRIL 29, 2003 CGMP STAKEHOLDER MEETING ATTENDEES

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FDA Proposed Regulation
Current Good Manufacturing Practices (CGMPs)
Dietary Ingredients and Dietary Supplements
Public Stakeholder Meeting
April 29, 2003, College Park, MD

9:00-9:10 AM	**Welcome and Opening Remarks** Virginia Wilkening, Deputy Director, Office of Nutritional Products, Labeling, and Dietary Supplements, CFSAN/FDA, College Park, MD Peter Vardon, Economist, Division of Market Studies FDA/CFSAN, College Park, MD
9:10-9:40 AM	**Background and Proposal Highlights** Karen Strauss, Consumer Safety Officer, FDA/CFSAN, College Park, MD
9:40- 9:55 AM	Questions and Answers
9:55-10:10 AM	**Proposed Production and Process Controls** Sara J. Dent Acosta, Consumer Safety Officer FDA San Diego Resident Post, San Diego, CA
10:10-10:25 AM	Questions and Answers
10:25-10:40 AM	Morning Break
10:40-11:00 AM	**Proposed Laboratory Operations** Steven Musser, Lead Scientist for Chemistry FDA/CFSAN, College Park, MD
11:00-11:15 AM	Questions and Answers
11:15-11:20 AM	**Public Comment Period and Next Steps** Karen Strauss, Consumer Safety Officer
11:20-11:35 AM	**Economic Impact Analysis** Peter Vardon, Economist, Division of Market Studies FDA/CFSAN, College Park, MD
11:35-12:00 Noon	Questions and Answers
12:00-1:30 PM	Lunch (on your own—see restaurant guide)
1:30-1:50 PM	**Regulatory Flexibility Act and How to Comment** Richard Williams, Director, Division of Market Studies FDA/CFSAN, College Park, MD Marie Falcone, Small Business Representative, FDA Central Region
1:50-2:00 PM	Questions and Answers

2:00-2:30 PM	**Small Business Questions on Proposed Requirements** Richard Williams, Karen Strauss, Sara Dent Acosta, and Peter Vardon
2:30-3:45 PM	**Breakout Sessions**
3:45-5:00 PM	**Breakout Session Summaries and Discussion**

U.S. Food and Drug Administration
FDA News
Department of Health and Human Services

FDA Proposes Manufacturing and Labeling Standards for all Dietary Supplements

March 7, 2003

TODAY'S ACTION:

The Food and Drug Administration (FDA) today took action to help Americans get accurately labeled and properly manufactured dietary supplements, through its **Proposed Rule for Dietary Supplement Current Good Manufacturing Practices** (CGMPs). FDA is submitting this proposed rule as part of the agency' s ongoing effort to help Americans take more control over their own health.

FDA's Proposed Rule for Dietary Supplement Labeling and Manufacturing Standards

This proposed rule would establish the standards necessary to ensure that dietary supplements and dietary ingredients are not adulterated with contaminants or impurities and are labeled to accurately reflect the active ingredients and other ingredients in the product.

Specifically this proposal would:

- Require the use of new industry-wide standards in the manufacturing, packing, and holding of dietary supplements, thus reducing risks associated with dietary supplements that are contaminated with harmful or undesirable substances such as pesticides, heavy metals, or other impurities or are not properly labeled to accurately describe what they contain.

- Ensure that the identity, purity, quality, strength, and composition of dietary supplements are accurately reflected on the product label, which would be a significant step in assuring consumers they are purchasing the type and amount of ingredients declared.

Science-Based Consumer Protection

Previously, dietary supplements have not been subject to mandatory standards for manufacturing or labeling. Congress gave FDA the authority to develop and implement CGMPs as part of the Dietary Supplement Health and Education Act of 1994 (DSHEA).

years, analyses of dietary supplements by a private sector laboratory suggest that a substantial number of dietary supplement products analyzed may not contain the amounts of dietary ingredients as reflected on the product 's labeling.

- In addition, dietary supplements have been recalled because of microbiological, pesticide, and heavy metal contamination – adulteration that might be prevented through a uniform set of manufacturing requirements.

- Examples of product quality problems that the proposed rule would help prevent are:

    - dietary supplements that contain much more than listed on the label and may be harmful
    - dietary supplements that contain less ingredients than listed on the label
    - wrong ingredient,
    - drug contaminant,
    - other contaminant (e.g., bacteria, pesticide, glass, lead),
    - foreign material in a dietary supplement container,
    - improper packaging, and
    - mislabeled

Additional materials:

- Press Release
- Proposed Rule (PDF 551 KB)
- Fact Sheet

Office of Public Affairs

The proposed rule addresses the quality of manufacturing processes for dietary supplements, and the accurate listing of supplement ingredients. It does not limit consumers' access to dietary supplements, or address the safety of their ingredients, or their effects on health when proper manufacturing techniques are used. Rather, the proposed rule creates a level playing field for the industry by ensuring that every firm uses high-quality manufacturing procedures and uses the same rules for describing their ingredients.

In December, FDA issued a report on its new policies for taking legal action against dietary supplements that make misleading health claims. Last week, to address concerns about the safety of ephedra, FDA announced a proposed warning label, issued warning letters on certain ephedra marketing practices, and announced a public comment period regarding potential further restrictions on ephedra products.

Background

Under DSHEA, dietary supplement manufacturers have an essential responsibility to substantiate the safety of the dietary ingredients they use in manufacturing a product. Manufacturers are also responsible for determining that any representations or claims made about their products are substantiated by adequate evidence to show that they are not false or misleading. With this proposed rule, FDA will have the authority to determine standards that firms should apply in production and labeling.

- The proposed CGMPs provide much-needed requirements in these areas:

    - Design and construction of physical plants,
    - Quality control procedures,
    - Testing of final product or incoming and in-process materials
    - Handling consumer complaints, and
    - Maintaining records to demonstrate compliance with these regulations.

- Since 1993, FDA has received about 7000 dietary supplement-related voluntary adverse event reports. Below is a breakout of adverse event reports over the past four years:

    - Year 2002: 1,214 adverse event reports
    - Year 2001: 553 adverse event reports
    - Year 2000: 500 adverse event reports
    - Year 1999: 528 adverse event reports

- Many of these adverse events may be related to misbranding or adulteration. In recent

U.S. Food and Drug Administration
FDA News
Department of Health and Human Services

FOR IMMEDIATE RELEASE
PO3-14
March 7, 2003

Media Inquiries: 301-827-6250
Consumer Inquiries: 888-INFO-FDA

FDA Proposes Labeling and Manufacturing Standards For All Dietary Supplements

The Food and Drug Administration today took action to help consumers get accurately labeled and unadulterated dietary supplements by proposing a new regulation to require current good manufacturing practices (CGMPs) in their manufacturing, packing, and holding. The proposed rule would, for the first time, establish standards to ensure that dietary supplements and dietary ingredients are not adulterated with contaminants or impurities, and are labeled to accurately to reflect the active ingredients and other ingredients in the product.

This proposed rule includes requirements for designing and constructing physical plants, establishing quality control procedures, and testing manufactured dietary ingredients and dietary supplements. It also includes proposed requirements for maintaining records and for handling consumer complaints related to CGMPs.

"Americans must have confidence that the dietary supplements they purchase are not contaminated and that they contain the dietary ingredients and the amounts claimed on the labels," said HHS Secretary Tommy G. Thompson. "Millions of Americans use dietary supplements, and we owe it to them to ensure that they are getting the products they're paying for."

In recent years, analyses of dietary supplements by a private sector laboratory suggest that a substantial number of dietary supplement products analyzed may not contain the amounts of dietary ingredients that would be expected to be found based on their product labels. For example:

- Five of 18 soy and/or red clover-containing products were found to contain only 50 percent to 80 percent of the declared amounts of isoflavones.
- Of 25 probiotic products tested, 8 contained less than 1 percent of the claimed number of live bacteria or the number of bacteria that would be expected to be found in such a product.

FDA has also encountered products being marketed that are not accurately labeled or

quality problems the CGMPs would help prevent include products that are superpotent or subpotent; that contain the wrong ingredient, a drug contaminant, or other contaminants (e.g., bacteria, pesticide, glass, lead); that contain foreign material; and that are improperly packaged and mislabeled.

This proposal is intended to cover all types of dietary supplements. However, to limit any disruption for dietary supplements produced by small businesses, FDA is proposing a three-year phase-in of a final rule for small businesses. The proposal includes flexible standards that can evolve with improvements in the state of science, such as in validating tests for identity, purity, quality, strength, and composition of dietary ingredients.

FDA is soliciting comments from the public and industry on how this proposed regulation can best achieve the goals of promoting accurate labeling information and preventing adulteration without imposing unnecessary regulatory burdens. Written comments will be received until 90 days after the date of publication in the Federal Register and may be addressed to Dockets Management Branch (HFA-305), Food and Drug Administration, 5630 Fishers Lane, Room 1061, Rockville, MD 20852.

Additional information, including the proposed rule, may be found on FDA's Website at the following addresses:

- Fact Sheet
- Backgrounder
- Proposed Rule (PDF 551 KB)
- Dietary Supplements Home Page

Office of Public Affairs

contain contaminants that should not be present or may be harmful. For example:

- One firm recalled its dietary supplements that were contaminated with excessive amounts of lead, which may have posed a health risk to many consumers, especially children and women of childbearing age.
- Another firm recalled a niacin product after it received reports of nausea, vomiting, liver damage, and heart attack associated with the use of its product. A dietary ingredient manufacturing firm had mislabeled a bulk ingredient container that subsequently was used by another firm in making a product that contained almost ten times more niacin than the amount that may be safe.
- Another firm recalled its product after it was found that a dietary supplement containing folic acid, which is often taken by women to reduce the risk of having a baby with neural tube defects, contained only 35 percent of the amount of folic acid claimed on the label.

"This proposed regulation is another major step in our efforts to help Americans take more control over their own health. Too often, consumers purchase dietary supplements based on inaccurate or incomplete information on what they are getting. This proposed regulation would require that dietary supplements provide accurate information on the type and amount of ingredients they contain and that dietary supplements are produced using safe methods, " said Mark B. McClellan, M.D., Ph.D., Commissioner of Food and Drugs. "Consumers should have access to dietary supplements that are accurately labeled and are free from contaminants."

FDA's action will also permit more informative research on dietary supplements, to improve the science available on their safety and effectiveness. "We commend FDA for proposing good manufacturing practices that will help ensure that all dietary supplements are of the quality that the public deserves. Since credible research studies cannot be performed using many of the current, highly variable products, these practices will also speed our ability to provide the public with more definitive data about the safety and effectiveness of popular dietary supplements," said Dr. Stephen Straus, Director, National Center for Complementary and Alternative Medicine at the National Institutes of Health.

This proposed regulation follows the agency's consumer initiative announced last December intended to improve FDA's policies on providing information about health consequences of food and dietary supplements and to increase enforcement efforts to prevent misleading health claims made by certain dietary supplement manufacturers. By putting in place requirements that will ensure universal good manufacturing practices, the proposed regulation should serve to eliminate the guesswork for consumers about which dietary supplements may or may not be of high quality. In turn, manufacturers of dietary supplements will have to compete based on the quantity of their product, not through potentially misleading labels or inexpensive but less safe manufacturing processes.

Under the CGMP proposal, manufacturers would be required to evaluate the identity, purity, quality, strength, and composition of their dietary ingredients and dietary supplements. If dietary supplements contain contaminants or do not contain the dietary ingredient they are represented to contain, FDA would consider those products to be adulterated. Some product

U.S. Food and Drug Administration
FDA News
Department of Health and Human Services

FDA Proposes Labeling and Manufacturing Standards Dietary Supplements

FDA's Proposed Rule

- FDA's proposed rule, if adopted as proposed, would establish new standards or "current good manufacturing practices" (CGMPs) to help reduce risks associated with adulterated or misbranded dietary supplement products.
- The proposed rule would establish industry-wide standards necessary to ensure that dietary supplements are manufactured consistently as to identify, purity, quality, strength, and composition.
- The minimum standards include requirements on the design and construction of physical plants that facilitate maintenance, cleaning, and proper manufacturing operations, for quality control procedures, for testing final product or incoming and inprocess materials, for handling consumer complaints, and for maintaining records.
- Examples of product quality problems the CGMPs will help prevent are: superpotent, subpotent, wrong ingredient, drug contaminant, other contaminant (e.g., bacteria, pesticide, glass, lead), color variation, tablet size or size variation, under-filled containers, foreign material in a dietary supplement container, improper packaging, and mislabeling.
- The proposed CGMPs would apply to all firms that manufacture, package, or hold dietary ingredients or dietary supplements, including those involved with the activities of testing, quality control, packaging and labeling, and distributing them. The proposed regulations also would apply to both domestic firms and foreign firms that manufacture, package, or hold dietary ingredients and dietary supplements for distribution into the U.S.
- FDA is soliciting comments from the public and industry on this proposal. Written comments will be received until 90 days after the date of publication in the Federal Register.

Consumer Benefits

- Consumers should have access to dietary supplements that meet quality standards and that are free from contamination and are accurately labeled.
- The proposed rule would not limit consumers' access to dietary supplements. The proposed rule, if it becomes final as proposed, would give consumers greater confidence that the dietary supplement they use will have the identity, purity, quality, strength, and composition that is claimed on the label.
- The proposed rule addresses the quality of manufacturing processes for dietary

supplements and the accurate listing of supplement ingredients. It does not limit consumers' access to dietary supplements, or address the safety of their ingredients, or their effects on health when proper manufacturing techniques are used.

- Last week, to address concerns about the safety of ephedra, FDA announced a proposed warning label, issued warning letters on certain ephedra marketing practices, and announced a public comment period regarding potential further restrictions on ephedra products.
- This proposed regulation follows FDA's consumer initiative announced last December intended to improve FDA's policies on providing information about health consequences of food and dietary supplements and to increase enforcement efforts to prevent misleading health claims made by certain dietary supplement manufacturers.

Manufacturers

- Under DSHEA, manufacturers have an essential responsibility to substantiate the safety and efficacy of the dietary ingredients they use in manufacturing a product.
- Dietary supplements have been recalled because of microbiological, pesticide, and heavy metal contamination - adulteration that might be prevented through a uniform set of manufacturing requirements.
- The CGMPs will assist manufacturers in producing unadulterated and properly labeled dietary supplements and will provide a basis for consumers to have confidence that the dietary supplement products they purchase contain the identity, purity, quality, strength, and composition that the label claims.
- Manufacturers are also responsible for determining that any representations or claims made about their products are substantiated by adequate evidence to show that they are not false or misleading. With this proposed rule, FDA will have the authority to determine standards that firms should apply in production and labeling.
- Under the CGMP proposed rule, manufacturers would be required to:

    - Employ qualified employees and supervisors;
    - Design and construct their physical plant in a manner to protect dietary ingredients and dietary supplements from becoming adulterated during manufacturing, packaging, and holding;
    - Use equipment and utensils that are of appropriate design, construction, and workmanship for the intended use;
    - Establish and use a quality control unit and master manufacturing and batch production records;
    - Hold and distribute materials used to manufacture, package, and label dietary ingredients, dietary supplements, and finished products under appropriate conditions of temperature, humidity, light, and sanitation so that their quality is not affected.
    - Keep a written record of each consumer product quality complaint related to CGMPs; and
    - Retain records for 3 years beyond the date of manufacture of the last batch of dietary ingredients or dietary supplements.

- Examples of product quality problems that the proposed rule would help prevent are:

  - dietary supplements that contain much more than listed on the label and may be harmful
  - dietary supplements that contain less ingredients than listed on the label
  - wrong ingredient,
  - drug contaminant,
  - other contaminant (e.g., bacteria, pesticide, glass, lead),
  - foreign material in a dietary supplement container,
  - improper packaging, and
  - mislabeled

- Manufacturers are also responsible for determining that any representations or claims made about their products are substantiated by adequate evidence to show that they are not false or misleading. With this proposed rule, FDA will have the authority to determine standards that firms should apply in production and labeling.

Background

- FDA has found that manufacturing problems have been associated with dietary supplements. Products have been recalled because of microbiological, pesticide, and heavy metal contamination and because they do not contain the dietary ingredients they are represented to contain or they contain more or less than the amount of the dietary ingredient claimed on the label.
- In recent years, several private sector laboratories analyses found that a substantial number of dietary supplement products analyzed did not contain the amount of dietary ingredients claimed in their product labels.
- The Dietary Supplement Health and Education Act of 1994 provide the Secretary of Health and Human Services, and the FDA by delegation, the express authority to issue regulations on dietary supplement CGMPs.

U. S. Food and Drug Administration
Center for Food Safety and Applied Nutrition
October 21, 2002

Guidance for Small Businesses Submission of Comments for CFSAN Rulemaking

Guide for Small Businesses to Submit Comments

The Regulatory Flexibility Act of 1980 (RFA), as amended by the Small Business Regulatory Fairness and Enforcement Act of 1996 (SBREFA), requires agencies to ask for and consider regulatory proposals that consider the size of the businesses or other organizations subject to regulation. When a proposed regulation will have a significant economic impact on a substantial number of small businesses, the RFA requires, among other things, that agencies analyze and take into consideration small business concerns. Under the RFA, when an agency issues a rule that will have a significant economic impact on a substantial number of small entities, the agency must provide small businesses the opportunity to participate in the rulemaking. Providing the opportunity to participate may include soliciting and receiving comments from small businesses. The participation of small businesses helps agencies fulfill their statutory objectives while reducing, as much as possible, the burden on small businesses. This guide is primarily directed towards owners or operators of small food, cosmetic or dietary supplement businesses that are regulated by the Center for Food Safety and Applied Nutrition in the Food and Drug Administration.

Making Regulations

One of the most common ways that agencies create regulations is through "informal rulemaking." In this type of rulemaking, agencies will usually publish in the Federal Register a proposed rule that contains both a "codified" part of the regulation (the actual rules that, when finalized, will appear in the Code of Federal Regulations) and a "preamble," which has a discussion of why and how the agency thinks the rules will accomplish the mission. In addition, there will be a cost-benefit analysis (Preliminary Regulatory Impact Analysis) of the rules, which is required by Executive Order (from the President), and an Initial Regulatory Flexibility Analysis (IRFA), which is an analysis of how the regulation will affect small businesses or other small entities.

Before putting out the proposed rule or "proposal," the agency may publish an Advanced Notice of Proposed Rulemaking (ANPR) in the Federal Register, or it may meet with various constituencies to solicit comments on how the rule should be crafted. Once it has been published in the Federal Register, anyone may send the agency a written comment on the proposal. A time limit for the acceptance of comments is specified in the proposal.

The final rule is also published in the Federal Register, where the agency sets the date by when the regulated community must comply with the rule. In the final rule, unless the agency certifies that the rule will not have a significant economic impact on a substantial number of small entities, the agency will publish a Final Regulatory Flexibility Analysis addressing the small business impacts and small business comments that were raised during the comment period for the proposed rule.

Small Business Comments

Small businesses may be involved at any time in the rulemaking process -- before the proposal, during the comment period, or after the publication of the proposal. As previously discussed, submitting comments is one way that small businesses can participate in the rulemaking. These comments will be more likely to influence the agency, the higher their quality.

The following general guidance is intended to help you write useful and persuasive comments. Commenting will help FDA give full consideration to your particular needs. Remember that FDA files all comments in a public docket and that the information that

is submitted is also available to anyone who requests it under the Freedom of Information Act.

Suggestions for Submitting Comments

There are four general areas that you may wish to comment on concerning regulations:

A. The need for the rule - In the preamble of a proposed rule the agency describes the need for the rule. If you agree or disagree with the agency's explanation of the health, safety or fraud issue that is addressed by the rule, you could comment on that. Be as factual and detailed as you can.

B. Other options - If the agency has proposed or discussed requirements, you may be able to think of other things the agency could do that would solve the problem in a less costly way for your firm or industry. One option that has often been suggested is for the agency to give small firms more time to comply with a regulation, such as a change to a food label. Another option may be for the agency to identify a goal companies must meet, but to allow each firm to achieve the stated goal in its own way. Another option may be to request an exemption for certain types of businesses for which the requirements are not applicable. Because the quality and persuasiveness of your comment affects the agency's decision, including data, logical reasoning, and other information to support your comment always helps.

C. Benefits of the Rule - By Executive Order, the agency is required to estimate the benefits of each proposed and final rule. This requirement might mean, for example, estimating how many lives would be saved or illnesses averted by causing an industry to change manufacturing practices. You may want to explain (in detail if possible) whether you think a specific requirement would achieve the intended results. For example, you may want to provide detailed information documenting whether your industry has a particular problem. Furthermore, you may want to comment on the degree to which a proposed requirement is already common practice, and how much a federal rule would change practices in your industry. Finally, you may want to comment on how a proposed regulation would benefit your firm through reduced costs or increased revenues.

D. Costs of the Rule - In many cases, the regulatory options and costs of the rule will be the areas that you will know most about and may want to include in your submission. Under the Executive Order the agency must consider the costs of the rule to the entire industry. Under SBREFA and the RFA the agency must consider the costs that will be incurred by a small business. The chart below gives examples of costs that your company or industry may experience as a result of a regulation. You may find it helpful in preparing a comment.

Cost Factor Chart

The factors below can be used for commenting on each proposed requirement in the codified section. This chart is only a suggestion for submitting comments. You are free to comment in any manner you wish or not at all. You may also, for example, respond by plant, firm, industry group, or in any other manner.

Category	Explanation	Examples
1. What type of worker will have to do something different due to this regulation?	Divide workers into categories based on their wages and salaries. Include anyone you will need to hire because of the rule.	Managers, quality control workers, production line workers, contractors, laboratory workers, secretaries
2. What will those workers have to do differently?	Using the requirements of the rule, explain the new duties each person will take on. If it is something they are already doing, you should not include it, even though it is a requirement of the rule.	A manager may have to oversee implementation of the regulation; a quality control worker may focus more on a safety activity rather a quality control activity; a new production line worker may be hired.
3. How much time will the new activity take for each category of worker?	Estimate by day, week, month or year how much time will be spent on the new activity and whether the new activity is a one-time event or is a repeated activity.	A lab worker must perform 2 new tests per week taking a total of 4 hours per week or 200 hours per year (plant closed 2 weeks each year) every year.
4. What are the average salaries by group or person engaged in a new activity?	Estimate the full annual cost of labor (salary + overhead) or hourly rate for each category of worker who must change activities.	Managers are paid $35,000 per year including overhead. Production workers get $19 per hour including overhead.
5. What new capital equipment or materials will you have to buy to comply with the regulation?	Estimate the actual cost of new capital equipment or materials that you will have to purchase (one time or annually) and any loss of equipment that can no longer be used.	Chemicals for new tests will cost $40 per test for each of the 4 tests per week. The depreciated value of an extruder that will no longer be able to be used is $7500.
6. What is the size of your firm?	Estimate the size of your firm either by number of employees or by annual sales. A range may be given.	Our firm has 200 full time employees and 20 part time employees. Annual sales are between $10 and $50 million

7. What products do you make?	Describe the type of products that your firm makes that are covered by the potential regulation.	Our firm makes 2 varieties of herbal supplements in 3 sizes each. We make 4 flavors of Larry's Ice Cream in 2 sizes each.
8. What are your average annual profits?	Again, do not report sensitive information but you may wish to provide an approximate annual amount that you can use to finance new requirements.	My firm makes between $20,000 and $50,000 per year.
9. Who owns your firm? How many plants do you have?	Explain whether or not you are a subsidiary of a larger firm. If so, it may disqualify you from being a small business unless the entire firm is small.	We are a solely owned firm with 2 plants.

Statement of Nonbinding Effect

This guidance document represents the agency's current thinking on comment submission by small businesses. It does not create or confer any rights for or on any person and does not operate to bind FDA or the public. Comments will be accepted in forms other than that which this document suggests.

For further information about this guide contact:

Small Business Guide
Division of Market Studies, HFS-726
Center for Food Safety and Applied Nutrition
Food and Drug Administration
5100 Paint Branch Parkway
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Federal Register

Thursday,
March 13, 2003

Part II

Department of Health and Human Services

Food and Drug Administration

21 CFR Parts 111 and 112

Current Good Manufacturing Practice in Manufacturing, Packing, or Holding Dietary Ingredients and Dietary Supplements; Proposed Rule

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration

21 CFR Parts 111 and 112

[Docket No. 96N–0417]

RIN 0910–AB88

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

AGENCY: Food and Drug Administration, HHS.

ACTION: Proposed rule.

SUMMARY: The Food and Drug Administration (FDA) is proposing current good manufacturing practice (CGMP) regulations for dietary ingredients and dietary supplements. The proposed rule would establish the minimum CGMPs necessary to ensure that, if you engage in activities related to manufacturing, packaging, or holding dietary ingredients or dietary supplements, you do so in a manner that will not adulterate and misbrand such dietary ingredients or dietary supplements. The provisions would require manufacturers to evaluate the identity, purity, quality, strength, and composition of their dietary ingredients and dietary supplements. The proposed rule is one of many actions related to dietary supplements that we (FDA) are taking to promote and protect the public health.

DATES: Submit written or electronic comments by June 11, 2003. Submit written or electronic comments on the collection of information by April 14, 2003.

ADDRESSES: Submit written comments to the Dockets Management Branch (HFA–305), Food and Drug Administration, 5630 Fishers Lane, rm. 1061, Rockville, MD 20852. Submit electronic comments to *http://www.fda.gov/dockets/ecomments.*

Fax written comments on the information collection to the Office of Information and Regulatory Affairs, Office of Management and Budget (OMB), Attn: Stuart Shapiro, Desk Officer for FDA, Fax (202) 395–6974, or electronically mail comments to *sshapiro@omb.eop.gov.*

FOR FURTHER INFORMATION CONTACT: Karen Strauss, Center for Food Safety and Applied Nutrition (HFS–821), Food and Drug Administration, 5100 Paint Branch Pkwy., College Park, MD 20740, 301–436–2375.

SUPPLEMENTARY INFORMATION:

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I. Background

A. Dietary Supplement Health and Education Act (DSHEA)

DSHEA (Pub. L. 103–417) was signed into law on October 25, 1994. DSHEA, among other things, amended the Federal Food, Drug, and Cosmetic Act (the act) by adding section 402(g) (21 U.S.C. 342(g)). Section 402(g)(2) of the act provides, in part, that the Secretary of Health and Human Services (the Secretary) may by regulation prescribe good manufacturing practices for dietary supplements. Such regulations shall be modeled after CGMP regulations for food and may not impose standards for which there is no current and generally available analytical methodology. No standard of CGMP may be imposed unless such standard is included in a regulation issued after notice and opportunity for comment in accordance with 5 CFR chapter V.

Congress enacted DSHEA to ensure consumers' access to safe dietary supplements. In the findings accompanying DSHEA, Congress stated that improving the health status of U.S. citizens is a national priority and that the use of dietary supplements may help prevent chronic diseases and maintain good health (Ref. 1). If dietary supplements are adulterated because they contain contaminants (such as filth), because they do not contain the dietary ingredient they are represented to contain (for example, a product labeled as vitamin C that actually contains niacin), or because the amount of the dietary ingredient thought to provide a health benefit (for example, folic acid to reduce the risk of neural tube defects or calcium in an amount to reduce the risk of osteoporosis) is not actually present in the supplement, then the consumer may suffer harm or may not obtain the purported health benefit from their consumption. CGMP regulations for dietary ingredients and dietary supplements will help to ensure that the potential health benefits that Congress identified as the basis for DSHEA are obtained and that consumers receive the dietary ingredients that are stated on the product label.

DSHEA directed the President to appoint a Commission on Dietary Supplement Labels (the Commission) to consider several issues under DSHEA needing clarification. The Commission was to conduct a study on, and provide recommendations for, the regulation of label claims and statements for dietary supplements, including the use of literature in connection with the sale of dietary supplements and procedures for the evaluation of such claims. In making its recommendations, the Commission was to evaluate how best to provide truthful, scientifically valid, and nonmisleading information to consumers so that such consumers could make informed and appropriate health care choices for themselves and their families. The Commission's report (Ref. 80) states that the Commission supports the efforts of industry and FDA to develop appropriate CGMPs for dietary supplements. Guidance on the type of information that a responsible manufacturer should have to substantiate statements of nutritional support and safety is also included in the Commission's report. The Commission's report states that the substantiation files should include assurance that CGMPs were followed in the manufacture of the product.

B. The Advance Notice of Proposed Rulemaking

On November 20, 1995, representatives of the dietary supplement industry submitted to FDA an outline for CGMP regulations for dietary supplements and dietary supplement ingredients. We evaluated the outline and determined that it provided a useful starting point for developing CGMP regulations. Nonetheless, we believed that the industry outline did not address certain issues that should be considered when developing a proposed rule on CGMPs for dietary ingredients and dietary supplements. For example, the industry outline did not address the need for specific controls for automatic, computer-controlled or assisted systems.

In addition to identifying a number of issues that were not included in the industry outline but on which we wanted public comment, we also recognized that other interested parties, such as consumers, other industry segments who had not participated in developing the outline, and the health care community should have an opportunity to provide comments on CGMPs for dietary supplements before we developed a proposal. Therefore, in the **Federal Register** of February 6, 1997 (62 FR 5700), we issued an advance notice of proposed rulemaking (ANPRM) asking for comments on whether to institute rulemaking to develop CGMP regulations for dietary ingredients and dietary supplements and what would constitute CGMP regulations for these products.

The ANPRM contained the entire text of the industry outline. We also asked nine questions (which we discuss later in section II.B of this document) in the ANPRM. The questions focused on issues that the industry outline did not address such as those issues noted above. We received approximately 100 letters in response to the ANPRM. Each of those letters contained one or more comments. The comments came from consumers, consumer advocacy groups, health care professionals, health care professional organizations, industry, and industry trade associations. The majority of comments responded both to the nine questions we asked in the ANPRM and on certain provisions in the industry outline. We also address the comments on the nine questions in section II.B of this document. We discuss significant comments about certain provisions in the industry outline in our discussion of related proposed requirements.

Included with its comments to the ANPRM, the United States Pharmacopeia (USP) submitted a copy of its general chapter, "Manufacturing Practices for Nutritional Supplements," (Ref. 2) and in March/April 2002, USP proposed revisions to this general chapter to introduce provisions pertaining to botanical preparations (Ref. 82). In February 2000, we received a copy of the National Nutritional Foods Association's (NNFA) "NNFA Good Manufacturing Practice in Manufacturing, Packing, or Holding Dietary Supplements" (Ref. 3). We found that the industry outlines published in the ANPRM, the USP manufacturing practices, and the NNFA standards were useful in developing this proposed rule. We included certain provisions found in these outlines in this CGMP proposed rule. These three outlines indicate that dietary ingredient and dietary supplement manufacturers already recognize that there are basic, common steps needed to manufacture a dietary ingredient or dietary supplement that is not adulterated although, as established in the regulatory impact analysis, a large percentage of manufacturers do not follow a good manufacturing model. For example, these practices include requirements for:

- Designing and constructing physical plants that facilitate maintenance, cleaning, and proper

manufacturing operations or to prevent mixup between different raw materials and products;

- Establishing a quality control unit;
- Establishing and following written procedures for:

1. Maintaining and cleaning equipment and utensils;
2. Receiving, testing, or examining materials received and testing of finished product;
3. Using master and batch control records;
4. Handling consumer complaints; and
5. Maintaining records for laboratory tests, production control, distribution, and consumer complaints.

Based on the ANPRM, the comments that we received in response to the ANPRM, our outreach activities (which we discuss below), and our own knowledge and expertise about CGMPs for foods, drugs, cosmetics, devices, and biologics, we are proposing to establish these CGMP regulations for dietary ingredients and dietary supplements. The proposed regulations would impose requirements for: (1) Personnel, (2) physical plants, (3) equipment and utensils, (4) production and process controls, (5) holding and distributing, (6) consumer complaints related to good manufacturing practices, and (7) records and recordkeeping.

C. Industry and Consumer Outreach

During 1999, we conducted a number of outreach activities related to dietary supplements. We held several public meetings to obtain input from the public on developing our overall strategy for achieving effective regulation of dietary supplements, which could include establishing CGMP regulations. We also held public meetings focused specifically on CGMPs and the economic impact that any CGMP rule for dietary ingredients and dietary supplements may have on small businesses. Additionally, FDA staff toured several dietary supplement manufacturing firms to better understand the manufacturing processes and practices that potentially would be subject to a CGMP regulation for dietary ingredients and dietary supplements. Each of these activities contributed to our knowledge about the industry.

1. Dietary Supplement Strategic Plan Meetings

We held public meetings on June 8 and July 20, 1999, to collect stakeholder comments on the development of our overall strategy for achieving effective regulation of dietary supplements. We designed the meetings to provide an opportunity for public comment on both the activities we should undertake as part of an overall strategy and the prioritization of those activities. In the notices for these meetings, we identified the development of CGMPs for dietary supplements as one activity that should be considered in an overall strategy.

During and after the strategic meetings, we received comments from consumers, consumer advocacy groups, health care professionals, health care professional organizations, industry, and industry trade associations. The comments addressed a wide range of activities related to regulating dietary supplements. (These comments can be seen at our Dockets Management Branch (*see* **ADDRESSES**) in docket number 99N–1174.) The comments generally identified the development of CGMP regulations as a high priority activity that should be included in any FDA strategic plan for regulating dietary supplements. Some comments that addressed the development of CGMPs are summarized as follows:

- It would be useful to industry to have FDA establish CGMPs especially for small and intermediate-size firms that are not clear on what they should be doing;
- CGMPs would establish a level playing field for industry, which would help prevent irresponsible firms from making and selling adulterated products;
- CGMPs should be able to accommodate a wide variety of firms, that is, small and large firms that manufacture a wide array of different types of products and ingredients;
- CGMPs should ensure that consumers get dietary supplements with the strength and the purity that consumers expect;
- CGMPs should ensure that every dietary supplement on the market has the safety, identity, purity, quality, and strength it purports in the label to possess;
- CGMPs should include ingredient identity testing and other testing;
- CGMPs should ensure that dietary supplements are produced using a master formula procedure and produced in a sanitary facility;
- CGMPs should require that manufacturers have documented evidence that their manufacturing process is under control on a consistent basis;
- CGMPs should require manufacturers to test dietary ingredients, particularly imported botanicals, for heavy metals, pesticides, and industrial contaminants;
- CGMPs should require expiration dating and testing for dissolution and bioequivalence;
- CGMPs should require that companies report adverse reactions; and
- CGMPs should include guidance on testing for ingredient identity and adulteration with toxic substances.

2. Small Business Outreach Meetings

We held public meetings on July 12, September 28, and October 21, 1999, to collect information from industry and others that would help us to understand the economic impact on small businesses of CGMP regulations for dietary supplements. Transcripts of these public meetings (docket number 96N–0417, "Development of Strategy for Dietary Supplements") are available at our Dockets Management Branch or electronically at *http://www.fda.gov/ohrms/dockets/dockets/96n0417/tr00001.pdf*. Public comments from small businesses included both support of and concern for CGMP regulations. Small businesses expressed concerns about the cost and the time involved in complying with any rule that contains the following requirements:

- Conducting tests to determine identity, purity, quality, strength, and composition of dietary ingredients and dietary supplements;
- Maintaining written procedures and records documenting that procedures are followed; and
- Providing data that support expiration dating.

Public comments from small business expressed support for dietary supplement CGMP regulation. Some small businesses (1 with 15 employees) commented that they have CGMPs in place with written procedures tailored to the size of their operations. One small business with sales under $1 million commented that their plant materials received in fresh form are identified onsite by a botanist, and when the onsite botanist is not able to confirm identity, the plant material is sent to an outside laboratory that conducts chemical analysis to confirm identity.

3. Site Visits to Dietary Supplement Manufacturing Firms

During the summer and fall of 1999, we visited eight dietary supplement manufacturing firms. These visits included firms that: (1) Manufacture a vitamin using a fermentation process; (2) grind, sift, blend, and otherwise treat raw agricultural commodities (*e.g.*, botanicals); (3) manufacture dietary ingredients for use in manufacturing dietary supplement tablets, capsules, softgels, and powders; (4) manufacture dietary supplements for packaging and labeling by others; and (5) manufacture, package, and label dietary supplements under their own and others' labels. The

firms varied in size and were located in several parts of the country.

We found an array of manufacturing, packaging, and holding practices in the firms. The practices included the following:

- Using CGMPs similar to those included in the ANPRM;
- Using automatic systems to quarantine, segregate, approve, and release inventory;
- Following written procedures;
- Having quality control units with the responsibility and authority outlined in the ANPRM;
- Performing one or more tests on dietary ingredients and dietary supplements to determine the identity, purity, quality, strength, and composition;
- Verifying the reliability of suppliers' certifications; and
- Documenting and maintaining records for certain procedures, such as master and batch production, quality control and laboratory operations, distribution, and processing consumer complaints.

D. Food Advisory Committee Report

In February 1998, the Food Advisory Committee (FAC) established a Dietary Supplement Working Group to consider what constitutes adequate testing for identity of different dietary ingredients and what records are necessary to demonstrate that CGMPs are maintained throughout the manufacturing and distribution process. The working group issued a report that discussed the selection of the most appropriate and reliable identity test and the general principles for consideration in setting performance standards for such tests (Ref. 4). The report also identified the types of records that would be necessary to demonstrate that CGMPs are maintained throughout the manufacturing and distribution process. On June 25, 1999, the working group presented its report, in draft form, during an FAC public meeting. We received public comments during and after the June 25, 1999, public meeting.

Although this proposal does not address dietary ingredient identity testing in the same detail as the working group's report, we considered the report in developing requirements for identity testing and CGMP records requirements in this proposal. The working group's report may be useful in developing industry guidance to supplement a CGMP regulation for dietary ingredients and dietary supplements. We discuss dietary ingredient and dietary supplement identity testing and recordkeeping for CGMP proposed requirements in more detail later in this document.

E. FDA's Decision To Propose a Rule

This proposed regulation, which sets forth proposed CGMPs for dietary ingredients and dietary supplements, is part of our overall strategy for regulating dietary supplements in a manner that promotes and protects the public health. Before drafting the proposal, FDA considered public comment in response to the ANPRM and to public meetings, observations at site visits to dietary supplement manufacturers, and advisory group reports. In drafting this proposal, FDA used, in part, the industry coalition outline that was published as an ANPRM (62 FR 5700) in which the industry adopted broad provisions beyond those found in part 110 (21 CFR part 110). FDA's purpose at this proposed rule stage is to present a broad enough scope so that it may receive comment on the depth and breadth of what should be considered by the agency in developing a final rule. Our intent is to provide the proper balance of regulation so that dietary ingredients and dietary supplements are manufactured in a manner to prevent adulteration using recognized scientific principles and both industry and consumer expectations that are reasonable and appropriate. Therefore, FDA seeks comment on whether each of the proposed provisions are necessary to ensure the safety and quality of dietary ingredients and dietary supplements and whether they are adequate to protect the public health. In addition, we seek comment on whether there are certain provisions that are not proposed but that may be necessary. Comments should include justification for why provisions may or may not be necessary, including supporting data where appropriate. If comments assert that certain provisions are not necessary, comments should include an explanation on how, in the absence of the requirement, one can ensure that there would be adequate protection of the public health when there is risk of adulteration. Comments also should address whether the gains to consumers in product safety and quality are warranted. Moreover, assuming that this proposal does advance the public health, comments should address whether there is any reason to apply different requirements, including greater or lesser requirements on small firms as compared to larger firms and the rationale for doing so. Finally, comments should address the agency's legal authority to issue these regulations.

In deciding whether to propose CGMP regulations for dietary supplements, we asked ourselves:

- Why Are CGMP regulations needed?
- How will CGMP regulations take into account technical feasibility? and
- How can FDA help industry achieve compliance with CGMPs?

1. Why Are CGMPs Needed?

CGMP regulations for dietary ingredients and dietary supplements are necessary to promote and protect the public health. In addition, CGMP regulations would benefit consumers economically and would benefit industry.

a. *CGMPs help protect the public health.* The dietary supplement industry is one of the fastest growing product areas that FDA regulates. In 1999, *Prevention* magazine conducted a survey entitled "Consumer Use of Dietary Supplements" (Ref. 5). The survey used data from telephone interviews with a nationally-representative sample of 2,000 adults living in households with telephones in the continental United States. The telephone interviews were done in April and May, 1999. Using population estimates based on the Census Bureau's March 1998 Current Population Survey Estimates, the survey stated that approximately 186,014,712 adults live in the households with telephones in the United States and that an estimated 158.1 million of these Americans in households with telephones use dietary supplement products. These consumers spend approximately $8.5 billion a year on dietary supplements. The survey also found that:

- Only 41 percent of the surveyed consumers who use vitamins and minerals think they are very safe and only 50 percent think they are somewhat safe;
- Only 24 percent of the surveyed consumers who use herbal products think they are very safe; and only 53 percent think they are somewhat safe; and
- Twelve percent of the surveyed consumers who have used dietary supplements say they have experienced side effects or adverse reactions from their use of dietary supplements.

The survey also found strong public support for increased Government regulation of dietary supplements; 74 percent of the surveyed consumers reported that they think that the Government should be more involved in ensuring that these products are safe and do what they claim to do.

However, unlike other major product areas, there are no FDA regulations that

are specific to dietary ingredients and dietary supplements that establish a minimum standard of practice for manufacturing, packaging, or holding. The absence of minimum standards has contributed to the adulteration and misbranding of dietary ingredients and dietary supplements by contaminants or because manufacturers do not set and meet specifications for their products, including specifications for identity, purity, quality, strength, and composition. Thus, CGMP regulations are necessary to protect the public health because a CGMP rule would establish a minimum standard of practice for manufacturing, packaging, and holding dietary ingredients and dietary supplements.

The following examples illustrate the wide range of dietary ingredient and dietary supplement adulteration caused by manufacturing, packaging, or holding practices. The examples, although not exhaustive, demonstrate why CGMPs are necessary to protect public health:

- In 1997, we received an adverse event report (AER) regarding a young woman who had taken a dietary supplement and experienced a life-threatening abnormal heart function (Ref. 6). We investigated the AER and determined that the dietary supplement the woman consumed contained *Digitalis lanata*, a plant that can cause life-threatening heart reactions (Refs. 6 through 10). We found *D. lanata* in samples of raw material labeled "plantain" that was a dietary ingredient in one of the dietary supplement products used by this woman (Ref. 6). A nationwide listing of manufacturers indicated that 183 firms may have used the contaminated dietary ingredient in dietary supplements. The proposed CGMP regulations, had they been in effect, would have required identity and purity tests of dietary ingredients and dietary supplements and would likely have prevented the use of the *D. lanata* in these dietary supplements.
- In 1998, the American Herbal Products Association (AHPA) surveyed its members about commonly adulterated botanicals and methods useful in detecting adulteration in botanicals (Ref. 11). AHPA members identified 43 botanicals, including *D. lanata* contaminated plantain, that are commonly adulterated with contaminants, the common adulterant for each botanical, and a method for identifying the adulterant. For example, aflatoxin and mycotoxin (toxic compounds produced by certain molds) are known to contaminate certain herbal and botanical dietary supplements (Refs. 11 through 14). Under this proposed rule, a manufacturer would have to establish specifications for botanicals that may contain toxic compounds and conduct testing to ensure that there are not toxic compounds present that may adulterate the dietary ingredient or dietary supplement.
- We have found manufacturers using nonfood-grade chemicals to manufacture dietary supplements (Ref. 15). The proposed rule would require that manufacturers establish specifications for components used in manufacturing and also would require manufacturers to establish and follow laboratory control procedures that include criteria for establishing appropriate specifications. The proposal would further require manufacturers to conduct testing to confirm that their specifications are met. These requirements, if finalized, would ensure that manufacturers establish and use appropriate criteria, such as using food-grade rather than industrial-grade chemicals, and would ensure that manufacturers conduct testing to confirm that food-grade chemicals were received from the supplier.
- Also during inspections, we have found insanitary conditions in physical plants where dietary ingredients or dietary supplements were manufactured, packaged, or held (Ref. 16). Pest infestation, building and equipment defects, and leaking pipes that drip onto dietary supplements are examples of insanitary conditions that we have found that may lead to product adulteration and could cause consumer illnesses and injuries. The proposed rule would require a manufacturer, packager, or holder to maintain its physical plant used for these activities in a sanitary condition.
- In the past, we have been involved in the recall of dietary supplements contaminated with lead (Ref. 17), salmonella (Ref. 18), *Klebsiella pneumonia* (Ref. 19), botulism (Ref. 20), and glass (Ref. 21). These contaminants can cause serious illness or injury and, in the case of lead, may result in chronic irreversible cognitive defects in children and progressive renal failure in adults. The proposed rule would require dietary ingredients and dietary supplements to be manufactured, packaged, and held in a manner that prevents adulteration, including adulteration by the contaminants such as those described.
- We also have been involved in recalls for super- and subpotent dietary supplements. Recalls of superpotent dietary supplements have included the following dietary ingredients: Vitamin A (Ref. 22), vitamin D (Ref. 23), vitamin B6 (Ref. 24), and selenium (Ref. 25). Each of these dietary supplements contained dietary ingredient levels that could have caused serious illness or injury. Illnesses or injuries such as nausea, vomiting, liver damage, and heart attack were reported from superpotent niacin at an average level of 452 milligrams (mg) niacin, well above the upper limit for adults of 45 mg daily (Ref. 26). Recalls for subpotent dietary supplements have included a recall of folic acid because the dietary supplement contained 34 percent of the declared level (Ref. 27). Such a product would be misbranded under section 403 of the act (21 U.S.C. 343). Folate plays a well-documented and important role in reducing the risk of neural tube defects. Neural tube birth defects, primarily spina bifida and anencephaly, cause serious lifetime debilitating injuries and disabilities, and even death. Thus, use of subpotent folic acid by women who are or may become pregnant may result in increased risk of having a child with a neural tube defect. The proposed rule would require manufacturers to establish specifications for the dietary supplement the manufacturer makes and then meet those specifications. Therefore, if the proposed rule is finalized, if the label for a folic acid supplement declares that the dietary supplement contains a certain level of folic acid, the folic acid supplement must actually contain that level, or we would consider the folic acid supplement to be adulterated under section 402(g) of the act.
- Other recalls have been necessary because of undeclared ingredients, including color additives (Refs. 28 and 29), lactose (Ref. 30), and sulfites (Ref. 31). Undeclared ingredients, such as color additives, lactose, and sulfites, may cause potentially dangerous reactions in susceptible persons (Ref. 32). The proposed rule would require manufacturers to verify that the correct labels have been applied to dietary ingredients and dietary supplements produced. The master manufacturing record would have to identify each ingredient required to be declared on the ingredient list under section 403 of the act.
- A study found that dietary ingredient content varied considerably from the declared content (Ref. 33). The study examined ephedra alkaloids in 20 herbal dietary supplements containing ephedra (Ma Huang) to determine their ephedra alkaloid content. This study found that norpseudoephedrine was often present in the ephedra dietary supplements. The study also observed significant lot-to-lot variations in alkaloid content for four products,

including one product that had lot-to-lot variations of ephedrine, pseudoephedrine, and methylephedride that exceeded 180 percent, 250 percent, and 1,000 percent, respectively. Half of the products tested differed in their label claims for ephedra alkaloid content and their actual alkaloid content. In some cases, the discrepancy exceeded 20 percent. One product did not have any ephedra alkaloids. Lot-to-lot variation in dietary ingredients is a public health problem particularly because conditions of use recommended or suggested in the labeling of dietary supplements are presumably based on the dietary supplement containing a certain amount of the dietary ingredient. If the dietary supplement contains more or less than the amount that the manufacturer represents, then the consumer does not receive the potential health benefit from the dietary supplement or is exposed to an amount that could present risk of injury or illness. The proposed rule would require manufacturers to establish controls, including master manufacturing and batch production records to ensure that they use the correct amount of the dietary ingredient to produce the dietary supplement, and that they apply the correct label to the dietary supplement.

- A private company analyzed a sample of dietary supplements and found that some dietary supplements did not contain the dietary ingredients claimed on the label (Ref. 34). The study found that 25 percent of gingko biloba products, 20 percent of saw palmetto, 33 percent of glucosamine, chrondroitin and combined glucosamine/chondroitin, and 50 percent of SAMe did not contain the dietary ingredients claimed in their product labels. The proposed rule would require manufacturers to establish and meet specifications for the identity, purity, quality, strength, and composition of dietary supplements.

Given the wide range of public health concerns presented by the manufacturing, packaging, and holding practices for dietary ingredients and dietary supplements, a comprehensive system of controls is necessary to prevent adulteration and misbranding. CGMPs are intended to establish such a comprehensive system. Manufacturers who operate in accordance with CGMPs would be less likely to distribute adulterated and misbranded dietary ingredients or dietary supplements than those who do not meet the requirements. Quality assurance will maximize the probability that unadulterated dietary supplements will reach the marketplace.

Establishing CGMP regulations for dietary supplements is only part of our broad science-based regulatory program for dietary supplements that is necessary to give consumers a high degree of confidence in the safety, composition, and labeling of dietary supplements. Aside from our CGMP efforts, we have taken other steps to protect the public health, such as:

- Reviewing claim notifications under section 403(r)(6) of the act to identify unlawful claims;
- Reviewing new dietary ingredient notifications to ensure that new dietary ingredients are reasonably expected to be safe under section 413 of the act (21 U.S.C. 350b);
- Evaluating the nutrition labeling of dietary supplements;
- Monitoring, through AERs voluntarily submitted to FDA, the occurrence of adverse events to identify potentially unsafe products; and
- Taking compliance actions against products that are adulterated or misbranded.

The CGMP regulation, if finalized, would, along with our other dietary ingredient and dietary supplement initiatives, contribute further to the protection of public health.

b. *CGMPs benefit consumers.* In addition to the public health benefits for consumers, CGMP regulations for dietary ingredients and dietary supplements will benefit consumers in other ways. Consumers should not have to wonder whether the dietary supplements they buy are adulterated or whether they contain the correct dietary ingredients or contain the dietary ingredients in the amount stated on the product's label. Consumers who purchase a product that does not contain the amount or strength listed on the label experience an economic loss because they are paying for something that they did not receive. CGMPs would require manufacturers to establish and meet specifications for identity, purity, quality, strength and composition of dietary supplements to help ensure that consumers buy dietary supplements that are not adulterated, contain the dietary ingredients declared on the product's label, and contain the amount or strength listed on the label. Therefore, CGMPs would benefit consumers.

2. How Will CGMP Regulations Take Into Account Technical Feasibility?

In developing this proposed rule, we were careful not to propose requirements that are not technically feasible to meet. In some areas where there has been scientific study but where the science is still evolving, the proposal recognizes the evolving state of the science, but would give you maximum flexibility in meeting the requirement. For example, there are tests available for identity, purity, quality, strength, and composition of certain dietary ingredients or dietary supplements. Because many tests for identity, purity, quality, strength, and composition of dietary ingredient or dietary supplements have not been officially validated, the proposal would permit tests using methods other than those that are officially validated. By using the term "officially validated," we mean that the method is validated using an interlaboratory collaborative study by which a proposed method is validated by independent testing in separate laboratories under identical conditions (Ref. 35). An AOAC International (formerly the Association of Official Analytical Chemists) Official Method is an example of an officially validated method. We discuss test methods validation in more detail later in this document.

In areas where scientific study is still evolving, we did not propose specific requirements. For example, we did not propose requirements for dissolution, disintegration, bioavailability, or expiration dating. In those areas, it may be premature to propose a requirement at this time. In the preamble to this rule, we identify those areas where additional scientific study is necessary before we can propose a dietary supplement CGMP requirement. For example, we did not identify defect action levels (DALs) for dietary ingredients because there are not enough data available to identify an appropriate DAL for most dietary ingredients. Likewise, further study is needed for some dietary ingredients before dissolution, disintegration, bioavailability, expiration dating, or other quality standard requirements can be proposed.

3. How Can FDA Help Industry Achieve Compliance With CGMPs?

During small business outreach public meetings and in comments to the ANPRM, members of the dietary supplement industry told us that they would like our help in determining how to implement CGMP regulations for dietary ingredients and supplements. We have heard that issuing guidance documents and education and training would be helpful. We invite comment on the use of guidance documents, education, training, or other approaches and potential sources of education and training that you believe would assist industry efforts to implement the proposed CGMP regulations, if finalized as proposed.

F. Proposal Highlights and Requests for Comments

This proposed rule is intended to ensure that manufacturing practices will not result in an adulterated dietary supplement and that supplements are properly labeled. This proposed rule, if finalized as proposed, will give consumers greater confidence that the dietary supplements they choose to use will have the identity, strength, purity, quality, or composition claimed on the label. A manufacturer of a dietary ingredient or a dietary supplement cannot make claims that state or imply that the dietary ingredient or dietary supplement is safe and/or effective simply because it has been manufactured in compliance with current good manufacturing practice (CGMP) requirements. However, we believe that a voluntary labeling statement about the fact that a dietary ingredient or dietary supplement has been made in compliance with CGMP requirements might be made lawfully under the act, provided that such a statement is made in an appropriate context and with adequate disclaimers so that consumers fully understand it and are not misled by it. The proposed rule governing CGMP requirements for dietary supplements address manufacturing controls to ensure that dietary ingredients and dietary supplements are produced in a manner that will not adulterate or misbrand such products. Compliance with any final rule, based on the proposal, will not ensure that the dietary ingredient or dietary supplement itself is safe or effective. Thus, the agency believes that an unqualified statement saying simply "produced in compliance with dietary supplement current good manufacturing practice requirements," without more, could well suggest that a product may be safe and effective or somehow superior to other dietary ingredient and dietary supplement products that are subject to the same CGMP requirements. Such a statement would likely be considered misleading by FDA under sections 403(a)(1) and 201(n) of the act. We believe however, that it might be possible to cure an unqualified statement by including language clarifying to consumers that all dietary ingredients and dietary supplements must be manufactured in compliance with CGMP requirements and that such compliance does not mean that the dietary ingredient or dietary supplement is safe or effective. As usual, the manufacturer would be responsible for ensuring that any such voluntary labeling statements on its dietary ingredient and dietary supplement products are truthful and not misleading. The agency would review the lawfulness of such statements under sections 403(a)(1) and 201(n) of the act.

We propose requirements for: (1) Personnel, (2) the physical plant environment, (3) equipment and utensils, (4) production and process controls, (5) holding and distributing, (6) consumer complaints related to CGMPs, and (7) records and recordkeeping. Key provisions of the proposed rule are highlighted below. We also seek comment on whether certain additional provisions should be included as requirements in a final rule.

Proposed "personnel" requirements would require that you have qualified employees and supervisors, to take measures to exclude any person from your operations who might be a source of microbial contamination, and to use hygienic practices to the extent necessary to protect against contamination.

Proposed "physical plant" requirements are intended to help prevent contamination from your physical plant environment. You would be required to design and construct your physical plant in a manner to protect dietary ingredients and dietary supplements from becoming adulterated during manufacturing, packaging, and holding. You would be required to keep your physical plant in a clean and sanitary condition and in sufficient repair to prevent contamination of components, dietary ingredients, dietary supplements, or contact surfaces.

Proposed "equipment and utensils" provisions would require that you use equipment and utensils that are of appropriate design, construction, and workmanship for their intended use and that you provide for adequate cleaning and maintenance. You would be required to maintain and calibrate your instruments and controls for accuracy and precision and to ensure that automatic, mechanical, and electronic equipment works as intended. You would also be required to maintain, clean, and sanitize, as necessary, all equipment utensils and contact surfaces that are used to manufacture, package, or hold dietary ingredients or dietary supplements.

Under the proposed "production and process controls" requirements, you would be required to establish and use a quality control unit in your manufacturing, packaging, and label operations. We propose requirements for establishing and using master manufacturing records and batch control records to ensure batch-to-batch consistency. Specifications would be required for any point, step, or stage in the manufacturing process where control is necessary to ensure that the dietary supplement contains the identity, purity, quality, strength, and composition claimed on the label. We propose flexible testing requirements: You would be required to test final products for adherence to specifications, unless a scientifically valid analytical method does not exist; in the latter case, you would be required to test incoming shipment lots of components, dietary ingredients, or dietary supplements for any such specification, and to test in-process for any such specification in accordance with the master manufacturing record where you determine control is necessary to ensure the identity, purity, quality, strength, and composition of the product.

Proposed "holding and distributing" requirements would protect components, dietary ingredients, dietary supplements, packaging, and labels against contamination and deterioration. You would be required to hold components, dietary ingredients, dietary supplements, packaging, and labels under appropriate conditions of temperature, humidity, and light so that their quality is not affected; and under conditions that do not lead to the mixup, contamination, or deterioration.

Proposed "consumer complaints" requirements would require that you keep a written record of each consumer complaint related to good manufacturing practices; review such complaints to determine whether the consumer complaint involves a possible failure of a dietary ingredient or dietary supplement to meet any of its specifications, or any other requirements of this part, including those that may result in a possible risk of illness or injury (*i.e.*, an adverse event); and investigate a consumer complaint when there is a reasonable possibility of a relationship between the consumption of a dietary supplement and an adverse event. For the purposes of this regulation, a consumer complaint about product quality may or may not include concerns about a possible hazard to health. However, a consumer complaint does not include an adverse event, illness, or injury related to the safety of a particular dietary ingredient independent of whether the product is produced under good manufacturing practices.

Proposed "records and recordkeeping" requirements would tell you how long you must keep certain records to show how you complied with the CGMP requirements. We would require that you keep written records for 3 years beyond the date of manufacture of the last batch of dietary ingredients

or dietary supplements associated with those records and have all required records, or copies of such records, readily available during the retention period for authorized inspection and copying by FDA when requested.

CGMP records document the manufacturer's operation throughout time and are essential to an enforceable regulation. Because FDA does not observe the manufacturer's operation fulltime, records can ensure that the FDA has the information needed to identify noncompliance and to bring a non-compliant manufacturer into compliance. Records can show that appropriate monitoring is performed, pinpoint with confidence when a deviation began and ended, and prove that required quality control measures and practices were performed as often as necessary to ensure control. Review of manufacturing records with sufficient frequency can ensure that any problems are uncovered promptly and can facilitate prompt modification, have an impact on the production of subsequent batches of the product, and prevent introduction of potentially hazardous dietary supplements into the market place. Review of consumer complaint records can facilitate the identification of trends in reports of illness or injury, identify related batch records to identify previously undetected manufacturing deviation, and have an impact on the prompt recall of any potentially hazardous dietary supplement.

We seek comment on whether the proposed recordkeeping requirements are not necessary to prevent adulteration; to ensure the identity, purity, quality, strength, and composition of the dietary ingredient or dietary supplement; to an enforceable regulation; and for the other reasons cited. If comments assert that recordkeeping provisions are not necessary, comments should include an explanation of why recordkeeping requirements are not necessary including how, in the absence of the requirements, one can prevent adulteration, ensure the identity, purity, quality, strength, and composition of the dietary ingredient or dietary supplement, ensure an enforceable regulation, and the other reasons cited. If comments agree that the recordkeeping requirements are necessary for reasons other than those we have provided, the comments should so state and provide an explanation.

Although records are not required in 21 CFR Part 110, CGMPs in manufacturing, packing, or holding human food, records are required in the other commodity-driven food CGMPs (*i.e.*, 21 CFR Part 129, Processing and bottling of bottled drinking water; 21 Part CFR 120, Hazard Analysis and Critical Control Point (HAACP) Procedures for the Safe and Sanitary Processing and Importing of Juice; 21 CFR Part 123, Fish and fishery products; 21 CFR Part 106 Infant formula quality control procedures; and 21 CFR Part 113, Thermally processed low-acid foods packaged in hermetically sealed containers). Further, records are included in the CGMPs submitted to FDA by industry, the National Nutritional Foods Association Standards, the NSF International draft standards (Ref. 83), and the USP draft Manufacturing Practices for Dietary Supplements.

We seek comment on whether certain additional provisions should be included as requirements in a final rule. For example, we invite comment on whether a final rule should include a requirement for certain personnel records; for written procedures in a number of areas; for equipment verification; and for expiration dating and related testing. Written procedures are included in the dietary supplement CGMP outline submitted to FDA by industry, National Nutritional Foods Association standards, the NSF International draft standards, and the USP draft Manufacturing Practices. In order to limit the burden to manufacturers, FDA is not proposing to require written procedures. However, FDA is proposing that manufacturers maintain appropriate records to ensure the identity, purity, quality, strength, and composition of a given product and records that are necessary for efficient enforcement and to permit trace back. Although we have not proposed requirements for written procedures as did these other groups, we seek comment on whether such practices should be included in a final rule. Later in this document, we request comments on specific written procedures and describe FDA's current thinking concerning what could be included in such a written procedure.

We also seek comment on whether this rule should include specific requirements for the use of animal-derived dietary ingredients, and requirements for persons who handle raw agricultural commodities. Specific requests for comment of this type are contained below in relevant sections of this preamble.

II. General Issues

A. Legal Authority

We are proposing these regulations under sections 201, 393, 409, 701(a), 704, and 801 of the act (21 U.S.C. 321, 903, 348, 371(a), 374, and 381) and sections 402 and 403 of the act and section 361 of the Public Health Service Act (the PHS Act) (42 U.S.C. 264).

Section 402(g) of the act gives us explicit authority to issue a rule regulating conditions for manufacturing, packaging, and holding dietary supplements. Section 402(g)(1) of the act states that a dietary supplement is adulterated if "it has been prepared, packed, or held under conditions that do not meet current good manufacturing practice regulations." Section 402(g)(2) of the act authorizes us to, by regulation, "prescribe good manufacturing practices for dietary supplements." In addition, section 402(g)(2) of the act states that any 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."

In section 402(g)(2) of the act, which describes the general parameters of CGMPs for dietary supplements, Congress stated that the regulations were to be "modeled after current good manufacturing practice regulations for food." To determine what Congress meant, we look to the plain meaning of the phrase. *Webster's II New Riverside University Dictionary* defines "model" as "[a] preliminary pattern serving as the plan from which an item not yet constructed will be produced" (Ref. 81). Thus, when Congress used the term "modeled after" Congress intended that we use the food CGMPs as a "preliminary pattern" for the dietary supplement CGMPs. If Congress had intended for the agency to adopt food CGMPs as the CGMPs for dietary supplements, Congress could have explicitly stated that dietary supplements were subject to food CGMPs.

The provisions in the dietary supplement CGMP proposal are modeled after food CGMPs. The general CGMP provisions for food in part 110 relate not only to insanitary production practices, but other practices, such as having appropriate quality control operations, to ensure that a food is manufactured in a manner that will not adulterate the food. Further, the CGMPs in part 110 describe the minimally acceptable practices for all food handling operations. They are not intended to cover specific issues that may relate to a particular product type, rather, are general provisions concerned with practices relating to the receiving, inspecting, quality control operations, packaging, segregating, processing, storing, and transporting of food. The specific provisions of the food CGMPs

are linked to hazards that are inherent to foods (*e.g.*, microbial contamination and contamination with macroscopic filth).

The proposed dietary supplement CGMPs are modeled after the food CGMPs in part 110 in that they cover the scope of practices related to the receiving, inspecting, quality control operations, packaging, segregating, processing, storing, and distribution of dietary ingredients and dietary supplements. Dietary supplements require many of the same types of sanitary practices and other practices as conventional food production in order to produce a product that is not adulterated; dietary supplements are subject to many of the same hazards as are conventional foods. However, dietary supplements have their own set of unique requirements as a result of the characteristics and hazards due to their "hybrid" nature, *e.g.*, dietary supplements can be considered as falling somewhere along the continuum between conventional foods on the one hand and drugs on the other. Thus, the CGMPs for dietary supplements need to address the characteristics and hazards of dietary supplements, the operations and processes used to manufacture dietary supplements, particularly those necessary to ensure the identity, purity, quality, strength, and composition claimed on the label.

Dietary supplements, unlike conventional foods, contain ingredients that are consumed in very small quantities, for example, in a tablet or capsule. Such ingredients may be intended to have an anticipated, specific physiological response. Such ingredients are more "drug-like" than "food-like," in part, because very small changes in the strength, purity, or quality of the ingredient can have significant, and possibly adverse, health consequences to those who ingest it. Thus, the dietary supplement CGMPs, by necessity, need to include provisions related to identity, purity, strength, quality, and composition of the product so that the dietary supplement "food" product will be manufactured in a manner that will not result in adulteration.

Further, plant products that are used to produce dietary supplements may be ground or in a powder and not easily recognized compared to conventional food that is readily identifiable (*e.g.*, one can readily distinguish between white flour and white sugar, but not between ground plaintain and ground *D. lanata*). Thus, for the manufacturer to be sure that the dietary supplement contains the correct ingredient and the amount of the ingredient that is intended, the manufacturer must test or examine the ingredient using appropriate methods. The "modeled after" language in section 402(g) of the act provides the agency with the flexibility to devise CGMPs that make sense for dietary supplements, and that are based on the same principles as food CGMPs in part 110, *i.e.*, to prevent adulteration related to insanitary conditions or other conditions that may be necessary to prevent adulteration, given the nature of the specific food product and the characteristics of, and hazards inherent in, that food.

The scope of the legal authority for the proposed dietary supplement CGMPs includes the legal authorities upon which the food CGMPs are based. For example, section 402(a)(3) of the act states that a food is deemed adulterated if "it consists in whole or in part of any filthy, putrid, or decomposed substance, or if it is otherwise unfit for food." Section 402(a)(4) of the act states that a food is deemed adulterated if "it has been prepared, packed, or held under insanitary conditions whereby it may have become contaminated with filth, or whereby it may have been rendered injurious to health." While section 402(a)(3) of the act focuses on the food itself, section 402(a)(4) of the act focuses on the conditions under which the food is prepared, packed, or held. Courts have adopted a broad reading of section 402(a)(4) of the act when we have taken actions to advance the public health (*see U.S.* v. *Nova Scotia Food Products Corp.*, 568 F. 2d 240, 248 (2d Cir. 1977)). The agency tentatively concludes that the authorities that it relied on for its umbrella CGMPs in part 110 for food are relevant to the authorities that it needs for this proposed rule for dietary supplement CGMPs. In addition, section 409 of the act is another provision that is relevant to dietary supplement CGMPs. Section 409 of the act addresses circumstances under which a food may be deemed adulterated based on the use of a food additive. Section 409 of the act is relevant to good manufacturing practices for foods, including dietary supplements, because a food would be deemed adulterated if it contained a food additive that was not used in a manner consistent with the statutory and regulatory requirements under section 409 of the act (*see* sections 402(a)(2)(C) and 409 of the act). Although Congress explicitly excluded "dietary ingredients," as defined in section 201(ff) of the act, from the definition of food additive, (*see* section 201(s)(6) of the act), ingredients other than dietary ingredients in a dietary supplement are subject to regulation as a food additive under section 409 of the act, unless they are subject to an exception to the definition of "food additive" under section 201(s) of the act.

Moreover, dietary ingredients and dietary supplements may contain pathogenic bacteria or viruses that pose serious public health and safety concerns (Ref. 36). Botanical dietary ingredients are living plants that may contain different microorganisms. These include *Lactobacillus, Leuconostoc, Pseudomonas,* and *Xanthomonas* species and molds. Potential pathogens such as *Listeria monocytogens, Pseudomonas aeruginosa* and *Enterobacteriacae* may also be present. Secondary microbial contamination from soil (*Bacillus cereus, Clostridium perfringens* and mycotoxin-producing molds, *etc.*), animal feces (*Salmonella* and *Shigella* spp., *Escherichia coli*) and handling (*Staphylococcus aureus*) can also occur during harvesting, processing, and transportation (Ref. 36). Animal-derived dietary ingredients or dietary supplements may also pose a risk. For example, bovine colostrum, the lacteal secretion which precedes milk after a cow gives birth, is a substance that is used in dietary supplements and likely presents the same potential health risks as does milk. Bovine milk may contain pathogenic organisms capable of causing diseases in man such as tuberculosis or undulant fever. Glands and other animal tissues may contain the infective agent that causes transmissible spongiform encephalopathy (TSE) if they originate from an animal infected with the disease (Ref. 37).

We have authority to issue regulations under section 361 of the PHS Act. The Secretary delegated authority to the Commissioner of FDA (the Commissioner) to exercise the functions vested in the Secretary under section 361 of the PHS Act (see 21 CFR 5.10(a)(3)). This authority authorizes the Commissioner to issue and enforce regulations that, in the Commissioner's judgment, are necessary to prevent the introduction, transmission, or spread of communicable diseases from one State to another. Because this authority is designed to eliminate the introduction of diseases from one State to another, the Commissioner may exercise the authority over the disease-causing substance within the State where the food is manufactured, packaged, or held. The Commissioner, therefore, assumes the authority to issue regulations under the PHS Act to assure that foods are manufactured, packaged, and held under conditions that will prevent the introduction, transmission,

U.S. FOOD AND DRUG ADMINISTRATION
OFFICE OF REGULATORY AFFAIRS AND
CENTER FOR FOOD SAFETY AND APPLIED NUTRITION

Presents via Satellite Broadcast

"Current Good Manufacturing Practice in Manufacturing, Packing or Holding Dietary Ingredients and Dietary Supplements" PROPOSED RULE

CLOSED CAPTIONED

May 9, 2003

12:30 – 3:30 PM ET
(Test Signal: 12:00 PM ET)

PROGRAM OBJECTIVES: This program will:

- Describe proposed CGMP provisions for the manufacturing, packaging, labeling, testing, quality control, releasing for distribution, and holding of dietary ingredients and dietary supplements
- Indicate how to make general comments and what types of comments FDA would find helpful in developing a final rule
- Describe how the Small Business Administration (SBA) offers help to small firms
- Offer an opportunity to ask questions about the proposed rule

WHO SHOULD PARTICIPATE: Stakeholders including:

- Dietary ingredient and supplement manufacturers, packagers, distributors, and holders
- Small businesses, their representatives and consultants
- State and local representatives
- FDA Small Business Representatives
- Other interested parties.

READING MATERIALS*: IMPORTANT:*

Specific material for this program is posted on the CFSAN Dietary Supplement home page as indicated below. We suggest that participants read these references prior to the downlink.

1. Guidance for Small Businesses Submission of Comments for CFSAN Rulemaking: Guide for Small Businesses to Submit Comments, October 21, 2002, http://www.cfsan.fda.gov/~dms/sbguide.html

2. **Press Release**: FDA Proposes Labeling and Manufacturing Standards For All Dietary Supplements, March 7, 2003, http://www.fda.gov/bbs/topics/NEWS/2003/NEW00876.html.

3. **Proposed Rule**: *Federal Register*: March 13, 2003, Current Good Manufacturing Practice in Manufacturing, Packing, or Holding Dietary Ingredients and Dietary Supplements, pages 12164 and 12165-Proposal Highlights and Requests for Comments, http://www.cfsan.fda.gov/~lrd/fr030313.html

4. **Fact sheet**: FDA Proposes Labeling and Manufacturing Standards Dietary Supplements,
http://www.fda.gov/bbs/topics/NEWS/dietarysupp/factsheet.html.

5. **Backgrounder**: FDA Proposes Manufacturing and Labeling Standards for all Dietary Supplements, March 7, 2003, http://www.fda.gov/bbs/topics/NEWS/dietarysupp/background.html.

General information about dietary ingredients and supplements is posted on http://www.cfsan.fda.gov/~dms/supplmnt.html.

PROGRAM VIEWING:
This program will be delivered via satellite to any location that has access to a steerable C-band satellite dish. The Technical Information Sheet is attached. For up-to-date technical information (coordinates, updates; potential "Open" downlink sites) visit the following web page prior to the broadcast:

http://www.fda.gov/cdrh/ohip/dcm/html/program calendar.html

BUSINESS VIEWERS:
Small businesses may wish to contact their local FDA Regional Small Business Representative concerning availability of the program. Small Business Representatives are listed at ORA's web site:
http://www.fda.gov/ora/fed_state/Small_Business/sbrtext.htm

STATE AND LOCAL OFFICIALS:
State and local counterparts who wish to participate may wish to consider any local viewing location that has the appropriate steerable C-Band dish.

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Dial-in numbers will be provided for FDA sites that do not have access for satellite or fiber reception. Dial-in number will be provided by DHRD to ORA Videoconference Coordinators via separate e-mail.

AUDIO-CONFERENCING:
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OTHER (FDA ONLY): Participants time spent viewing this program should be reported into the appropriate Operation code and PAC number 03R8000.

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ORA FIELD: Contact your local downlink site coordinator for local viewing information.

"Current Good Manufacturing Practice in Manufacturing, Packing or Holding Dietary Ingredients and Dietary Supplements" PROPOSED RULE "

TECHNICAL FACT SHEET

DATE: May 9, 2003

TEST TIME: 12:00 pm – 12:30 p.m. EDT
11:00 am - 11:30 a.m. CDT
10:00 am - 10:30 a.m. MDT
9:00 am - 9:30 a.m. PDT

PROGRAM TIME: 12:30 pm - 3:30 p.m. EDT
11:30 am - 2:30 p.m. CDT
10:30 am - 1:30 p.m. MDT
9:30 am - 12:30p.m. PDT

SATELLITE TROUBLE NUMBER: 1-888-626-8730
Q&A NUMBER: 1-800-527-1401
FAX Q & A NUMBER: 1-888-361-4011

C-Band: Galaxy 4R (G4 or G6) 99 degrees West				
Transponder	Polarization	Channel	Downlink Freq.	Audio
22	Vertical	22	4140 MHz	6.2/6.8

IMPORTANT SATELLITE INFORMATION TO HELP YOU TUNE IN

1. Galaxy 4R **is located at 99 degrees West. You can probably find it by choosing** G4 or G6 or G2 **on your receiver. (This popular location has been the "home" for the first Galaxy 4, Galaxy 6, and Galaxy 2, in the**

past.) If you would like to set up and/or test your receiver early, the following programming exists on Galaxy 4R (as of this writing):

Channel 15	World Harvest (religious)
Channel 16	Shepherd's Chapel (religious)

2. If you see this programming, it is highly likely you will be able to receive our programming, however, if after several tries you don't see this programming, you may need to have your equipment checked out by a professional. After successfully finding programming on these channels, don't forget to change to Channel 22 for our program.

3. It is very important for you to test your equipment as soon as possible to ensure that it is functioning properly and to see if you can get programming from the satellite we'll be on. Storms can cause damage and/or move your antenna out of alignment or you may not have your satellite of choice programmed in. Do not wait until test time to discover problems. If you think your dish and/or receiver are malfunctioning or not programmed correctly, have them checked out by a professional well before the program.

4. Although a Troubleshooter will be provided, we cannot guarantee the performance of your equipment.

"Current Good Manufacturing Practice in Manufacturing, Packing or Holding Dietary Ingredients and Dietary Supplements" PROPOSED RULE

May 9, 2003

12:30 – 3:30 PM ET
(Test Signal: 12:00 PM ET)

AUDIO CONFERENCE PARTICIPANT ACCESS INFORMATION

IMPORTANT!
Listening sites MUST keep your phones on MUTE.

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Please join me on MAY-09-2003 (Friday) at 12:00 PM EASTERN TIME. Access information is below.

AUDIO PARTICIPANT ACCESS
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CALL DATE:	MAY-09-2003 (Friday)
CALL TIME:	**12:00 PM EASTERN TIME**
DURATION:	**3 hr 30 min**
LEADER:	**MS BARBARA GIGANTI**

USA Toll Free Number: **877-546-1567**

PASSCODE: 10827

The pass code and the leader's name will be required to join this call.