Council for Responsible Nutrition

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Dockets Management Branch (HFA 305)
Food and Drug Administration
5630 Fishers Lane, Room 1061
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RE: DOCKET NO. 96N-0417, GOOD MANUFACTURING PRACTICES FOR DIETARY SUPPLEMENTS

TOPIC: PURPOSE AND SCOPE OF THE RULE

This is the second in a series of comments submitted by the Council for Responsible Nutrition regarding the above-mentioned proposed rule. These comments will address the purpose and scope of the proposed rule, as indicated below. The specific topics addressed in this set of comments are as follows:

On this same date, CRN is submitting separate comments on the importance of process control and on legal aspects of the proposal. In addition, we will submit a separate comment summarizing our section-by-section recommendations. At a later date, but before September 9, we will submit comments on the economic impact of the proposed

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rule. CRN has requested and been granted this additional time for submission of economic data based on new information we have just obtained pursuant to a FOIA request for underlying data not previously included in the administrative record, relating to FDA's assumptions and calculations on the estimated economic impact of the rule. The first comment in this series (July 8, 2003) provided a four-way comparison of the proposed GMP with current food GMPs, the industry draft published as the ANPR in 1997, and current drug GMPs.

The Council for Responsible Nutrition (CRN) is one of the leading trade associations representing the dietary supplement industry. CRN has been a strong supporter of Good Manufacturing Practices (GMPs) over the years, and we have an active Regulatory Affairs Committee composed of industry experts in dietary supplement regulation and in the technical aspects of production processes, including GMPs. CRN's member company experts in this arena drafted the guidelines for nutritional supplement manufacturing practices adopted by USP over a decade ago and also prepared the industry draft GMPs submitted to FDA in November 1995 by CRN, joined by other industry trade associations. FDA published the industry draft verbatim in the ANPR on dietary supplement GMPs in 1997.

CRN member companies currently include 35 manufacturers of finished dietary supplement products and 31 manufacturers and suppliers of bulk dietary ingredients or other components of dietary supplements, as well as a number of associate members that provide services to the industry. **Attached is a list of our manufacturer and supplier members, together with examples of the types and brands of products they market.** The list is designed in such a way that readers of the electronic version can click on a company name and access its website. CRN's membership includes some very large companies that manufacture the leading U.S. brands of dietary supplement products, that manufacture the store brands marketed by large food and drug chains, and that manufacture and supply key ingredients used both in conventional foods and in dietary supplements. Our membership also includes a number of companies that are "small businesses" as defined by the Small Business Administration but that also have reputations as leading quality manufacturers of numerous products or ingredients.

CRN member companies account for a substantial fraction of the dietary supplement market in the U.S. in terms of sales volume. Using sales data from *Nutrition Business Journal*, we calculate that nine of the top fifteen manufacturers and marketers of dietary supplements in the U.S. are CRN members. These companies, plus a number of smaller CRN member manufacturers, account for about 40% of the wholesale sales volume of dietary supplements marketed through supermarkets, natural food stores, drug stores, and discount department stores. Six of the top twenty companies in direct sales (called multilevel marketing by *NBJ*) are CRN member companies, accounting for 26% of the sales volume marketed through that channel. Eight of the top ten vitamin ingredient suppliers are CRN member companies, providing 71% of the sales volume for commercial vitamins used in dietary supplements annually. Another 23 supplier members of CRN provide the industry with other key dietary ingredients including

calcium and other minerals, lutein and other carotenoids, botanicals, omega-3 fatty acids, and specialty ingredients such as glucosamine and chondroitin sulfate.

NEED FOR THE RULE

CRN and its members support enhanced dietary supplement GMPs because high quality products will better meet the needs and expectations of consumers for improved health. Also, stronger GMPs will better reflect actual current practices employed by responsible companies in the manufacture of dietary spplement products. FDA, in contrast, argues that new GMPs are needed because dietary supplement ingredients are different in kind from conventional food ingredients and are more risky than food ingredients. We disagree strongly with these assumptions. The fact that CRN supports enhanced GMPs for dietary supplements is not due to any difference in their nature, as compared to conventional foods, but is due to the fact that current manufacturing practices in our industry typically go beyond current food GMPs, and we believe it makes sense for GMP regulations for our category to recognize and incorporate current "best practices."

In the preamble to the proposed rule, FDA asserts that "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." Dietary supplements in fact fall squarely within the food category and have been treated as a subset of foods for their entire history. In the 1938 Food, Drug and Cosmetic Act, dietary supplements were included in the category called "foods for special dietary use." Such uses, as further defined by FDA in 1941, included supplying vitamins, minerals, or other ingredients for use in supplementing the diet by increasing the total dietary intake. DSHEA in 1994 confirmed the food status of dietary supplements and provided an expanded definition of the category.

Dietary supplements and dietary ingredients are currently covered by the general food GMPs in 21 CFR Part 110. Dietary supplements are foods, comparable to fortified foods or functional foods. The ingredients used in them are similar, and the suppliers of key ingredients serve the conventional food industry as well as the dietary supplement industry. The vitamins and minerals contained in leading brands of multivitamins are exactly the same vitamins and minerals that are found in leading brands of breakfast cereal -- and the amounts per serving are in many cases similar. To the extent that potential superpotency or subpotency exists from errors during manufacturing, that potential exists for conventional foods as well as for dietary supplements. Indeed, the Upper Level of Tolerable Intake (UL) for niacin, established in the Dietary Reference Intakes for B vitamins published by the Institute of Medicine in 1998, is based in part on an incident involving accidental addition of excess niacin in the commercial preparation of bagels and the resultant flushing reaction experienced by some of the people who consumed the product.

Going beyond vitamin and mineral ingredients, numerous other dietary supplement ingredients are also identical to or similar to those used in conventional foods. The soy

components in dietary supplements are the same ones added to cereals and breads and other conventional food products, and the amounts provided per serving are similar. Botanical ingredients are derived from unique plant materials, in the same manner as common spices, and the processing techniques and quality challenges are similar.

FDA's preamble points out that "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*)." FDA staff members, in public briefings on the proposed GMP rule, have also emphasized this presumed distinction, saying that foods contain recognizable ingredients like peas and beans, while dietary supplements contain less easily identifiable ingredients, usually in powdered form. These statements do not fairly characterize the complex nature of the modern food supply or the types of ingredients utilized in the highly processed foods that make up a large fraction of today's market.

White flour and white sugar are hardly the only powdered and ground ingredients used in food production or in the home, and many of the other highly processed ingredients used in foods are also widely used in dietary supplements. These include vitamins; soy isoflavones and other soy components; minerals such as calcium carbonate (used for many functions in addition to providing the nutrient calcium); antioxidants such as erythorbate, BHA, and BHT; artificial sweeteners; various food starches; carboxymethylcellulose and other celluloses; various silicates; polysorbates; mono and diglycerides; fatty acid salts and esters; protein ingredients such as casein; and various calcium phosphates. *Food Chemicals Codex* is an excellent source for a more complete list of ingredients commonly used both in conventional foods and in dietary supplements. Many of these ingredients have the physical form of a "white crystalline powder."

Finally, in attempting to distinguish between conventional food manufacturers and dietary supplement manufacturers, FDA says "dietary ingredient and dietary supplement manufacturing requires technical knowledge and skill (e.g., in research and development, production equipment and procedures, and analytical equipment and methodology) that a vast majority of companies in the food processing industry do not have." This is demonstrably untrue, and FDA's assertion would come as a shock to the many sophisticated food manufacturers that supply a large fraction of the food ingredients and conventional foods found in supermarkets today -- and that also provide key ingredients to the dietary supplement industry. Current food GMPs have for many decades provided an adequate underpinning for the manufacture of both conventional foods and dietary supplements, even though the current practices of leading companies in both industries go beyond the procedures required under the food GMP regulations. CRN supports enhanced dietary supplement GMPs because we believe the regulations should better reflect current good manufacturing practices as actually observed in the industry, in order to raise the bar for those companies that are not currently producing quality products and to provide an appropriate model for new companies entering the industry.

PURPOSE OF THE RULE

As FDA points out in the preamble to the proposed rule (68 FR 12159), "Congress enacted DSHEA to ensure consumers' access to safe dietary supplements." The agency goes on to note that dietary supplements that are adulterated or that fail to provide labeled amounts of dietary ingredients may harm consumers or may fail to provide the expected health benefit. FDA asserts that regulations on Good Manufacturing Practices (GMPs) "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."

CRN agrees that new GMPs for dietary supplements will be beneficial to consumers and to the industry, provided the regulations are appropriately modeled after food GMPs and reasonably reflect current "best practices" and provided they strike the correct balance between adequate control and necessary flexibility. Responsible manufacturers and marketers of dietary supplements already produce high quality, safe, beneficial dietary supplements that are used and valued by more than half the American population as well as by consumers throughout the world, and some of these companies have been providing high quality products for over half a century. New GMP regulations are not required in order to provide a quality framework for responsible manufacturers. Rather, their practices define current GMPs and should provide the basis for the rule.

CRN disagrees strongly with the implication in the preamble to the proposed rule that product safety and quality cannot be ensured in the absence of new GMP regulations. Existing food GMPs and other regulations combined with the requirements of the Food, Drug, and Cosmetic Act (FD&C Act) provide a powerful foundation for ensuring product safety and quality, provided those requirements are enforced. Issuing new GMP regulations will not eliminate the need for enforcement of existing regulations or persuade rogue companies to comply with requirements they currently ignore. Only effective enforcement against outliers can accomplish that goal. CRN urges effective and consistent enforcement of current food GMPs applicable to dietary supplements, of other regulatory and legal requirements, and of any new GMPs once they become effective.

In the preamble, (68 FR 12161-2) the agency notes that "unlike other major product areas," dietary supplements do not have category-specific GMPs. The implication is that most other food products do have category-specific GMPs. However, this is not the case. General food GMPs (21 CFR, Part 110) apply to all food and food ingredient manufacturers, including companies producing dietary supplements and dietary ingredients. Unique GMPs have been developed for only a very few specific product areas, such as low-acid canned foods, acidified canned foods, and bottled water. These GMPs address only the requirements unique to the product category and specify that companies in these categories must still comply with general food GMPs as set forth in 21 CFR 110. There are quality standards for infant formula, but as yet no GMPs for this critical food category. Only two FDA-regulated food categories (juices and seafood) are covered by HACCP rules.

Most food categories are covered only by general food GMPs, and these combined with the general provisions of the law have proven adequate to protect the food supply over the years. Unique GMPs have been instituted generally in the wake of specific incidents leading to a call for further action, often at the instigation of the affected industry. In the case of dietary supplements, industry supported the inclusion in DSHEA of language granting FDA authority to establish unique GMPs for this product category, and CRN took the initiative in preparing the industry draft that FDA published in 1997 in the ANPR. This effort was undertaken as a positive move toward improved product quality and as an affirmation of the industry's commitment to good practices. CRN and its members are concerned by FDA's focus on the negative, by the implication that problems that may occur cannot be adequately addressed under existing regulations, and by FDA's erroneous assertion that GMPs can essentially eliminate human error in manufacturing. There needs to be full recognition of the fact that existing regulations cover a great deal of the ground that needs to be covered, and there needs to be a realistic expectation about what additional assurance can be provided by new GMPs.

FDA provides nine examples of problems that it says might be avoided by new GMP regulations. In every case, however, there were and are existing regulations already in place that could and should have prevented the problem from occurring and that provided the basis for effective regulatory action once the problem did occur. One more regulation, added to those already in place, will not make the critical difference and will not reduce human error to zero, as predicted in the FDA analysis. CRN makes this point, not to undermine the importance of new GMP regulations, but to provide some perspective on what GMPs can and cannot be expected to accomplish.

1. FDA's first example of a problem relating to dietary supplements relates to an occurrence that appears to be driving the direction and focus of the entire rule. It involves an instance in which an ingredient that purported to be plantain leaves was contaminated with leaves of *Digitalis lanata.* Worse, the product went through the hands of numerous manufacturers apparently without appropriate testing. FDA says that the proposed GMP regulations "would have required identity and purity tests" of the ingredient and the finished product and thus would likely have prevented the mixup. This may be true, but it is also important to acknowledge that the product was misbranded and adulterated under current law and under current food GMPs. FDA and industry responded rapidly as soon as the plantain mixup came to light. FDA promptly identified the problem and warned consumers, and industry recalled the products involved.

2. FDA cites a report by the American Herbal Products Association (AHPA) listing 43 botanicals that have the potential to be contaminated. Publication of this report was a responsible educational initiative on the part of AHPA. The report also suggests methods for testing products in order to ensure that the potential contaminant is not present. FDA observes that botanical manufacturers would have to establish specifications and perform testing under the new GMPs to ensure that there are no toxic compounds in such products. While this is true, the need for such testing and specifications is not unique to

dietary supplements. Many basic food commodities are subject to contaminants such as aflatoxin and mercury, for example, and FDA has established defect action levels for some contaminants in some commodities. Environmental chemicals present in air, soil and water are also present in foods, and microbial contamination is an ever-present hazard in foods that inherently provide a nutrient-rich growth medium for a wide variety of micro-organisms. These common hazards are managed in the food industry through application of general food GMPs. The existence of the same potential hazards in dietary supplement ingredients does not constitute a rationale for new GMPs that go beyond food GMP regulations.

3. FDA says some manufacturers use chemicals that are not food-grade and cites GBL as an example of this issue. However, the agency fails to mention that GBL is not a legal dietary supplement ingredient in the first place. It is available commercially as an industrial and household solvent. FDA has taken action against GBL and the related product GHB, which in CRN's view were illegal ingredients "masquerading" as dietary supplements. These FDA actions have been supported by the responsible industry. The enforcement actions were not taken on the basis of GMP violations, but on the grounds that GBL, GHB and related ingredients are illegal new drugs, not dietary supplements. One company filed a 75-day notification for GBL as a "new dietary ingredient," and FDA rejected it. New GMPs would not materially change this picture.

4. FDA indicates that unsanitary conditions have been found in some manufacturing facilities and says that the new GMPs would require the companies to maintain physical plants in sanitary condition. Existing food GMPs already require companies to maintain sanitary conditions in their physical plants, and FDA has successfully taken action in cases where inspections have revealed inadequate attention to sanitation. Thus, FDA is not reliant on new GMPs for dietary supplements in order to monitor and correct such problems. Indeed, with respect to sanitation, the new proposed GMPs are largely identical to the current food GMPs.

5. FDA cites some recalls of dietary supplements contaminated with lead, glass, or micro-organisms and says that the new GMPs would require manufacturers to prevent such adulteration. While this is true of the new GMPs, it is also true of the existing food GMPs, and it is inaccurate to imply that these contaminants cannot be adequately controlled under existing GMP regulations. Adequate enforcement of existing food GMPs would accomplish a great deal, even in the absence of new GMPs for dietary supplements.

6. FDA indicates that some recalls have been necessary for dietary supplements that contained too much or too little of a labeled ingredient such as vitamin A, vitamin D, vitamin B-6, selenium, or folic acid. FDA points out that, under the new GMPs for dietary supplements, a product will be required to have the amount of a substance indicated on the label. While this is true, it is already illegal under current law and regulations for a product not to contain the amounts of ingredients claimed on the label. Indeed, FDA has taken action against the products cited in this example, without needing to depend on unique dietary supplement GMPs. Nutrition labeling regulations

applicable to dietary supplements specifically require that added nutrients (or other substances) be present at levels that are at least 100% of the amount claimed on the label. The dietary supplement nutrition labeling regulations are identical in this respect to the nutrition labeling regulations applicable to conventional foods. Even if this specific regulation did not exist, the language of the FD&C Act declares a food to be misbranded if its labeling is false or misleading. Also, the Dietary Supplement Health and Education Act of 1994 (DSHEA) specifically provides that a dietary supplement is misbranded if it "fails to have the identity and strength" that it is represented to have or if it fails to meet the quality or specifications it is represented to meet. Thus, new GMPs would not be breaking new ground in requiring that a product contain what it claims to contain.

7. FDA indicates that some recalls of dietary supplements have been necessary because of undeclared ingredients such as color additives, lactose, and sulfites. FDA has full authority under the law and under existing food GMPs to take regulatory action against such products. This authority will not be enhanced or in any way altered under proposed dietary supplement GMPs. It should also be noted that there have been significantly more recalls of conventional foods than of dietary supplements due to undeclared ingredients such as these. CRN calculated the number of Class I and Class II recalls of all foods, including dietary supplements, during the decade of the 1990's (1990 to 1999) from the weekly recall reports available on the FDA website. We counted 6 recalls of dietary supplements in this period because of undeclared ingredients, compared to over 600 recalls for conventional foods because of undeclared ingredients. For dietary supplements, this is about 1 recall per $3 billion in sales, and for conventional foods this is just under 1 recall per $1 billion in sales (based on annual sales of about $18 billion and $500 billion, respectively).

8 and 9. In these two examples, FDA points out that a study of ephedra supplements found considerable variation in alkaloid content and that testing by a private company has revealed other instances in which various products failed to contain the amounts of dietary ingredients stated on the label. This suggests poor quality control on the part of some companies in the industry. Responsible manufacturers support enforcement of GMP regulations and other regulatory requirements in order to correct this situation, which undermines consumer confidence and gives the entire industry a black eye. FDA has full authority to take action against mislabeled products. Vigorous enforcement would effectively get the attention of the bad actors. CRN supports appropriate new GMPs, but the new rules will improve compliance only to the degree that they are enforced.

CRN ANALYSIS OF RECALL DATA

CRN analyzed the FDA weekly enforcement reports for the decade of the 1990's. **Attachment B is a table showing CRN's compilation of Class I and Class II recalls for dietary supplements, conventional foods, and drugs from 1990 through 1999, based on FDA's weekly enforcement reports for this period.** For this period, FDA weekly enforcement reports show a total of 2542 Class I and Class II recalls for conventional foods, dietary supplements, and drugs. Of this total, dietary supplements

account for only 52. Drugs account for 997, and conventional foods account for 1493. As a function of sales volume, the rate of recalls for dietary supplements is comparable to the rate of recalls for conventional foods. For both categories, there are just under 3 recalls per billion dollars in sales volume (based on a market size of approximately $18 billion for dietary supplements and approximately $500 billion for conventional foods). This illustrates that the two categories have a similar record for product quality and safety, to the extent that recalls are a reflection of these characteristics.

FDA ANALYSIS OF RECALL DATA

FDA's preamble text reports an average of 13 dietary supplement recalls per year during the 10-year period from 1990 through 1999, or an implied total of 130. This is more than twice the number identified by CRN, for the same period. One possible reason for this discrepancy is that FDA may be counting each separate item covered by a given recall as a separate event, as discussed below.

In the FDA tabulation of recalls, provided in Table 8 of the *Federal Register* publication of the proposed rule, FDA lists 41 Class II recalls relating to EMS. Based on new background information we recently received from FDA relating to the calculations of economic impact, this appears to have been an error. It seems that several lines of information were omitted from Table 8 and that these 41 Class II EMS recalls actually should have been identified as recalls of various dietary supplements with excessive lead content. In CRN's analysis of FDA's weekly enforcement reports, we identified 11 class II recalls of dietary supplements relating to excessive lead content and 45 class I and class II recalls of conventional foods due to excessive lead content. Some of the dietary supplement recalls covered more than one product distributed by a given manufacturer. Two of the recalls covered 5 products each, one covered 9 products, and one covered 10 products. Only by counting these as separate recalls can we approach FDA's reported total of 41 recalls for dietary supplements due to excessive lead content. If this was the agency's approach to counting dietary supplement recalls, we question its appropriateness.

Even excluding the 41 EMS recalls apparently included erroneously in Table 8, FDA's tabulation of dietary supplement recalls still includes 7 recalls of tryptophan products related to the outbreak of EMS. These should not have been included in the table of "ordinary" recalls, since the tryptophan case is separately analyzed by the agency as an example of a "rare catastrophic event," and costs associated with the EMS outbreak are also calculated separately. Because FDA assumes every recall is associated with an illness, then multiplies by 100 to compensate for under-reporting, these recalls represent a number of presumed illnesses incorrectly included in FDA's analysis of illnesses associated with ordinary recalls.

Of the recalls tabulated by FDA, 33 are attributed to the recalls involving dietary supplements that were intended to contain plantain leaf but that were contaminated with leaves from the plant *Digitalis lanata.* We have examined the FDA weekly recall reports found on the agency's website, and we can only identify 13 digitalis recalls during this

period. We believe the agency may have counted each separate item mentioned in each of the 13 recalls, to reach the total of 33 reported in the table. For example, one recall for "Chomper" lists five sizes or varieties of the Chomper product covered by the recall. This item is listed as one recall in the FDA weekly enforcement report, and we count it as one recall in our tabulation of recalls. Unless FDA counted this as five recalls for purposes of its tabulation, we cannot understand how the agency arrived at a total of 33 recalls relating to plantain/digitalis. Counting each separate item covered by a given recall as a separate event does not appear to us to be appropriate.

Logically, we would suggest that the plantain recall, like the tryptophan recall, should be treated as a single rare event. Only two adverse events were reported in association with the plantain recall, including the one that triggered discovery of the problem. There was very substantial publicity at the time of this recall, and a number of related FDA consumer warnings. The FDA announcements and media attention should have led to essentially full reporting of any adverse events experienced by other consumers using the products. Thus, whatever the base number of plantain recalls FDA chooses to utilize in this analysis, it would not be appropriate to apply the 100-fold multiplication because the assumption of under-reporting in this case is not sound.

In the analysis of economic impacts, FDA assumes that new GMPs will reduce human error to zero and says there will be no more recalls of dietary supplements once these regulations are in place. This is unrealistic. In all FDA-regulated product categories, recalls occur with regularity for a variety of reasons. GMPs will not totally eliminate human error. CRN also disagrees with FDA's assumptions that at least one illness is associated with every recall, and that because of under-reporting every recall is a proxy for 100 presumed illnesses. We will be submitting additional data and views on these points in our comments, in the economic analysis to be submitted at a later date, as agreed to by the agency in response to our request for additional time to analyze underlying economic data recently provided by FDA in response to a FOIA request.

FDA PROPOSES TO COVER DIETARY INGREDIENTS AS WELL AS DIETARY SUPPLEMENTS

The FDA proposed rule on GMPs states in part 111.1: "You are subject to the regulations in this part if you manufacture, package, or hold a dietary ingredient or dietary supplement." Thus, FDA intends for the rule to apply to manufacturers (suppliers) of dietary ingredients as well as to manufacturers of finished dietary supplements.

Nutrition Business Journal publishes comprehensive reports on the U.S. market for dietary supplements. In *NBJ's Supplement Business Report 2002,* the dietary supplement industry value chain is estimated to include 250 suppliers of dietary ingredients and 925 manufacturers or processors of finished products. If these data are correct, then approximately one-fifth of the manufacturers covered by FDA's proposed rule would be suppliers of dietary ingredients.

The industry draft that was published in the ANPR also was intended to apply to manufacturers and suppliers of dietary ingredients as well as to finished product manufacturers. The industry draft was process-based and principle-oriented and provided enough flexibility to accommodate the needs of a wide variety of firms with different types of products and different types of processes. The nature of the FDA proposal has led to reconsideration of this approach.

More importantly, during the eight years that have elapsed since submission of the industry draft in 1995, companies and associations have had ample opportunity to further consider all aspects of the GMP issue and to give more attention to other GMP models, including category-specific food GMPs and drug GMPs. These other GMPs apply only to finished-product manufacturers and not to manufacturers and suppliers of ingredients used in those finished products. This now seems to CRN to be a preferable approach to accomplishing the greatest good while controlling costs and narrowing the range of companies subjected to new requirements.

There is of course continuing concern in all segments of the industry regarding the best way to assure the quality of dietary ingredients as well as finished products. CRN believes sound regulatory policy suggests focusing the rule are carefully as possible, and we believe the best way to do this would be to focus it on manufacturers with control over the selection of ingredients they choose to use in their dietary supplements, as well as over all aspects of the processing of the finished product. We are aware that the various industry trade associations are adopting differing approaches to this matter, as of the date of this submission. We believe this illustrates the need for further high-level consideration of this issue by the agency as well as by the industry, and **we urge FDA to convene a public hearing or workshop on this and other issues relating to dietary supplement GMPs before proceeding to a final rule.**

CRN PROPOSES THAT THE RULE APPLY ONLY TO MANUFACTURERS OF FINISHED PRODUCTS

The Council for Responsible Nutrition urges FDA to limit the applicability of the proposed rule to manufacturers of finished dietary supplements. These manufacturers should be viewed as the companies primarily responsible for the overall quality of dietary supplements, including the quality of the ingredients used in their formulation and the selection of reliable suppliers of those ingredients.

The term "dietary ingredient" is not defined by FDA in the proposed rule, but CRN will be suggesting that a definition be included. Of course, the definition should be based on the provisions of the Dietary Supplement Health and Education Act (DSHEA). Under DSHEA, a dietary supplement is a product intended to supplement the diet that contains one of more of the following "dietary ingredients:" a vitamin; a mineral; an herb or other botanical; an amino acid; a dietary substance for use by man to supplement the diet by increasing the total dietary intake; or a concentrate, metabolite, constituent, extract, or combination of any of these.

These "dietary ingredients" include a large number of ingredients that are also commonly used in conventional foods, including specialty products such as functional foods, medical foods and infant formula. These ingredients are also commonly used in animal feed and pet foods, as well as in some pharmaceutical products. Calcium carbonate, for example, is often used as a source of the essential mineral calcium in dietary supplements, in fortified foods, in infant formula, in medical foods, and in pet foods and animal feed. It is also used in conventional foods as well as dietary supplements for functional purposes other than its nutrient value, for example as a dough conditioner or firming agent in conventional foods and as a filler or binder in dietary supplements. In addition, calcium carbonate is used as an active ingredient in OTC antacid drugs. A similarly wide range of uses can be observed for other dietary supplement ingredients, including minerals other than calcium, all of the vitamins, a large number of amino acids, many botanical ingredients including soy and garlic, and numerous extracts or constituents of botanical ingredients including isoflavones, carotenoids, and polyphenols.

In many cases, the use of a particular ingredient in the formulation of dietary supplements accounts for only a fraction of its total use in food and feed products in the United States. Taking vitamins as a case in point, *NBJ's Supplement Business Report 2002* indicates that only 33% of the commercial supply of vitamins in this country is purchased for use in dietary supplement products. For individual vitamins, the percent that goes into dietary supplements ranges from 21 percent to 44 percent, as shown in **Table A** below. Fifty-six percent to eighty percent of the usage for each of the vitamins goes into conventional foods, animal feed, and cosmetics. The vitamins that go into dietary supplements are identical to those used for other purposes, are provided by the same suppliers, and are produced in the same facilities under the same conditions. The key vitamin suppliers are among the largest and most expert manufacturers involved in this industry and have a long history of providing quality materials for use in all the industries that rely upon them. Indeed, their manufacturing practices **should be considered to define "good manufacturing practices"** for commercial vitamin production.

Table A: Fraction of U.S. Commercial Vitamin Usage by Various Industries

U.S. Vitamin Usage - 2001	Supplements	Animal Feed	Food	Cosmetics	Total
Vitamin A	41%	36%	18%	5%	100%
B Vitamins	31%	45%	20%	4%	100%
Vitamin C	34%	37%	26%	3%	100%
Vitamin E	44%	36%	15%	5%	100%
Other Vitamins	21%	29%	45%	5%	100%
Total Vitamins	**33%**	**36%**	**27%**	**4%**	**100%**

Source: *NBJ's Supplement Business Report 2002*

Worldwide, the share of the commercial vitamin supply that is used in the U.S. dietary supplement market is relatively small. **Table B**, below, shows that only 14% of the worldwide commercial supply of vitamins goes into the U.S. supplement market. For individual vitamins, the share of the world supply that goes into the U.S. dietary supplement market ranges from 12 to 18 percent.

Table B: Share of Worldwide Commercial Vitamin Supply Used in U.S. Dietary Supplement Market, 2001 ($mil)

VITAMIN	WORLDWIDE	U.S. TOTAL	U.S. SUPPS	U.S. SUPPS % OF TOTAL
Vitamin C	$1,960	$700	$240	12%
Vitamin E	1,330	550	240	18%
B Vitamins	1,180	490	150	13%
Vitamin A	700	220	90	13%
Other	1,160	750	160	14%
TOTAL	**$6,330**	**$2,710**	**$880**	**14%**

Source: *NBJ's Supplement Business Report 2002*

A potential outcome of requiring suppliers of dietary ingredients to comply with new dietary supplement GMPs could be to significantly raise costs in order to cover new and extensive testing beyond what many responsible companies consider to be necessary for a high level of quality assurance. Another potential impact could be to reduce the supply of dietary ingredients, if suppliers find it too costly to supply the dietary supplement segment of the market and withdraw from that segment rather than change their basic procedures to comply with new provisions that are considered to exceed what is necessary or reasonable for the manufacture of quality products. The potential for some key suppliers to withdraw from the U.S. dietary supplement market may seem more real when it is recognized that a large fraction of the supply for many ingredients is from foreign sources.

The top 10 vitamin manufacturers in 2000 accounted for 77% of worldwide production. As indicated by data in **Table C,** for the two largest suppliers (Roche and BASF), only 13% of their vitamin production volume went into the U.S. dietary supplement market. Among the other eight top suppliers, 12 to 47% of their total vitamin production went into the U.S. dietary supplement market. Only one of the top ten vitamin manufacturers (ADM) is headquartered in the U.S., although all of the top ten have large U.S. facilities. Of the other nine that were market leaders in 2000, three were headquartered in Germany, two in Switzerland, one in France, and three in Japan. Two of the Japanese firms (Takeda and Eisai) have since withdrawn from the U.S. vitamin market, although they still have a U.S. presence in other markets, including pharmaceuticals. Market share for Chinese suppliers is growing and is undoubtedly much greater today than it was in 2000.

Table C: Top Vitamin Suppliers Worldwide, 2000

COMPANY	GLOBAL VITAMIN SALES ($mil)	U.S. SALES FOR SUPPLEMENT USE ($mil)	% OF COMPANY SALES IN U.S. SUPPLEMENTS
Roche	2,100-2,200	250-300	13%
BASF	1,000-1,100	120-150	13%
Takeda	100-200	50-60	37%
Lonza	100-200	30-40	23%
Eisai	100-200	20-30	17%
Rhone Poulenc	100-200	15-20	12%
Daiichi Fine Chem.	50-100	20-30	33%
ADM	50-100	40-50	60%
Cognis	50-100	20-30	33%
Degussa	50-100	30-40	47%
Chinese and others	1,000	200	20%
TOTAL	**$5,100**	**$850**	**17%**

Source: *NBJ's Supplement Business Report 2002*

On the botanical side of the business, eleven of the top 26 suppliers are headquartered outside the U.S. and account for 36% of the current supply of botanical ingredients, as shown in **Table D**, below.

Table D: Top U.S. Herbal/Botanical Ingredient Suppliers, 2000

Rank	Company	HQ	2000 US Herb/Bot Raw Matl Sales ($mil)	Cum Share of Market *
1	Martin Bauer Group	Germany	60-70	10%
2	Hauser Inc.	United States	60-65	20%
3	Indena	Italy	35-40	25%
4	Degussa AG	Germany	30-40	30%
5	A.M. Todd Botanicals	United States	25-30	34%
6	Frutarom Ltd.	United States	25-30	38%
7	Pharmachem	United States	25-30	42%
8	Arkopharma	France	20-25	46%
9	Technical Sourcing Intl (Inabata)	United States	20-25	49%
10	Cognis (Henkel)	Germany	20-25	52%
11	Triarco Industries	United States	20-25	55%
12	Pure World Botanicals	United States	20-25	58%
13	Sabinsa	United States	15-20	61%
14	Maypro	United States	15-20	64%
15	Trout Lake Farm (Amway)	United States	15-20	67%
16	Mafco Worldwide Corp.	United States	10-15	69%
17	Schwabe	Germany	10-15	71%
18	Schweizerhall (Aceto Corp.)	Switzerland	10-15	73%
19	InterHealth	United States	10-15	75%
20	Euromed (Madaus)	Spain	10-15	77%
21	Quality Botanical Ingredients	United States	10-15	79%
22	Pharmline	United States	10-15	81%
23	Bio-Botanica	United States	10-15	83%
24	Chai-Na-Ta	Canada	5-10	84%
25	Flachsmann	Germany	5-10	85%
26	Linnea	Switzerland	5-10	86%

Source: *NBJ's Supplement Business Report 2002*

Table E, below, shows that 89% of the botanical suppliers have less than $20 million in sales, so an increase in compliance costs could have an especially severe impact. Increases in costs and regulation have the potential to seriously reduce supplies of botanical ingredients. To the extent that such an impact "weeds out" poor quality suppliers, it may actually prove beneficial. However, the impact would be negative if it caused responsible and reliable botanical suppliers such as those listed above to withdraw from the U.S. market. Obviously, the quality of botanicals used in dietary supplements must be assured, and CRN is suggesting that burden be placed on finished product manufacturers to select reliable suppliers, to take responsibility for assuring overall product quality, and to negotiate an appropriate division of labor with their individual suppliers with respect to necessary testing of the ingredient.

Table E: Revenue for Suppliers of Botanical Ingredients Used In U.S. Dietary Supplements, 2000

REVENUE	COMPANIES (NUMBER)	TOTAL REVS. ($mil)	SHARE OF REVS.
More than $20 mil	12	$397	59%
$5 to $20 mil	14	167	25%
Less than $5 mil	79	106	16%
TOTAL WHOLESALE ($mil)	**105**	**$670**	**100%**

Source: *NBJ's Supplement Business Report 2002*

The agency cites as an example of the need to regulate dietary ingredients the case in which an ingredient marketed as plantain leaf was contaminated with *Digitalis lanata* and was sold to consumers as a dietary supplement to be used for the purpose of "cleansing" the body. This contamination is an example of an egregious error that could and should have been detected by multiple players in the supply chain, but it was not in fact detected prior to the occurrence of an adverse event. This incident, however, must be recognized as rare and does not justify invoking a rule that is broader than it needs to be in order to ensure the quality of products in the future. Careful observance of existing food GMPs should have prevented this event. New and stronger GMPs applicable to finished product manufacturers would clearly place the responsibility for ensuring identity of the ingredient on the manufacturer of the finished product and would provide for adequate controls to prevent such an occurrence.

Many dietary ingredients are manufactured by large agricultural or chemical firms in a continuous process. Many of these firms have a long history of supplying reliable quality ingredients for the food, feed, and pharmaceutical industries in the U.S. and worldwide. For such companies, an incoming "lot" may be the soybeans produced by an entire farm, and a dietary ingredient may be produced as a sidestream of the processing of the core

commodity. The notion of quarantining incoming lots or analyzing individual batches has little practical application in such a production system. In some cases, lots and batches may be identified only as the amount of material produced during a certain period of time.

Many dietary ingredients and food ingredients are derived from non-food-grade materials, and become food-grade only after appropriate processing. Calcium carbonate, for example, is quarried as stone and is transformed into a "white microcrystalline powder" (*Food Chemicals Codex*) only after extensive processing in a sophisticated manufacturing plant. Thus, the proposed GMP requirement that only food-grade bulk ingredients be used as raw materials is not appropriate to the supplier environment, since by definition some suppliers begin with cruder materials and create from them new ingredients of food or pharmaceutical grade. Our member companies have informed us that there are not food grade specifications for some ingredients, including some of the essential trace minerals.

An ingredient does not become a "dietary ingredient" until it is purchased by a dietary supplement manufacturer specifically for the purpose of being included in the formulation of a dietary supplement product. Thus, CRN believes it is the manufacturer of the finished dietary supplement product who bears the responsibility for selecting ingredients appropriate for their intended use and for verifying the reliability of the supplier as well as the quality of the ingredients purchased for that use. Thus, the manufacturer of the finished product should be subject to the new GMP rule. The manufacturer of the bulk dietary ingredient should, as heretofore, be covered by general food GMPs.

CRN will be making specific recommendations regarding areas in which special provisions need to be drafted for suppliers, if FDA decides to apply the final GMP rule to suppliers, but we believe the more rational approach would be to apply the GMP rule only to finished product manufacturers. The proposed GMP regulations include a substantial number of provisions intended to control the quality of dietary ingredients used in the manufacturing of finished dietary supplements. Thus, the ingredients will be subject to specific quality controls under the requirements applicable to manufacturers of finished products.

DSHEA AUTHORIZES FDA TO ESTABLISH DIETARY SUPPLEMENT GMPs, NOT DIETARY INGREDIENT GMPs

The specific language of the Dietary Supplement Health and Education Act says that the Secretary (or by delegation FDA) "may by regulation prescribe good manufacturing practices for dietary supplements." The language in this section of DSHEA does not include any reference to dietary ingredients. Accordingly, CRN questions whether FDA has authority to establish new GMPs for dietary ingredients, as opposed to finished dietary supplement products.

NEED TO DEFINE "MANUFACTURER"

It is clear that a company that formulates and produces finished dietary supplement products is a "manufacturer" of such products. However, it is not entirely clear from the text of the regulation what other types of companies may also be considered "manufacturers" for purposes of the rule. For example, some companies may not actually manufacture specific products but may purchase the bulk tablets or capsules from another company and then package or label the finished products. The infant formula proposed GMPs provide a definition of "manufacturer" that may be useful in defining the types of companies that will be covered. Proposed 21 CFR 106.3(j) would define an infant formula manufacturer as follows:

> "Manufacturer means a person who prepares, reconstitutes, or otherwise changes the physical or chemical characteristics of an infant formula or packages or labels the product in a container for distribution."

The FDA preamble to the infant formula proposed GMP explains at 62 FR 36156: "In the past there has been some confusion about who is and who is not a manufacturer of infant formula. This definition makes clear that a manufacturer is not only a person who combines raw ingredients together to produce an infant formula but also is a person who reconstitutes or otherwise changes the physical or chemical characteristics of an infant formula or who packages or labels the product in a container for distribution." (emphasis added)

Adoption of a specific definition such as this would eliminate confusion over the responsibilities of product handlers such as contract packagers, repackers and relabelers. For dietary supplement GMPs, we would suggest a definition such as the following:

> "Manufacturer means a person who formulates or changes the composition or physical characteristics of a dietary supplement or who packages or labels the product in a container for distribution."

CRN agrees with FDA that foreign manufacturers should be subject to the same requirements as domestic manufacturers, and that importers of foreign products share the responsibility for assuring that imports of dietary supplements are accurately labeled and have the appropriate identity, purity, quality, strength and composition they are represented to have. FDA discusses this issue in the preamble to the proposed rule at 68 FR 12216, saying: "We recognize that the safety of dietary supplements cannot be adequately ensured if the imports are not subject to the same controls as domestic products. In addition, we believe that the importer who distributes a foreign product should share the responsibility with the foreign manufacture for safety. More often than not, it is a U.S. importer, rather than the foreign manufacturer, who actually distributes imported dietary supplements for sale in the United States."

LIMITED RESPONSIBILITIES OF THOSE WHO "HOLD" DIETARY SUPPLEMENTS

There are many types of companies or individuals in the supply chain who may "hold" a dietary supplement after final production, packaging and labeling is complete, as the product makes its way to the retail or consumer level. They may be described as brokers, distributors, or wholesalers. They would typically be receiving the finished product from manufacturers who are subject to this regulation, and that manufacturer would bear the responsibility for the content for the product and for its packaging and labeling.

As CRN reads the proposed rule, those who receive and distribute finished dietary supplements in the final packaged form would be subject only to part 111.95 of the regulation, which says: "Distribution of dietary supplements must be under conditions that will protect the dietary supplements against contamination and deterioration." CRN believes this is the appropriate extent of responsibility that should apply to those whose sole function in the supply chain is to "hold" dietary supplements for distribution.

The agency states that even these requirements for those who "hold" dietary supplements do not extend to retail establishments. FDA indicates at 68 FR 12214 that it will defer to State and local governments regarding any requirements that may be applicable to retailers. CRN agrees that this is an appropriate determination and that retailers should not be covered by any of the provisions of the GMP rule for dietary supplements. As we have noted in comments submitted on various aspects of the FDA regulations implementing the Bioterrorism Act, independent distributors of direct selling companies should be included in the definition of "retailers" and thus excluded from coverage by the rule.

CONCLUSION AND RECOMMENDATIONS

CRN believes careful consideration needs to be given to the purpose of the rule and to what can realistically be expected of new GMPs, over and above the protections already provided by existing food GMPs and other FDA policies and authorities. CRN and its member companies support enhanced dietary supplement GMPs, but we do not believe they are essential as a prerequisite to FDA action against misbranded or adulterated products, and we do not believe they will reduce recalls to zero, as FDA's economic analysis predicts.

CRN also recommends that FDA limit the applicability of any new GMP rule to finished product manufacturers, who will not only be able to control their own processes but who also have the ability to control the quality of the ingredients they purchase for use in dietary supplements and to evaluate the reliability of the firms that supply dietary ingredients. We also believe applicability to "dietary supplements" as opposed to "dietary ingredients" is the scope permitted by the language of DSHEA.

Because of the importance of issues such as these, we urge the agency to hold a public hearing or perhaps a series of public workshops on key aspects of the proposed rule, in order to help craft an appropriate and workable final rule.

Sincerely,

Annette Dickinson, Ph.D.
President

Attachment A: Council for Responsible Nutrition Manufacturer Members

Manufacturers of Finished Products	
Member Company	**Products**
Access Business Group/Nutrilite	Nutrilite®, Trim Advantage®
Accucaps Industries Limited	Private Label Manufacturer of Vitamins and Minerals, Oils, Specialty Supplements, and Herbals
Arkopharma, LLC	Sokoja®, Azinc®, Potensium®, Arkocaps®, Memoboost®, Turbodiet®
B&C Nutritional Products, Inc.	Private Label Manufacturer of Vitamins and Minerals, Specialty Supplements, and Herbals
Bayer HealthCare LLC	One-A-Day®, Flintstones®
Bio San Laboratories Inc.	Private Label Manufacturer of Vitamins and Minerals, MegaFood®, DailyFoods®, Essentials®
Enzo Nutraceuticals	Enzogenol®
Experimental and Applied Sciences, Inc. (EAS)	AdvantEdge®, BetaGen®, CytoVol®, EcdyMax®, Lean DynamX®, Mass Factor®, Muscle Drive®, Myoplex®, Precision Protein®, Simply Creatine®, SimplyProtein®, Synthe Vol®, Thermo DynamX®, ZMA®
GNC Incorporated	GNC ProPerformance®, Preventive Nutrition®, Herb Plus®, GNC Natural Brand®, Total Lean®, Mega Men®, Womens Ultra Mega®, Herbal Plus®
GNLD International	Carotenoid Complex®, GR^2 Control®
Herbalife International	Herbalife, Thermo Complete®, Thermojetics®,
Jamieson Laboratories Ltd.	Mega Cal®, Vita Vim®
Kemin Consumer Care, L.L.C.	Satise®
Mannatech, Inc.	Glycentials®, Ambrotose®, Phyt•Aloe®, CardioBALANCE®, ImmunoStart®, Glyco•Bears®, Phyto•Bears®, EM•Pact®, GlycoLEAN®, Plus®, Ambrostart®, Sport®, Emprizone®
Mary Kay, Inc.	Daily Benefits for Women®, Daily Benefits for Men®
Natural Alternatives International Inc.	Pathway to Healing®, Jennifer O'Neill Essentials®, Private Label Manufacturer
NBTY, Inc.	Nature's Bounty®, Vitamin World®, Puritan's Pride®, Holland & Barrett®, Nutrition Headquarters®, American Health® and Nutrition Warehouse®, Private Label Manufacturer
Nu Skin International Inc./Pharmanex LLC	LifePAK®, Phamanex Solutions®, Pharmanex Bodydesign®

Attachment A: Council for Responsible Nutrition Manufacturer Members

Manufacturers of Finished Products	
Member Company	**Products**
Nutraceutical Corporation	Solaray®, KAL®, NaturalMax®, VegLife®, Premier One®, Sunny Green®, Natural Sport®, ActiPet®, Action Labs®, Miztique®, Ultimate Nutrition® and Thompson®, Private Label Manufacturer
Nutramax Laboratories, Inc.	Senior Moment®, Cosamin® DS
Perrigo Company	Private Label Manufacturer and Branded Contract Manufacturer
Pharmaton Natural Health Products	Ginsana®, Ginkoba®, Flexium®, Kyolic®, Venastat®, Supplifem®, Prostatonin®
Pharmavite LLC	Nature Made®, Nature's Resource®, Private Label Manufacturer, Olay™ Vitamins
Proper Nutrition, Inc.	SeaCure®, SeaVive®
Pulse Nutrition	Pulse® Water + Nutrients (Vitamins and Minerals)
Rainbow Light Nutritional Systems	Active Health®, Complete Nutritional System®, Complete Prenatal System®, Nutristars®, Performance Energy®, Women's Answer® and other Single Nutrient, Herbal, and Specialty Supplements
Rexall Sundown, Inc. (now part of NBTY, Inc.)	Sundown®, Osteo Bi-Flex®, Pokemon®, Private Label Manufacturer
Ross Products	Glucerna®, Ensure®, Infant Formula
Shaklee Corporation	CorEnergy®, Mood-Lift®, Vita-Lea®, CoQHeart®, Immunity Formula I®, Herb-Lax®, Optiflora®, EZ-Gest®, Shaklee Fitness®, Performance®, Physique®, Liver DTX®, Fiber Plan®
Sigma Tau Health Sciences	ProXeed®, Megasol®, Megasol Q10®, Phototrop®, Avant®, Biorecord Plus®
Tom's of Maine	Botanicals
Vitamin Shoppe Industries, Inc.	Vitamins and Minerals, Specialty Supplements, and Botanicals distributed under the Vitamin Shoppe® name
VitaTech International, Inc.	Private Label Manufacturer
Warner Lambert Consumer Group of Pfizer	Finished Product Manufacturer
Weider Nutrition International, Inc.	Schiff®, Schiff® Move Free®, Tiger's Milk®, Weider®, Fi Bar®
Wyeth	Centrum®, Centrum Silver®, Centrum Performance®, Centrum Kids®, Caltrate®

Attachment A: Council for Responsible Nutrition Manufacturer Members

Suppliers	
Member Company	**Products/Ingredients/Services**
Access Business Group - Trout Lake Farms	Grower and Processor of Botanical Ingredients, Ocean Essentials®
Albion Laboratories, Inc.	Bulk Minerals
American Laboratories, Inc.	Processor and Supplier of Enzymes, Peptones, Liver Products and Glandulars
Archer Daniels Midland Company	Vitamin E, Soy Isoflavones, Lecithin
B&D Nutritional Ingredients, Inc.	Supplier of Vitamin E, Lecithin, Lutein, Phytosterols, Grape Seed
BASF Corporation	Vitamins A, C, D & E, B Vitamins, Carotenoids, Excipients, Clarifying Agents, Aroma Chemicals
Biotron Laboratories, Inc.	Supplier of Various Mineral Amino Acid Chelates
Capsugel	Encapsulated Products and Capsules
Cargill Health & Food Technologies	Soy Isoflavones, Chondroitin, Vitamin E
Cognis Nutrition & Health	Natural Vitamin E, Tonalin® CLA, Vegapure®, Sterols/Sterol Esters, Lutein Esters, Natural Mixed Carotenoids, ALA, Botanicals, Emulsifiers, Food Technology Ingredients
Colorcon	Excipients, Colors, Coating Systems, Printing Inks
Daiichi Fine Chemicals, Inc.	B Vitamins, Vitamin D, Carotenoids
E.T. Horn Company	Bulk Ingredients Including: Calcium Carbonate, Glucosamine, Cellulose
Generichem Corporation	Bulk Supplier of Minerals
Indena USA, Inc.	Botanicals Supplier
Kaneka America Corporation	Supplier of Co-Enzyme Q10
Kemin Foods, L.C.	Lutein - FloraGLO®, Antioxidants
Linnea, Inc.	Botanicals Supplier
Loders-Croklaan	Supplier of Oils Including: Clarinol®, Marinol®, Membranol®, Safflorin®
Lonza, Inc.	Supplier of L-Carnitine and B Vitamins
Mingtai Chemical, LLC	Microcrystalline Cellulose, Comprecal®
Nashai Biotech LLC	Supplier of Ingredients Including TeaFlavin®
Nutrinova	DHActive®, Fiber - Caromax®, Nutrinova® Sorbates
Nutrition 21, Inc.	Chromax® Chromium Picolinate, Zinmax® Zinc Picolinate, Selenomax® High Selenium Yeast, Selenopure® l-selenomethionine, Zenergen™ Chromium Picolinate plus CLA
Ocean Nutrition Canada Ltd.	Omega-3 Fatty Acids
Omya, Inc.	Supplier of Calcium Carbonate

Attachment A: Council for Responsible Nutrition Manufacturer Members

Suppliers	
Member Company	**Products/Ingredients/Services**
Polyphenolics	MegaNatural® Gold Grape Seed Extract, MegaNatural® Grape Skin Extracts, MegaNatural® Rubired Grape Juice Extract, MegaNatural® Red Wine Extract
Pronova Biocare, a.s.	Omega-3 Fatty Acids - EPAX®, Triomega®, Pikasol®, Omacor®
Rhodia, Inc.	Antioxidants - Embanox®, Calcium Phosphate, Probiotics
Roche Vitamins, Inc.	Vitamins A, C, D, & E, B Vitamins, Carotenoids, Omega-3 Fatty Acids
Seven Seas Limited	Fish Oils, Multivitamins, Evening Primrose Oil, Herbals, ActionPlan50+®

Attachment B

Class I and Class II Recalls for
Dietary Supplements, Foods and Drugs
1990-1999

	Class I Recalls			Class II Recalls		
Reason for Recall	**DS**	**Food**	**Drug**	**DS**	**Food**	**Drug**
Undeclared Ingredient/Color	1	229	1	5	381	6
Unapproved Ingredient/Color	--	--	--	1	39	12
Contaminant –Microorg.	3	310	15	2	34	27
Contaminant – Digitalis	13	--	--	--	--	--
Contaminant – Lead	--	2	--	11	43	--
Contaminant – Mercury	--	--	--	--	4	4
Contaminant – Pesticide	--	--	--	--	16	--
Contaminant – Misc.	1	33	2	--	193	65
Super-Potent	2	1	--	3	6	17
Sub-Potent	--	--	8	1	2	123
L-Tryptophan	5	--	--	--	--	--
Mispackaged/Mislabeled	--	10	14	4	44	181
Processing/GMP Violation	--	4	10	--	23	228
Physical Characteristics	--	2	--	--	15	159
Regulatory Issue	--	1	1	--	1	42
Defective Packaging	--	--	--	--	8	4
Toxins/Poisons	--	--	--	--	14	2
Illness Related	--	--	--	--	58	2
Histamine	--	--	--	--	14	--
Unapproved Drug/Claim	--	--	11	--	2	22
Non-Sterile	--	--	4	--	--	33
Other/Misc.	--	--	--	--	--	4
TOTAL RECALLS	**25**	**592**	**66**	**27**	**901**	**931**

Council for Responsible Nutrition

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August 11, 2003

Dockets Management Branch (HFA 305)
Food and Drug Administration
5630 Fishers Lane, Room 1061
Rockville, MD 20852

RE: DOCKET NO. 96N-0417, GOOD MANUFACTURING PRACTICES FOR DIETARY SUPPLEMENTS

TOPIC: PROCESS CONTROL

This is the third in a series of comments submitted by the Council for Responsible Nutrition regarding the above-mentioned proposed rule.

This comment will address what we believe to be the critical core issue in considering the framework of Good Manufacturing Practices -- the essentiality of establishing a quality assurance system of process controls that serve the purpose of preventing errors throughout the processing system, from the selection of ingredient suppliers and the receipt of bulk materials through the entire processing operation. It is axiomatic in the quality assurance literature that quality cannot be "tested into" a product but must be "built into" the product from beginning to end. We believe the proposed rule is overly focused on end-product testing and fails to fully incorporate the elements of a well-controlled system. Such a system, once established, is a more reliable guarantee of quality than exhaustive finished-product testing.

This comment also includes a statement of concerns about the proposed rule from Carl Reynolds, a GMP expert with 36 years of experience at FDA. He is now a Senior Consultant to AAC Consulting Group, where he conducts GMP training seminars, advises companies on GMP issues, and performs audits of GMP procedures. CRN retained Mr. Reynolds to assist our members in analyzing the proposed rule and to provide guidance to us in preparing our response. We refer to his statement in the course of this comment and include its full text in Attachment C.

This comment covers the following specific topics:

On this same date, CRN is submitting separate comments on the purpose and scope of the rule and on legal aspects of the proposal. In addition, we will submit a separate comment summarizing our section-by-section recommendations. At a later date, but before September 9, we will submit comments on the economic impact of the proposed rule. CRN has requested and been granted this additional time for submission of economic data based on new information we have just obtained pursuant to a FOIA request for underlying data not previously included in the administrative record, relating to FDA's assumptions and calculations on the estimated economic impact of the rule. The first comment in this series (July 8, 2003) provided a four-way comparison of the proposed GMP with current food GMPs, the industry draft published as the ANPR in 1997, and current drug GMPs.

PROCESS CONTROL SYSTEMS CRITICAL TO QUALITY ASSURANCE

CRN member companies currently include 35 manufacturers of finished dietary supplement products and 31 manufacturers and suppliers of bulk dietary ingredients or other components of dietary supplements, as well as a number of associate members that provide services to the industry. **Attachment A is a list of our manufacturer and supplier members, together with examples of the types and brands of products they**

market. The list is designed in such a way that readers of the electronic version can click on a company name and access its website. CRN's membership includes some very large companies that manufacture the leading U.S. brands of dietary supplement products, that manufacture the store brands marketed by large food and drug chains, and that manufacture and supply key ingredients used both in conventional foods and in dietary supplements. Our membership also includes a number of companies that are "small businesses" as defined by the Small Business Administration but that also have reputations as leading quality manufacturers of numerous products or ingredients.

CRN member companies account for a substantial fraction of the dietary supplement market in the U.S. in terms of sales volume. Using sales data from *Nutrition Business Journal*, we calculate that nine of the top fifteen manufacturers and marketers of dietary supplements in the U.S. are CRN members. These companies, plus a number of smaller CRN member manufacturers, account for about 40% of the wholesale sales volume of dietary supplements marketed through supermarkets, natural food stores, drug stores, and discount department stores. Six of the top twenty companies in direct sales (called multilevel marketing by *NBJ*) are CRN member companies, accounting for 26% of the sales volume marketed through that channel. Eight of the top ten vitamin ingredient suppliers are CRN member companies, providing 71% of the sales volume for commercial vitamins used in dietary supplements annually. Another 23 supplier members of CRN provide the industry with other key dietary ingredients including calcium and other minerals, lutein and other carotenoids, botanicals, omega-3 fatty acids, and specialty ingredients such as glucosamine and chondroitin sulfate.

The draft GMPs submitted to FDA by CRN and other associations in 1995 and published in the ANPR in 1997 were modeled after food GMPs and current "best practices" observed by leading large and small companies in the industry. Some of these "best practices" incorporated some elements of current drug GMP regulations. The industry draft GMPs were based on modern concepts of quality assurance and were heavily process-oriented, requiring extensive written procedures for key processing operations in order to ensure uniform practices and to provide a strong basis for employee training and supervision. CRN and its members are fully supportive of the need for the application of an appropriate process control system for the manufacturing of dietary supplements.

The Dietary Supplement Health and Education Act (DSHEA) authorized FDA to establish dietary supplement GMPs "modeled after food GMP regulations." **CRN and its members do not believe the current proposal is sufficiently modeled after food GMPs, and in addition we are concerned that it is not sufficiently based on sound quality assurance theory and practice.**

CRN believes that FDA's proposed exhaustive finished-product testing provisions are not appropriate, are duplicative and unnecessary in the context of a rigorous process control system, and would be excessively costly to manufacturers. This is the single greatest point of discrepancy between the industry draft GMPs and the agency's proposed GMPs. The industry draft is heavily focused on defining and regulating the whole production process, while the agency's proposal covers some aspects of the process but is more

heavily focused on finished-product testing. One CRN member representative who is a recognized expert in dietary supplement manufacturing and quality assurance commented that FDA's proposal would "set us back 20 years" by requiring resources to be diverted to excessive testing at the endstage of production rather than being appropriately utilized to enhance overall process control based on modern approaches to quality assurance.

An appropriate and rigorous process control system would provide the following benefits:

1. Assure the identity, purity, quality, strength and composition of the dietary supplement.
2. Provide consistency in training, education and supervision of employees.
3. Provide consistency from batch to batch.
4. Define control points requiring monitoring.
5. Incorporate written standards and specifications for all parts of the process.
6. Allow tracing of deviations and facilitate corrective actions.
7. Permit verification of reliability of processes and systems.
8. Justify reliance on sampling and testing of indicator nutrients to verify output.

FDA recognizes the importance of process control, but does not make process control the focus of the proposed rule. At 68 FR 12194-5, the agency states that "using a production and inprocess control system covering all aspects of processing is necessary to insure that the dietary ingredient or dietary supplement is manufactured in an manner that will prevent adulteration." Also, FDA recognizes that "a production and inprocess control system is necessary to provide consistency in producing different batches of dietary ingredients and dietary supplements and to facilitate preparing each batch." However, FDA does not recognize that the existence of an appropriate process control system justifies reliance on sampling the finished product as a test of the system, but rather proposes also to require exhaustive finished product testing.

CRN urges FDA to recognize that a rigorous system of process controls can and should reduce the need for exhaustive testing of the finished product. The elements of a rigorous process control system are outlined in **Attachment B**. Such a system would include a strong supplier qualification program, including verification of the supplier's reliability and test results, supported by **identity testing of every incoming ingredient** by the finished product manufacturer. In addition, the system would require extensive in-process controls including master and batch records, written specifications, verification of ingredient additions, calculated yield, and data demonstrating that the process consistently delivers expected results. Criteria relevant to the finished product would include written specifications and representative testing of chemical, physical, and microbiological parameters.

CRN urges that the proposed rule be modified to recognize that an effective system of process controls (as exemplified by the outline in **Attachment B**) is required and that such a systematic approach to process control justifies a parametric approach to finished-product testing, in place of the exhaustive testing scheme proposed by the agency.

ESSENTIALITY OF WRITTEN PROCEDURES

FDA's proposal does not include any requirements for written procedures for key elements of the processing system, except in the sole area of calibration. The stated reason for the agency's failure to require written procedures in the proposed rule is to contain costs. However, CRN and its member companies do not believe written procedures can be viewed merely as a cost and a recordkeeping burden. Rather, written procedures are essential to the development and maintenance of a well-controlled production process. Written procedures are necessary for the definition, operation and documentation of a process control system, without which uniformity of operations cannot be assured and adequate training and supervision cannot be undertaken. GMP expert Carl Reynolds, whose separate statement is included with these comments in **Attachment C**, shares this view and refers to written procedures or SOPs as "one of the hallmarks or cornerstones of good manufacturing practices."

In the preamble to the proposed rule at 68 FR 12170, FDA says: "We are proposing requirements for documenting certain operations and processes while not requiring written procedures to remove underlying costs for establishing and updating such written procedures while preserving the records necessary to permit trace back. When manufacturers develop and follow written procedures such procedures help to ensure that manufacturers produce a consistent dietary ingredient or dietary supplement that is of a predictable quality and that is not adulterated. Following written procedures and documenting compliance with those procedures will ensure regular performance of a firm's established program and procedures and will provide additional assurance of effective communication from the firm's management to the line personnel."

A requirement for written procedures was a key element of the industry draft published in the ANPR, and is also prominent in drug GMPs and in the proposed infant formula GMPs. Written procedures are important in the control of dietary supplement production processes for the same reasons they are critical to the control of procedures used in manufacturing formulated nutritional products such as infant formula. CRN members have identified the following areas as ones in which written procedures should be required:

- Cleaning and maintaining equipment and utensils used in the manufacture of dietary products.
- The receipt, identification, examination, handling, sampling, testing and approval or rejection of raw materials.
- Appropriate tests and/or examinations to be conducted that may be necessary to assure the purity, composition and quality of the finished product, and to establish release specifications.
- The method for reprocessing batches or operational start-up materials that do not conform to finished goods standards or specifications.
- Control procedures employed for the receipt, storage, handling, sampling, examination, and/or testing that may be necessary to assure the identity of

labeling and the appropriate identity, cleanliness and quality characteristics of packaging materials for dietary products.

- Procedures to assure that correct labels, labeling, and packaging materials are issued and used.
- Handling of all written and oral complaints.

As to the issue of the costs involved in preparing and following written procedures, CRN and its member companies believe that requiring written procedures would be more effective and less costly for achieving the goals of the regulation than the exhaustive testing program proposed by FDA. Also, FDA's Survey of Manufacturing Practices in the Dietary Supplement Industry indicates that a very high proportion of manufacturers are already utilizing Standard Operating Procedures (written procedures). Overall, 65% of all respondents indicated they were currently following a published GMP model, but 80% reported that they were using Standard Operating Procedures for key procedures. Some specific responses by size of company are shown in **Table A**, below:

Table A: Percent of Companies that Use Written Procedures (SOPs), As Reported in FDA's Survey of Manufacturing Practices

	Very Small	Small	Large
Have written personnel procedures (4 procedures surveyed)	54-70%	71-84%	93-100%
Have written equipment procedures	61%	81%	100%
Have written QC/lab procedures (2 procedures surveyed)	64-75%	81-86%	94-100%
Have written production/process control (2 procedures surveyed)	71-88%	91-93%	94-95%
Have written consumer complaint procedure	55%	78%	95%

Due to the relatively high current usage of written procedures, CRN does not believe a requirement for written procedures would be a large additional burden, even for small and very small manufacturers. As written procedures tend to be fixed and less expensive to maintain than to develop, they ultimately would be less of a burden than the proposed exhaustive testing program, which is a continuing cost that does not decline -- but rather increases -- with time and with volume of production.

ELEMENTS OF APPROPRIATE WRITTEN PROCEDURES (SOPs)

Written procedures are also commonly referred to as Standard Operating Procedures (SOPs). Written procedures or SOPs should be clear and concise and define policies, procedures or instructions for operating processes, practices and equipment.

SOPs should be written appropriately for the target audience and should generally follow a standardized format. General information should include:

- Company identification
- Title that reflects the activities to be performed
- Identification or control number with a revision level code
- Effective date
- The number of pages in the procedure (e.g., 1 of 4, 2 of 4, etc.)
- Approval date and signature(s)

Typically there is a final approval date and an effective date. The effective date may be later in order to allow for training employees on the new or revised procedures.

The ultimate goals of an SOP are to consistently achieve the desired quality output and to reduce or eliminate variation in day to day operations. To achieve this, SOPs should contain enough detail to allow different personnel on different days to perform the necessary operations consistently. The task description for each procedure should cover appropriate details, unless these are covered in other referenced documents such as master batch records, for example. The SOP should cover the following topics, as appropriate:

- Purpose and scope
- References to linked or related procedures or forms
- Definitions of technical terms and acronyms
- List of equipment, materials, and supplies needed in performing the task
- Who has the responsibility for performing each task
- What activity or task is to be performed
- When and where the task is to be performed
- Concise step by step instructions for performing the task
- The expected results from performing the task
- What data to collect and how to analyze, file, and/or report the information

Background information will often help employees better understand their assignment and remember how to perform it. It is especially important for newer employees to understand the reason for the procedure and why it must be performed in a certain, prescribed manner.

When a manufacturer makes permanent changes or modifications to specifications, procedures or documentation, the changes should be reviewed, justified, documented, approved and implemented in a defined manner. Change control procedures define what is and what isn't covered by the procedure and how proposed changes will be identified or recommended, processed, reviewed and approved.

While the proposed rule assigns final approval responsibility to the quality control unit, other specialty groups may also be assigned or required to review and approve proposed changes or procedures. These may include personnel with special expertise including engineers, scientists, or computer experts, for example.

The quality control unit or function is also responsible for maintaining the master copies of all current and approved SOPs, for distributing copies of approved written procedures to relevant personnel, and for collecting and destroying outdated SOPs (except designated historical SOP files).

RIGOROUS PROCESS CONTROL IS EFFECTIVE IN ENSURING QUALITY AND CAN JUSTIFY A REDUCED TESTING BURDEN

CRN fully agrees with FDA's assertion at 68 FR 12176 that the end result of improved GMPs throughout the industry will be to "provide consumers with greater confidence that dietary supplements contain the dietary ingredients that they are supposed to contain and that these dietary ingredients were evaluated for their identity, purity, quality, strength, or composition."

However, CRN believes the agency's proposal for an extensive and exhaustive level of testing of finished products would be much more costly in terms of time and resources but would be less effective than rigorous process control in fulfilling the goal of good manufacturing practices. The maxim of quality assurance theory and practice is that **"you can't test in quality."** Rather, quality must be built into the product through a rigorous process control system. In an appropriate process control system, testing is a means to monitor the functioning of the control system, relying on process monitoring and parametric testing as indicators of the adequacy of the system. Reliance on end-product testing alone can identify failures of the product or the system, but does not facilitate tracing the cause of the failure in order to promptly correct any problem that may exist.

Comments prepared by GMP expert Carl Reynolds (**Attachment C**) emphasize this same concern. He says, "One familiar with the concepts of GMPs recognizes that end process controls are not adequate because they cannot build quality into a product."

Of course, any rigorous process control system will include appropriate testing of incoming materials for identity, control by monitoring or testing of in-process materials and processes, and sampling of the final product. Complete testing of every ingredient in every batch is not necessary to maintain sufficient control over the process to accomplish the goals of the program. The agency itself has stated at 68 FR 12172 that the focus of the rule is on "ensuring that the manufacturer knows what it is putting in its products and is manufacturing, packaging and holding the product in a manner that will not adulterate or misbrand the product." This can be accomplished through careful attention to the quality of bulk ingredients and thorough control over the process, without testing every ingredient in every batch of finished product.

The proposed rule requires testing of all dietary ingredients and relevant specifications in each batch of the finished product. The testing must cover the "identity, purity, quality, strength and composition" of the product. Other specifications are to be established by the manufacturer, based on knowledge of the ingredient or product and its potential

contaminants. If testing of the finished product is not possible because of methodology issues, then testing is required of the bulk ingredients and of in-process materials. The cost estimates for the rule assume that only one or the other of these tests are required -- that is, testing at the end or testing at the beginning and the middle.

Some of FDA's assumptions in suggesting these alternative testing schemes are faulty. For example, if a product cannot be tested at the final product stage for technical reasons or due to "complex finished product matrices that would make such testing impracticable," then it also cannot be tested at the final blending stage in the process. The composition and nature of the product at the final blending stage is virtually the same as the nature of the product when it is finished, except for compression into a tablet or encapsulation in a softgel or hard capsule, and the methodological issues are the same at both points.

Testing at the end point or finished product stage is extremely costly and wasteful if materials are out of specification, because the full costs of materials, labor and overhead have already been applied to the product at that stage. FDA recognizes this fact at 68 FR 12198: "If you are able to perform testing on each finished batch of dietary ingredients or dietary supplements to confirm that specifications are met for the identity, purity, quality, strength and composition intended, then we would recommend, but would not require, that you also test materials received for these same specifications to ensure that they are the right ingredients and so that you do not end up having to destroy an entire batch of finished product after using an erroneous ingredient that could have otherwise been identified earlier before being added to a batch." CRN's members believe relying on finished product testing as a key component of quality assurance is not representative of good manufacturing practices.

The proposed rule indicates that testing is also required at key control points in the process. At a minimum these control points must include the receipt of bulk materials and a check on in-process quality. As FDA states at 68 FR 12197, "Proposed 111.35(e) would require that you establish a specification for any point, step, or stage in the manufacturing process where control is necessary to prevent adulteration...These specifications are regulatory specifications and you would be required to perform testing or examination to confirm such regulatory specifications are met.... In addition, proposed 111.35(e) identifies certain points, steps, or stages where a regulatory specification is required. Regulatory specifications are required for materials that you receive, at the inprocess stage, and that you manufacture, e.g. at the finished product stage. Specifically, we are proposing to require that you establish specifications at these control points for the identity, purity, quality, strength and composition of the components (upon receipt only) and for dietary ingredients or dietary supplements (at all of these control points)."

Given that an appropriate process control system will test all incoming ingredients for identity; that economic necessity requires that testing be in place to identify deviations as early in the process as possible; and that the proposed regulations require testing (or other monitoring if it can show the identity, purity, quality, strength and composition of the

material) at multiple specified points; then the proposed rule *de facto* requires testing at all stages – incoming, inprocess and finished – unless technically not feasible at the end stage. This level of testing is unnecessary, duplicative, and prohibitively expensive.

NEED TO DEFINE CRITERIA FOR ACCEPTABILITY OF VENDOR CERTIFICATES OF ANALYSIS FOR INGREDIENTS

In the preamble to the proposed GMPs for dietary supplements, FDA indicates that manufacturers would not be allowed to accept an ingredient or component supplier's Certificate of Analysis (C of A) as evidence that the content of a shipment is in compliance with the specifications and labeling of the material. **CRN and its members take strong exception to this position, which is contrary to existing provisions in specific food GMPs and even in drug GMP regulations.**

The general food GMPs in 21 CFR 110 specifically allow the use of Certificates of Analysis to verify that ingredients meet requirements for safety, for allowable microorganism content, and for non-contamination with toxins, pests and extraneous materials. Part 110.35 specifies that the safety and adequacy of cleaning compounds "may be verified by any effective means including purchase of these substances under a supplier's guarantee or certification." Part 110.80 indicates that the microbiological quality of raw materials or ingredients, as well as their compliance with tolerances for natural toxins, extraneous material, or other contaminants, may be "verified by any effective means including purchase of these substances under a supplier's guarantee or certification."

GMPs for low-acid canned foods in 21 CFR 113.81 specifically allow the use of Certificates of Analysis to certify that ingredients meet requirements for allowable microorganism content.

Even the proposed Infant Formula GMPs, which apply to nutrient-critical products for a vulnerable population, allow the use of supplier Certificates of Analysis under appropriate conditions. 21 CFR 106.20 provides that, in general, "no analysis before use in manufacturing is needed for ingredients that are generally stable in shipping and storage, and that either are received under a supplier's guarantee or certification that the mixture has been analyzed as to nutrient composition or are labeled as having nutrient compositions complying with specifications in the U.S. Pharmacopoeia, the National Formulary, the Food Chemicals Codex, or other similar recognized standards."

Drug GMP regulations also permit reliance on certificates of analysis. 21 CFR Part 211.84 requires that each component of a drug product be tested for conformity with specifications for purity, strength, and quality, but provides that in lieu of testing by the manufacturer of the finished product, "a report of analysis may be accepted from the supplier of a component, provided that at least one specific identity test is conducted on such component by the manufacturer and provided that the manufacturer establishes the reliability of the supplier's analyses through appropriate validation of the supplier's test results at appropriate intervals."

As CRN has discussed above in other sections of these comments, manufacturers of dietary supplements should have strict process control systems in place, including rigorous provisions relating to the receipt of all ingredients and components. Manufacturers should conduct an identity test (using a scientifically valid method) on incoming materials to verify that the material is correctly labeled. Information regarding other specifications could reasonably be based on a Certificate of Analysis from a qualified vendor, provided the certificate is based on actual scientifically valid testing by the vendor of the particular lot or batch of material in the shipment, which should be identified with a lot or batch tracking number. An appropriate test-based Certificate of Analysis needs to be distinguished from a more general Certificate of Compliance or a Continuing Guarantee. These two latter documents may not be based on actual testing of a specific shipment of materials.

Responsible manufacturers of dietary supplements will rely on a relatively extensive "vendor qualification program" for key material vendors. Such programs are essential to permit the manufacturer to assess the reliability of the vendor and accordingly determine the amount of incoming material testing that may be required to provide the necessary level of confidence that the material will meet specifications.

Vendor qualification programs may include plant visits and inspections, GMP audits or process reviews, verification of laboratory test results against certificates of analysis, and 100% inspection and testing of incoming materials for a specified period of time while reliability is being assessed. By extending process control mechanisms back into the supplier environment, the manufacturer can make appropriate use of the expertise of the vendor and eliminate the need for extensive and duplicative testing of received materials. In a properly defined supplier/manufacturer relationship, the supplier's testing should be considered to be as reliable as testing performed by any other qualified laboratory.

Manufacturers who have process control systems and written specifications and procedures in place will be able to identify the conditions under which certificates of analysis can be considered reliable, and the final rule should recognize the appropriateness of such reliance.

APPLICABILITY OF THE RULE TO FOREIGN FIRMS

FDA indicates in the preamble to the proposed rule that its provisions are applicable to foreign as well as domestic manufacturers. CRN's member companies are concerned that there be teeth in this requirement, to ensure a level playing field for U.S. firms and foreign competitors. It would not be appropriate for foreign firms to be permitted a "free ride" while U.S. firms are incurring the additional costs of compliance with any final GMP rule. Failure to require compliance by foreign firms would also expose U.S. consumers to risk, since the GMPs are intended to prevent the manufacture or distribution of adulterated products.

Third-party certification programs have been initiated by the U.S. Pharmaceopeia and by NSF International, based on the auditing of GMP practices and the testing of specific products. These programs may have applicability as a means of certifying compliance of foreign firms with required GMPs, just as they currently certify GMP compliance of U.S. firms that choose to participate in their respective programs.

Even if dietary ingredient manufacturers are not ultimately covered by the GMP rule, as CRN is proposing, responsible finished product manufacturers will seek to procure materials from ingredient suppliers that are in compliance with sound GMPs. Large firms may verify the reliability of their suppliers by conducting their own audits of the ingredient manufacturers, foreign as well as domestic. Third-party certification would provide another option for identifying reliable ingredient manufacturers.

GMP expert Carl Reynolds also emphasizes the importance of securing compliance by foreign firms (see separate statement in **Attachment C**). He calls attention to the difficulties of ensuring compliance of foreign firms and makes note of special requirements for imports set forth in the seafood HACCP rule (21 CFR part 123) in this regard. These include provisions encouraging audits or third party certifications as tools for evaluating whether foreign firms are in compliance.

COST OF FDA'S PROPOSED TESTING REQUIREMENTS

FDA estimates that the total increased cost of the proposed GMP requirements for large manufacturers would be $83,000 in the first year and $47,000 in subsequent years, and this includes the additional costs related to exhaustive testing of finished products. For small companies, FDA estimates an incremental cost of $99,000 in the first year and $61,000 in subsequent years. CRN's member companies include a number of large firms as well as many companies that qualify as "small businesses" under the criteria established by the Small Business Administration.

CRN believes the agency's cost estimates are massively understated. To take testing costs as a single example, FDA estimates that for large companies there will be an average of 309 batches per year to be tested. CRN's large members are reporting that they produce 2000 to 6000 batches of finished products per year -- or about an order of magnitude more than FDA's estimate. Since FDA's cost estimates are based on the amount of testing required per batch, the low estimate for the number of batches produced per year by large companies would lead to a drastically low estimate of testing costs. Similar issues exist with regard to the production volume of smaller companies.

FDA's basic economic analysis assumes that only finished product testing will be required. However, the language of the rule in 111.35(e) appears to require additional testing at critical control points where a specification is necessary to prevent adulteration. The preamble at 68 FR 12196-7 indicates that, at a minimum, control points should include the receiving of materials and at least one in-process step, in addition to final product testing. Thus, the actual requirements of the rule as written appear to be more in line with the "more restrictive" alternative considered in FDA's economic analysis.

CRN will be submitting separate comments on the estimated costs of the proposed rule. We have recently received some additional information from FDA regarding the agency's underlying assumptions and calculations of economic impact, and we have requested additional time to analyze these materials and utilize them in the preparation of our comments on the costs and benefits of the proposal. We have received assurance from FDA that our comments will be considered, provided they are submitted within 29 days after the official close of the comment period on August 11.

TEST METHODS AND THE COST OF METHOD DEVELOPMENT

The proposed rule requires in 111.35(h) that a "scientifically valid analytical method" be utilized in determining whether specifications are met. In the preamble, FDA cites AOAC and USP methods as examples of scientifically valid methods, but recognizes that other published methods as well as internally developed methods supported by scientific research may also be scientifically valid. CRN recommends that the term "scientifically valid" be defined in the rule and that recognition be given to methods developed by the American Herbal Pharmacopeia (AHP) in that context.

In the preamble, the agency says it is "not aware of a situation where an appropriate scientifically valid analytical method is not available," and FDA's economic analysis does not address costs of method development. However, industry members have been deeply involved in numerous efforts to develop valid methods for many ingredients, including the longstanding efforts of USP and the INA/MVP testing initiative. The NIH Office of Dietary Supplements (ODS) recently received special funding by Congress for the development of analytical methods, and AOAC is working with ODS on this project. These ongoing activities in our view are testimony to the fact that there will be an extensive need for method development into the future, and that its cost will continue to be substantial. We will providing more information on these efforts and their associated cost in our analysis of economic impacts, which we have received FDA permission to submit within 29 days following the close of this comment period.

In our separate comments on legal issues raised by the FDA proposal, CRN notes that the language of DSHEA specifies that any GMP regulations prescribed by the agency "may not impose standards for which there is no current and generally available analytical methodology." The proposed rule requires that "scientifically valid" tests be used in testing for specifications, and section 111.60 requires that these tests must be not only scientifically valid but must be "validated." Given the substantial ongoing efforts directed toward method development, we believe the agency's expectations as described in the preamble would in fact for many ingredients and products impose standards which cannot be met through current and generally available analytical methodology. In addition, CRN believes the agency goes beyond food models for GMPs in suggesting that analytical methodologies must be "validated."

The comments included from GMP expert Carl Reynolds in **Attachment C** also express these concerns, saying FDA's proposal "assumes scientifically valid analytical methodology exists when such may not be the case."

EXPIRATION DATING

The current proposed GMP regulations for dietary supplements do not require shelf life or expiration dating for dietary supplements. The proposal also does not address what type of evidence may be needed to support expiration dating voluntarily provided by the manufacturer, although FDA offers some suggestions in preamble language.

FDA has not proposed shelf life or expiration dating requirements because, the agency says, not all dietary supplement materials have a commonly accepted "active" or "marker" component. FDA believes this is particularly the case for many botanical components.

FDA also comments on the presumed difficulty of documenting the basis for an expiration date for dietary supplement products, at 68 FR 12203-12204: "The agency considered whether to propose requirements in this proposed rule for expiration dating, shelf-life dating, or best if used by dating (hereinafter referred to as expiration dating). Although we recognize that there are current and generally available methods to determine the expiration date of some dietary ingredients, for example vitamin C, we are uncertain whether there are current and generally available methods to determine the expiration dating of other dietary ingredients, especially botanical dietary ingredients. We are not proposing expiration dating at this time because we have insufficient scientific information to determine the biological activity of certain dietary ingredients used in dietary supplements, and such information would be necessary to determine an expiration date. Further, because official validated testing methods (i.e., AOAC or FDA) for dietary supplements are evolving, especially for botanical dietary ingredients, few official methods are available to assess the strength of a dietary ingredient in a dietary supplement. Nevertheless, if you use an expiration date on a product, you should have data to support that date. You should have a written testing program designed to assess the stability characteristics of the dietary supplement, and you should use the results of the stability testing to determine appropriate storage conditions and expiration dates."

As a practical matter, CRN members believe expiration dating or shelf life dating is essential to the ability to market most dietary supplements in today's business environment. Consumers expect and demand expiration dating, major retail chains will not accept dietary supplements without expiration dating, and virtually all responsible manufacturers already utilize expiration dating and have stability programs in place to support the establishment of shelf life or expiration dating.

Nutrition labeling regulations for dietary supplements in 21 CFR 101.36 require that products provide at least 100% of the level of added substances quantified in the Nutrition Facts box, throughout the shelf life of the product. In addition, the language of DSHEA declares a dietary supplement to be misbranded under Section 403 of the FD&C

Act if it "fails to have the identity and strength that the supplement is represented to have..." Thus, both FDA regulations and the law itself require that dietary supplements provide 100% of label claim. In order to define the period of time during which 100% of the label claim can be assured, it is essential for products to bear shelf life or expiration dating. Without such labeling, the manufacturer would theoretically be responsible for assuring 100% of label claim in perpetuity -- and this is not a feasible requirement.

Labeled potency may not be the only factor to be considered in establishing shelf life or expiration dating. The language of DSHEA also declares a dietary supplement to be misbranded under Section 403 of the FD&C Act if it "fails to meet the quality (including tablet or capsule disintegration), purity, or compositional specifications, based on validated assay or other appropriate methods, that the supplement is represented to meet."

All or most dietary supplements contain some quantification of dietary ingredients in the Supplement Facts box. These quantitative declarations would provide the primary basis for expiration dating. If substances are being quantified in labeling, then by definition there are tests being utilized for determining the quantities stated. Those same tests can be utilized in evaluating stability. Other product attributes relevant to shelf life dating may include disintegration performance, appearance, color, odor, taste, texture, and integrity of the dosage form (tablet, capsule, or softgel, for example).

CRN urges FDA to require shelf life or expiration dating for dietary supplements when needed to support quantitative claims made in labeling and to specify that such dating should be based on appropriate substantiation. Appropriate substantiation might include accelerated stability testing or might be based initially on the known stability profile of similar types of products manufactured by the company. Real time testing should also be undertaken to confirm the selected shelf life or expiration dating for the product.

If the product is stable under normal ambient conditions, then no special instructions are needed in labeling to support the shelf life or expiration dating. Only if special storage conditions are required would any specific label instructions be needed (e.g., "keep refrigerated").

The language of the Dietary Supplement Health and Education Act (DSHEA) suggests that expiration dating was envisioned as a feature of current industry practice and potentially as a feature of current GMP regulations. DSHEA added a new subsection 402 (g) to the FD&C Act, providing that a dietary supplement is adulterated "if it is a dietary supplement and it has been prepared, packed or held under conditions that do not meet current good manufacturing practice regulations, **including regulations requiring, when necessary, expiration date labeling...**" (emphasis added)

EMPLOYEE QUALIFICATIONS, EDUCATION AND/OR TRAINING

The general food GMPs in 21 CFR part 110 require that employees have "a background of education or experience, or a combination thereof, to provide a level of competency necessary for production of clean and safe food." (emphasis added)

The requirement in part 111.12 of the proposed dietary supplement GMPs is that employees "must have the training and experience to perform the person's duties." (emphasis added)

In the preamble to the proposed dietary supplement GMP rule, FDA disagreed with comments on the ANPR that suggested use of the word "or" in this section, saying that "the proposed rule uses the conjunction 'and' because, while some might consider experience to be a form of training, most consider experience to be knowledge that a person gains over time as he or she becomes increasingly familiar with a particular action or piece of equipment." FDA added that training is not meant to include just on-the-job training, but could also include formal instruction. FDA pointed out at 68 FR 12183: "The word 'and' includes situations where on-the-job training may be adequate and also situations where educational training may be required."

Earlier in the preamble, FDA also states at 68 FR 12183: "The extent and frequency of the training is left to the manufacturer's discretion."

CRN does not object to the use of the term "and" in the phrase "training and experience" in the proposed regulation, as long as the manufacturer's discretion in defining the required training is recognized. This is particularly important in light of the diversity of the industry, where the size of the company, the procedures utilized, the types of equipment employed, and the nature of the ingredients handled may vary widely from one firm to another, with each firm having unique requirements.

WATER QUALITY

Under the general food GMP regulations in 21 CFR part 110, the water to be used as a component of food products, for washing of foods, in processing operations and on food contact surfaces "shall be of safe and of adequate sanitary quality." No higher requirement is set forth for food products. No water standards are listed in the GMPs for low-acid canned foods in part 113 or in the GMPs for acidified foods in part 114. If this requirement is adequate to ensure the quality of the water used in most food products, then CRN believes it is also adequate to ensure the quality of the water used in dietary supplements.

Under the amended standards for bottled water (63 FR 25764-69), the proposed GMPs for infant formula (61 FR 36153-36219) and the currently proposed dietary supplement GMPs, the agency uses a new and higher standard for water based on the EPA Primary Drinking Water Regulations in 40 CFR part 141. If the agency retains the requirement based on the EPA standard, then it is important to include provisions recognizing the

acceptability of municipal sources of water and the frequency of testing required for other sources of water.

In the infant formula proposed GMPs, FDA describes an acceptable frequency for testing of water sources as follows: "Manufacturers shall conduct the tests....with sufficient frequency to ensure that the water meets the EPA's Primary Drinking Water Regulations but shall not conduct these tests less frequently than annually for chemical contaminants, every 4 years for radiological contaminants, and weekly for bacteriological contaminants."

The amendments to the bottled water regulations also specify an acceptable testing frequency as follows: "The bottled water CGMP regulations require a minimum yearly monitoring of source water and finished bottled water products for chemical contaminants for which allowable levels have been established in the bottled water quality standard."

PHYSICAL PLANT

FDA's proposed rule on GMPs would require in 111.20 that the physical plant have "floors, walls, and ceilings that are of smooth and hard surfaces that can be adequately cleaned and kept clean and in good repair." We can find no precedent in any food GMP for a provision specifying "smooth and hard surfaces" for ceilings, and indeed the only precedent we can identify is in the section of the drug GMPs relating to "aseptic processing." Regulations applicable to the aseptic processing of drugs are not an appropriate model for these dietary supplement GMPs. There are many portions of the plant in which smooth and hard ceilings are not necessary and where dropped ceilings, for example, are both suitable and commonly utilized. The cost of converting all ceilings in all parts of the plant to "smooth and hard surfaces" would be immense and unjustified. The language of the general food GMP specifies that the construction of floors, walls and ceilings must be such as to permit them to "be adequately cleaned and kept clean and kept in good repair." In CRN's view, such a provision would be the appropriate food model for the dietary supplement GMPs.

ANIMAL-DERIVED INGREDIENTS

FDA inquires whether the GMP rule should include additional provisions regarding the handling of imported animal-derived ingredients. The preamble indicates that FDA is "not aware of dietary supplement manufacturers' current procurement and handling practices" relating to animal-derived ingredients. This is a surprising assertion, since CRN and others have made significant efforts to inform FDA officials of the industry's practices in this regard. CRN and the other industry trade associations have been working actively with their member companies to ensure adherence to the requirements set forth in FDA's various letters regarding the need to develop plans "that ensure, with a high degree of certainty" that animal-derived ingredients are used only in accordance with FDA and USDA policies designed to protect against BSE. CRN convened an industry working group on this topic in February 2001, in which FDA and USDA

officials participated. The various industry trade associations jointly surveyed the industry regarding procurement and handling practices and submitted to FDA five large volumes containing lists of animal-derived ingredients used by various companies, along with examples of the certificates of origin and other documentation required for import of any animal-derived materials.

FDA has convened a TSE advisory committee within the Center for Biologics, and the deliberations of the advisory committee have been followed closely by all FDA-regulated industries, including the dietary supplement industry. Although FDA's efforts to protect against BSE (recently broadened to TSE) started with concerns relating to the safety of blood products regulated by the Center for Biologics, appropriate procedures and policies have since been enunciated for pharmaceuticals and for food products, including dietary supplements. Thus, there is no need at this point for FDA to continue to refer back to biologics as the model for provisions applicable to other product categories.

CRN believes the general reference that already appears in the GMP rule, emphasizing the obligation to comply with other applicable laws and regulations, is sufficient to cover the BSE issue. The dietary supplement industry is fully cognizant of both FDA's policies and guidance and the regulatory activities of USDA relating to the risk of BSE, and companies are making every effort to ensure compliance.

INGREDIENTS OTHER THAN "DIETARY INGREDIENTS"

Section 111.35(d) of the proposed rule contains specifications relative to the use in dietary supplements of ingredients other than "dietary ingredients." To the extent that this section is merely a restatement of existing FDA policy and regulations, it is unnecessary. Section 111.5 already requires observance of "other statutory provisions and regulations."

To the extent that section 111.35(d) is meant to break new ground, it is inappropriate in the context of a GMP rulemaking. For example, subparagraph (3) would require that color additives used in dietary supplements must specifically be listed for such use. Various color additives are currently approved generally for "food" use, but none are approved specifically for dietary supplements within the food category. If FDA intended by this provision to assert an additional requirement for dietary supplements, that would be beyond the scope of a GMP rulemaking.

Section 111.35(d)(4) contains requirements pertaining to substances that FDA has determined to be GRAS (Generally Recognized as Safe) or that have been have been determined by their manufacturers or marketers to be GRAS. The rule requires that companies be prepared to support the GRAS status of the ingredient by a citation to FDA regulations or "by an explanation for why there is general recognition of safety of the use of the substance in a dietary ingredient or dietary supplement." In the preamble to the proposed rule, FDA asserts that an FDA response letter cannot be relied upon to support the safety of an ingredient, when a manufacturer or one of its suppliers has determined the ingredient to be GRAS and has so notified FDA. This provision would undermine the

GRAS self-determination process, including especially the entire rationale for notifying FDA of the determination. If FDA in this section means to alter its position with regard to self-determination of GRAS status, that would appear to go beyond the scope of a GMP rulemaking.

CRN urges FDA to delete section 111.35(d) and rely on section 111.5 and existing policy and regulations with regard to the status of dietary supplement ingredients other than "dietary ingredients."

COMPLIANCE PERIOD

FDA proposes to provide for a one-year compliance period for large manufacturers, once a GMP rule is finalized, with a three-year compliance period for small firms. This would be reasonable for large firms only if the final rule is modified to better reflect existing GMPs among responsible companies whose practices should ideally provide the model for the rule. If the final rule, like the proposal, represents a great departure from current "best practices" and from sound GMP theory, then a one-year compliance period will not be realistic.

A three-year compliance period for small firms may be reasonable, with respect to any new GMP rule, but it should be recognized that even during that period -- and today and every day for the past several decades -- those firms will be and have been subject to general food GMP regulations and should be in compliance with them. Accordingly, FDA should be inspecting those firms to ensure such compliance. The agency's survey of manufacturing practices indicated that small and (especially) very small firms were less likely to be observing any formal GMP rule. FDA and the states should not wait until finalization of new dietary supplement GMPs to enforce compliance with basic food GMP requirements.

CONCLUSION AND RECOMMENDATIONS

CRN and its members have played a key role in bringing the topic of GMPs for dietary supplements to the table and in pursuing it to this point. We are committed to remaining engaged and to supporting the need for enhanced GMPs, but we do not believe the FDA proposal hits the right balance between sufficient control and essential flexibility. CRN urges FDA, as it crafts a final rule on GMPs for dietary supplements, to adjust the emphasis of the rule toward a focus on process controls rather than reliance on exhaustive finished-product testing. These process controls should include written specifications for key operations, in order to ensure uniformity of practice and to provide a sound basis for employee training and supervision. A key aspect of process control involves rigorous oversight over incoming ingredients, which is best accomplished through a vendor qualification program that will identify reliable suppliers and permit acceptance of analytically-based certificates of analysis documenting that bulk ingredients meet appropriate specifications.

We do not believe the prescriptive finished-product-based approach adopted by the agency is consistent with good quality assurance practice or theory, and we do not believe the proposal is sufficiently modeled after food GMP regulations, as required by DSHEA.

CRN urges the agency to carefully consider all the comments it receives on this proposal and then to schedule a public meeting or perhaps a series of public workshops to evaluate the numerous important issues involved and to develop a more workable solution.

Sincerely,

A Dickinson

Annette Dickinson, Ph.D.
President

Attachment A: Council for Responsible Nutrition Manufacturer Members

Manufacturers of Finished Products	
Member Company	**Products**
Access Business Group/Nutrilite	Nutrilite®, Trim Advantage®
Accucaps Industries Limited	Private Label Manufacturer of Vitamins and Minerals, Oils, Specialty Supplements, and Herbals
Arkopharma, LLC	Sokoja®, Azinc®, Potensium®, Arkocaps®, Memoboost®, Turbodiet®
B&C Nutritional Products, Inc.	Private Label Manufacturer of Vitamins and Minerals, Specialty Supplements, and Herbals
Bayer HealthCare LLC	One-A-Day®, Flintstones®
Bio San Laboratories Inc.	Private Label Manufacturer of Vitamins and Minerals, MegaFood®, DailyFoods®, Essentials®
Enzo Nutraceuticals	Enzogenol®
Experimental and Applied Sciences, Inc. (EAS)	AdvantEdge®, BetaGen®, CytoVol®, EcdyMax®, Lean DynamX®, Mass Factor®, Muscle Drive®, Myoplex®, Precision Protein®, Simply Creatine®, SimplyProtein®, Synthe Vol®, Thermo DynamX®, ZMA®
GNC Incorporated	GNC ProPerformance®, Preventive Nutrition®, Herb Plus®, GNC Natural Brand®, Total Lean®, Mega Men®, Womens Ultra Mega®, Herbal Plus®
GNLD International	Carotenoid Complex®, GR^2 Control®
Herbalife International	Herbalife, Thermo Complete®, Thermojetics®,
Jamieson Laboratories Ltd.	Mega Cal®, Vita Vim®
Kemin Consumer Care, L.L.C.	Satise®
Mannatech, Inc.	Glycentials®, Ambrotose®, Phyt•Aloe®, CardioBALANCE®, ImmunoStart®, Glyco•Bears®, Phyto•Bears®, EM•Pact®, GlycoLEAN®, Plus®, Ambrostart®, Sport®, Emprizone®
Mary Kay, Inc.	Daily Benefits for Women®, Daily Benefits for Men®
Natural Alternatives International Inc.	Pathway to Healing®, Jennifer O'Neill Essentials®, Private Label Manufacturer
NBTY, Inc.	Nature's Bounty®, Vitamin World®, Puritan's Pride®, Holland & Barrett®, Nutrition Headquarters®, American Health® and Nutrition Warehouse®, Private Label Manufacturer
Nu Skin International Inc./Pharmanex LLC	LifePAK®, Phamanex Solutions®, Pharmanex Bodydesign®

Attachment A: Council for Responsible Nutrition Manufacturer Members

Manufacturers of Finished Products	
Member Company	**Products**
Nutraceutical Corporation	Solaray®, KAL®, NaturalMax®, VegLife®, Premier One®, Sunny Green®, Natural Sport®, ActiPet®, Action Labs®, Miztique®, Ultimate Nutrition® and Thompson®, Private Label Manufacturer
Nutramax Laboratories, Inc.	Senior Moment®, Cosamin® DS
Perrigo Company	Private Label Manufacturer and Branded Contract Manufacturer
Pharmaton Natural Health Products	Ginsana®, Ginkoba®, Flexium®, Kyolic®, Venastat®, Supplifem®, Prostatonin®
Pharmavite LLC	Nature Made®, Nature's Resource®, Private Label Manufacturer, Olay™ Vitamins
Proper Nutrition, Inc.	SeaCure®, SeaVive®
Pulse Nutrition	Pulse® Water + Nutrients (Vitamins and Minerals)
Rainbow Light Nutritional Systems	Active Health®, Complete Nutritional System®, Complete Prenatal System®, Nutristars®, Performance Energy®, Women's Answer® and other Single Nutrient, Herbal, and Specialty Supplements
Rexall Sundown, Inc. (now part of NBTY, Inc.)	Sundown®, Osteo Bi-Flex®, Pokemon®, Private Label Manufacturer
Ross Products	Glucerna®, Ensure®, Infant Formula
Shaklee Corporation	CorEnergy®, Mood-Lift®, Vita-Lea®, CoQHeart®, Immunity Formula I®, Herb-Lax®, Optiflora®, EZ-Gest®, Shaklee Fitness®, Performance®, Physique®, Liver DTX®, Fiber Plan®
Sigma Tau Health Sciences	ProXeed®, Megasol®, Megasol Q10®, Phototrop®, Avant®, Biorecord Plus®
Tom's of Maine	Botanicals
Vitamin Shoppe Industries, Inc.	Vitamins and Minerals, Specialty Supplements, and Botanicals distributed under the Vitamin Shoppe® name
VitaTech International, Inc.	Private Label Manufacturer
Warner Lambert Consumer Group of Pfizer	Finished Product Manufacturer
Weider Nutrition International, Inc.	Schiff®, Schiff® Move Free®, Tiger's Milk®, Weider®, Fi Bar®
Wyeth	Centrum®, Centrum Silver®, Centrum Performance®, Centrum Kids®, Caltrate®

Attachment A: Council for Responsible Nutrition Manufacturer Members

Suppliers	
Member Company	**Products/Ingredients/Services**
Access Business Group - Trout Lake Farms	Grower and Processor of Botanical Ingredients, Ocean Essentials®
Albion Laboratories, Inc.	Bulk Minerals
American Laboratories, Inc.	Processor and Supplier of Enzymes, Peptones, Liver Products and Glandulars
Archer Daniels Midland Company	Vitamin E, Soy Isoflavones, Lecithin
B&D Nutritional Ingredients, Inc.	Supplier of Vitamin E, Lecithin, Lutein, Phytosterols, Grape Seed
BASF Corporation	Vitamins A, C, D & E, B Vitamins, Carotenoids, Excipients, Clarifying Agents, Aroma Chemicals
Biotron Laboratories, Inc.	Supplier of Various Mineral Amino Acid Chelates
Capsugel	Encapsulated Products and Capsules
Cargill Health & Food Technologies	Soy Isoflavones, Chondroitin, Vitamin E
Cognis Nutrition & Health	Natural Vitamin E, Tonalin® CLA, Vegapure®, Sterols/Sterol Esters, Lutein Esters, Natural Mixed Carotenoids, ALA, Botanicals, Emulsifiers, Food Technology Ingredients
Colorcon	Excipients, Colors, Coating Systems, Printing Inks
Daiichi Fine Chemicals, Inc.	B Vitamins, Vitamin D, Carotenoids
E.T. Horn Company	Bulk Ingredients Including: Calcium Carbonate, Glucosamine, Cellulose
Generichem Corporation	Bulk Supplier of Minerals
Indena USA, Inc.	Botanicals Supplier
Kaneka America Corporation	Supplier of Co-Enzyme Q10
Kemin Foods, L.C.	Lutein - FloraGLO®, Antioxidants
Linnea, Inc.	Botanicals Supplier
Loders-Croklaan	Supplier of Oils Including: Clarinol®, Marinol®, Membranol®, Safflorin®
Lonza, Inc.	Supplier of L-Carnitine and B Vitamins
Mingtai Chemical, LLC	Microcrystalline Cellulose, Comprecal®
Nashai Biotech LLC	Supplier of Ingredients Including TeaFlavin®
Nutrinova	DHActive®, Fiber - Caromax®, Nutrinova® Sorbates
Nutrition 21, Inc.	Chromax® Chromium Picolinate, Zinmax® Zinc Picolinate, Selenomax® High Selenium Yeast, Selenopure® l-selenomethionine, Zenergen™ Chromium Picolinate plus CLA
Ocean Nutrition Canada Ltd.	Omega-3 Fatty Acids

Attachment A: Council for Responsible Nutrition Manufacturer Members

Suppliers	
Member Company	**Products/Ingredients/Services**
Omya, Inc.	Supplier of Calcium Carbonate
Polyphenolics	MegaNatural® Gold Grape Seed Extract, MegaNatural® Grape Skin Extracts, MegaNatural® Rubired Grape Juice Extract, MegaNatural® Red Wine Extract
Pronova Biocare, a.s.	Omega-3 Fatty Acids - EPAX®, Triomega®, Pikasol®, Omacor®
Rhodia, Inc.	Antioxidants - Embanox®, Calcium Phosphate, Probiotics
Roche Vitamins, Inc.	Vitamins A, C, D, & E, B Vitamins, Carotenoids, Omega-3 Fatty Acids
Seven Seas Limited	Fish Oils, Multivitamins, Evening Primrose Oil, Herbals, ActionPlan50+®

Attachment B to CRN Comments:

Qualifying the Production Process Control System

There should be a written plan for qualifying the production process if process control is to be sufficiently rigorous as to justify parametric testing of finished products. There should also be written procedures for each stage of the process.

RAW MATERIAL AND PRIMARY PACKAGING

- Supplier qualification program based on manufacturer's evaluation of the supplier's process and testing procedures
- Appropriate written specifications for raw materials and packaging
- **Identity testing of every ingredient received**
- Specification testing of ingredients based on Vendor qualification data
- Review of Certificate of Analysis or Report of Analysis and other data as appropriate – must be actual testing and specific to batch/lot received
- Verification of supplier's test results at appropriate intervals

IN - PROCESS CONTROLS

- Master and batch records for every product
- Appropriate written specifications for in-process materials
- Dual signature verification of identity and weight of ingredients added
- Calculation of yields – plan vs. actual
- Data demonstrating that equipment is suitable and that the process consistently delivers expected results over time
- Specific in-process tests appropriate to specifications for unit operations

FINISHED PRODUCT APPROVALS

- Appropriate written specifications for finished product
- Representative testing of chemical, physical and microbiological parameters based on an appropriate parametric sampling plan and data from raw material data and in-process testing and procedures

A qualified process including the above features will assure that the product meets regulatory requirements more effectively than testing every ingredient in every batch.

ATTACHMENT C TO CRN COMMENTS

STATEMENT OF GMP EXPERT CARL REYNOLDS, SENIOR CONSULTANT, AAC CONSULTING GROUP

CONCERNS RELATING TO THE FDA PROPOSED RULE ON GOOD MANUFACTURING PRACTICES FOR DIETARY SUPPLEMENTS

August 11, 2003

The Dietary Supplement Health and Education Act of 1994 (DSHEA) authorizes FDA to prescribe good manufacturing practices (GMP) for dietary supplements, but what are GMPs? In the more than 60 years that FDA has used good manufacturing practices as a quality and regulatory standard, they have yet to define the term(s). DSHEA does not nor did the comprehensive Drug Amendments of 1962. Absent a definition of this important concept, the regulated industries have been forced to develop one of their own. I crafted the following definition for use during training programs:

> Good Manufacturing Practices: A system of procedures and documentation, written or analytical, to ensure that the product produced has the identity, strength, quality, composition and purity which it purports or is represented to possess.

While DSHEA authorizes FDA to prescribe cGMPs for dietary supplements, the Act prohibits FDA from imposing standards for which there are no current and generally available analytical methodology.

This proposed rule, as drafted, seems to ignore that restriction as well as some of the basic premises of GMPs especially as they relate to in process and finished product testing and documented policies and procedures. The proposed rule at § 111.35(g)(1) requires comprehensive testing of each finished batch of dietary supplements for *all* (emphasis added) components (every ingredient) to ensure the batch meets specifications for identity, purity, quality, strength, and composition provided scientifically valid analytical methodology exists. The proposed rule mentions "flexibility" but at § 111.35(g)(2)(i) and (g)(2)(ii) it requires testing of incoming components, dietary ingredients or dietary supplements to determine if specifications are met *and* requires in-process testing where control is necessary to ensure the identity, purity, quality, strength, and composition of dietary supplements.

This concept is flawed because it assumes scientifically valid analytical methodology exists when such may not be the case. One could read this and argue that FDA would expect the firm to validate any methods used in this regard. If this assumption is correct, it would appear to deviate from the provision of § 402(g)(1) of the Food, Drug, and Cosmetic Act as amended by DSHEA.

The heavy reliance on comprehensive end product testing allows one to argue against the need for good manufacturing practices at all. Why not just rely on comprehensive end product testing? The economic analysis discusses this approach before rejection based on 4 issues: (1) Finished product testing cannot build quality into a product; (2) Lack of comprehensive analytical methodology; (3) Possibility of false negatives, and (4) Reduce the ability to perform trace back investigation in the event defective products are discovered in the marketplace.

One familiar with the concepts of GMPs recognizes that end process controls are not adequate because they cannot build quality into a product. In testing protocols, all units or doses of a particular batch are not tested. Rather it is necessary to rely on inferences and assumptions. There is always the possibility of false analytical results but that's why you have defined sampling protocols and formal, documented procedures for addressing and investigating Out of Specification results. It's critical to understand that samples only produce meaningful information if the process is controlled.

The Agency has taken an interesting approach to one of the hallmarks or cornerstones of good manufacturing practices. They propose requiring documented procedures for some operations (calibration) but not in others (customer complaints). They do not define a written procedure nor is there differentiation between standard operating procedures (SOPs) and procedures required in the master manufacturing record to ensure that each batch of dietary supplement or dietary ingredient meets specifications. It would be preferable for FDA to clearly require written procedures for key operations identified in the proposed rule.

A general rule of thumb for the drug industry is that an SOP should be in place for operating or controlling each piece of equipment, system or process that must be cleaned, maintained, calibrated or otherwise affects the quality, composition or purity of the finished product. For dietary supplements, written policies and procedures should be required at least for those areas mentioned in the ANPR. SOP documents must be clear and concise and define policies, procedures or instructions for operating processes, practices and equipment. This same approach should also be considered for the dietary supplement industry.

When a manufacturer makes permanent changes or modifications to specifications, procedures or documentation to address regulatory changes or improvements or modifications in or with their procedures or facilities, the changes should be reviewed, justified, documented, approved and implemented in a defined SOP driven procedure know as change control. Temporary changes could be addressed in a formal SOP driven procedure for deviations.

The proposed rule discusses the application of HACCP in manufacturing dietary supplements and dietary ingredients and makes the following comment: ""HACCP principles can be applied to a broad range of manufacturing practices and HACCP principles are not solely focused on microbial contamination but instead, are intended to identify and appropriately control steps in manufacturing where any type of adulteration

can occur." This comment mistakenly describes HACCP. The HACCP approach addresses safety, not adulteration, and utilizes a preventive approach that addresses biological, chemical and physicals hazards through anticipation and prevention, rather than through end-product inspection and testing. The principles in and of themselves do not address sanitation or similar aspects of adulteration. I consider HACCP to be a companion program that becomes effective after implementation and enforcement of sanitation standard operating procedures (SSOPs.)

The rule at § 111.35(e) speaks of specifications being required for any point, step, or stage in the manufacturing process where control is necessary to prevent adulteration. It goes on to define such specifications as regulatory specifications that would require testing or examination to confirm they were met. A deviation from such specification would require investigation and a disposition decision approved by the quality control unit. The term specification(s) is not defined and some might consider specification to be synonymous with a numerical value. It would be helpful if specification were defined. In training sessions, I have defined specifications as being a defined parameter established for a specific characteristic that is ensured through visual, chemical, microbiological or physical testing.

The provisions of § 111.35(e) could be called the HACCP component of the rule. It requires compliance with five of the 7 principles of HACCP, including conducting a hazard analysis, determine the critical control points (CCP), establish critical limits, monitor the CCP, and establish corrective actions.

The proposed rule would not allow use of Certificate of Analysis (COA) as a basis for accepting ingredients or components. This is a significant issue that requires serious consideration. The drug GMPs at § 211.184 allows accepting a COA from a supplier "provided that at least one specific identity test is conducted on such component by the manufacturer and provided that the manufacturer establishes the reliability of the supplier's analysis through appropriate validation of the supplier's test results at appropriate intervals." Many manufacturers of dietary supplements have vendor certification programs that may include visits to plants, inspections, verification of laboratory procedures and data and comprehensive testing to confirm specifications. Only after satisfactory compliance with established specifications, will the manufacture consider accepting COAs in lieu of comprehensive testing. Even after acceptance, there are periodic SOP driven schedules to confirm continued conformance to specifications. For example, a firm may completely test the first 10 shipments of a raw material or component before they consider reducing the level of analysis. After acceptance, the firm will still test every 3rd or 5th shipment for conformance to specifications. Usually a vendor certification program is reevaluated annually. Identity testing is performed on every incoming shipment.

The proposed rule at § 111.1 identifies who would be subject to these regulations and the preamble states that foreign firms that manufacture, package, or hold dietary supplements that are imported or offered for import into the U.S. would be subject to these regulations. This is certainly important, but there are no provisions for effective enforcement. One

could say that a foreign firm is subject to FDA inspection(s) but the likelihood of FDA inspecting foreign dietary supplement or dietary ingredients firms is small unless there is a health issue that can be tied to the firm or material. Even then, FDA would not have foreign jurisdiction and any inspection or investigation would require advance notification and scheduling as well as consent of the firm and foreign government.

I contrast this approach with the requirements of Seafood HACCP (21 CFR 123) that outlines special requirements for imports and places certain requirements on the importer implementing affirmative steps to ensure that HACCP is practiced. Some aspects of this program could be used for dietary supplements including:

1. Obtaining products from a country that has a cGMP focused regulatory program for dietary supplements or dietary ingredients that is at least equivalent to that of the U.S.
2. Take affirmative steps to ensure that cGMPs are in place and enforced including obtaining a copy of the firm's SOP procedures and a written guarantee that they are being followed.
3. Obtaining third party certification that products are processed according to requirements.
4. Conduct your own inspection the ensure cGMPs are in place and being followed.

The benefits and cost analysis by FDA boldly declares "introducing cGMPs will reduce the probability of a recall to zero." They further state that cGMPs, if strictly used, "cause the discovery of all adulteration." This is certainly a hopeful goal but one that will probably not be achieved. Even with the long-term use of GMPs and enormous devotion of resources by the industry and FDA, recalls have not been reduced to zero in the drug and medical device industries. In fact, there have been more than 250 recalls of drug products this fiscal year.

# # # # # # #

Carl Reynolds is a Senior Consultant at AAC Consulting Group, Inc. where he assists clients in regulatory compliance and conducts audits of FDA regulated firms including dietary supplementary manufacturers and their suppliers. Prior to joining the firm, Mr. Reynolds had a 36-year career at the FDA, most recently as Director, Office of Field Programs in CFSAN. In that position, he served as the chief compliance official for foods and cosmetics and managed and directed all CFSAN programs affecting FDA's field organizations. Mr. Reynolds supervised all domestic and import regulatory activities, Federal/State cooperative programs, and inspection programs, including those designed to implement HACCP. He is an approved auditor for the NNFA GMP Certification Program and the USP Dietary Supplement Quality Demonstration Program.

Council for Responsible Nutrition

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August 11, 2003

Dockets Management Branch (HFA 305)
Food and Drug Administration
5630 Fishers Lane, Room 1061
Rockville, MD 20852

RE: DOCKET NO. 96N-0417, GOOD MANUFACTURING PRACTICES FOR DIETARY SUPPLEMENTS

TOPIC: SECTION-BY-SECTION RECOMMENDATIONS

This is the fourth in a series of comments submitted by the Council for Responsible Nutrition regarding the above-mentioned proposed rule. This comment will provide section-by-section recommendations, including detail not covered in our fuller comments submitted separately.

On this same date, CRN is submitting separate comments on the purpose and scope of the rule, on the core issue of process control, and on legal issues. At a later date, but before September 9, we will submit comments on the economic impact of the proposed rule. CRN has requested and been granted this additional time for submission of economic data based on new information we have just obtained pursuant to a FOIA request for underlying data not previously included in the administrative record, relating to FDA's assumptions and calculations on the estimated economic impact of the rule. The first comment in this series (July 8, 2003) provided a four-way comparison of the proposed GMP with current food GMPs, the industry draft published as the ANPR in 1997, and current drug GMPs.

The Council for Responsible Nutrition (CRN) is one of the leading trade associations representing the dietary supplement industry. CRN has been a strong supporter of Good Manufacturing Practices (GMPs) over the years, and we have an active Regulatory Affairs Committee composed of industry experts in dietary supplement regulation and in the technical aspects of production processes, including GMPs. CRN's member company experts in this arena drafted the guidelines for nutritional supplement manufacturing practices adopted by USP over a decade ago and also prepared the industry draft GMPs submitted to FDA in November 1995 by CRN, joined by other industry trade associations. FDA published the industry draft verbatim in the ANPR on dietary supplement GMPs in 1997.

CRN has serious concerns about the appropriateness of FDA's proposed rule, which differs in philosophy as well as content from the industry draft submitted by CRN and other associations eight years ago. These concerns are set forth in detail in our comments on the purpose and scope of the rule, the importance of process controls, and legal issues.

Attached is a two-column side-by-side with the FDA proposal in the lefthand column and CRN's section-by-section recommendations in the righthand column. We provide this summary with some trepidation, since it may imply that with the noted changes we could embrace the rule. In fact, our concerns about the rule go to the underlying philosophy and approach and may not be fully addressed by our detailed recommendations, although we have made every effort to be complete.

Because of its complexity and because of its importance to the future viability of the industry, this rule still requires further consideration and discussion. **CRN urges the agency to hold a public hearing or perhaps a series of public workshops to address the important issues raised by the rule and in order to craft a more workable solution.**

Sincerely,

A Dickinson

Annette Dickinson, Ph.D.
President

COUNCIL FOR RESPONSIBLE NUTRITION:

SECTION-BY-SECTION COMMENTS

August 11, 2003

Proposed cGMP for Dietary Ingredients and Dietary Supplements (FR: 3-13-03)	CRN COMMENT
Subpart A--General Provisions § 111.1 Who is subject to these regulations? You are subject to the regulations in this part if you manufacture, package, or hold a dietary ingredient or dietary supplement.	Amend to read: "You are subject to the regulations in this part if you manufacture, package or hold a dietary supplement." (omitting the term "dietary ingredient" and thus excluding manufacturers of dietary ingredients from coverage by the rule) ADD a sentence relating to dietary ingredient manufacturers: "Manufacturers of bulk dietary ingredients are subject to the general food GMPs in 21 CFR part 110." CRN urges the agency to make the GMP rule applicable only to manufacturers of finished products and not to manufacturers and suppliers of dietary ingredients, who would still be subject to the general food GMPs in 21 CFR part 110. Please refer to separately submitted CRN comments regarding who should be covered by the rule. FDA adoption of this recommendation would require omitting "dietary ingredient" in most places where it occurs in this proposed rule, but not in all places (not, for example, in places where the rule places requirements on finished product manufacturers for their handling of dietary ingredients).
§ 111.2 What are these regulations intended to accomplish? The regulations in this part establish the minimum current good manufacturing practices that you must use to the extent that you manufacture, package, or hold a dietary ingredient or dietary supplement.	

GMP PROPOSAL -- DEFINITIONS	CRN COMMENTS
§ 111.3 What definitions apply to this Part? The definitions and interpretations of terms in section 201 of the Federal Food, Drug, and Cosmetic Act (the act) apply to such terms when used in these regulations For the purpose of these regulations, the following definitions also apply:	
Actual yield means the quantity that is actually produced at any appropriate step of manufacture or packaging of a particular dietary ingredient or dietary supplement.	
	ADD definition for "adulteration." Adulteration has the meanings set forth in the FD&C Act, Section 402.
Batch means a specific quantity of a dietary ingredient or dietary supplement that is intended to meet specifications for identity, purity, quality, strength, and composition, and is produced during a specified time period according to a single manufacturing record during the same cycle of manufacture.	
Batch number, lot number, or control number means any distinctive group of letters, numbers, or symbols, or any combination of them, from which the complete history of the manufacturing, packaging, or holding of a batch or lot of dietary ingredients or dietary supplements can be determined.	
Component means any substance intended for use in the manufacture of a dietary ingredient or dietary supplement including those that may not appear in the finished dietary ingredient or dietary supplement. Component includes ingredients and dietary ingredients as, described in section 201(ff) of the act.	CRN is recommending that these GMPs should not apply to suppliers of dietary ingredients. If FDA decides to make them applicable to suppliers, then it should be made clear that the definition of "component" should NOT include starting materials for dietary ingredients, since many starting materials are not food grade or approved food ingredients until after appropriate processing.
	ADD definition of composition: Composition means having the intended mix of components or ingredients, including dietary ingredients.
Consumer complaint means communication that contains any allegation, written or oral, expressing dissatisfaction with the quality of a dietary ingredient or a dietary supplement related to good manufacturing practices. Examples of product quality related to good manufacturing practices are: Foul odor, off taste, super-potent, subpotent, wrong ingredient, drug contaminant, other contaminant	Not reasonable to require companies to treat consumer complaints related to GMP issues differently from other consumer complaints. Companies should have consistent system for handling all complaints, including adverse events.

(e.g., bacteria, pesticide, mycotoxin, glass, lead), disintegration time, color variation, mycotoxin, glass, lead), disintegration time, color variation, tablet size or size variation, under-filled container, foreign material in a dietary supplement container, improper packaging, or mislabeling. For the purposes of the regulations in this part, 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.	CRN is recommending that these GMPs should not apply to suppliers of "dietary ingredients." If FDA decides to include suppliers within the coverage of the rule, then there needs to be a definition of "consumer." A consumer is an individual who purchases or ingests the dietary supplement. Suppliers of dietary ingredients do not deal directly with consumers and thus are unlikely to receive consumer complaints. The customers for dietary ingredients are other companies, not individual consumers.
Contact surface means any surface that contacts a component, dietary ingredient, dietary supplement, and those surfaces from which drainage onto the component, dietary ingredient, dietary supplement, or onto surfaces that contact the component, dietary ingredient, or dietary supplement ordinarily occurs during the normal course of operations. Examples of contact surfaces include, but are not limited to, containers, utensils, tables, contact surfaces of equipment, and packaging.	
	ADD definition of control point: Control point means any point, step, or stage in the manufacturing process where control is necessary to prevent adulteration.
	ADD definition of dietary ingredient: Dietary ingredient has the meaning provided in the FD&C Act, Section 201(ff), describing the dietary ingredients that may be included in a dietary supplement.
	ADD definition of dietary supplement: Dietary supplement has the meaning given in the FD&C Act, Section 201(ff).
	ADD definition of identity: Identity means that a substance or product is what it is represented on the label to be.
Ingredient means any substance that is used in the manufacture of a dietary ingredient or dietary supplement that is intended to be present in the finished dietary ingredient or dietary supplement. An ingredient includes, but is not necessarily limited to, a dietary ingredient as described in section 201(ff) of the act.	

Inprocess material means any material that is fabricated, compounded, blended, ground, extracted; sifted, sterilized, derived by chemical reaction, or processed in any other way for use in the manufacture of a dietary ingredient or dietary supplement.	
Lot means a batch, or a specific identified portion of a batch intended to have uniform identity, purity, quality, strength, and composition; or, in the case of a dietary ingredient or dietary supplement produced by continuous process, a specific identified amount produced in a specified unit of time or quantity in a manner that is intended to have uniform identity, purity, quality, strength, and composition.	In both places it is mentioned, CHANGE "to have uniform identity..." to: "to meet specifications for identity..."
	ADD definition of manufacturer, based on model in infant formula quality control procedures: "Manufacturer means a person who formulates or changes the composition or physical characteristics of a dietary supplement or who packages or labels the product in a container for distribution."
Microorganisms means yeasts, molds, bacteria, viruses, and other similar microscopic organisms having public health or sanitary concern. This definition includes, but is not limited to, species that: (1) Have public health significance; (2) Could cause a component, dietary ingredient, or dietary supplement to decompose; (3) Indicate that the component, dietary ingredient, or dietary supplement is contaminated with filth; or (4) Otherwise may cause the component, dietary ingredient, or dietary supplement to be adulterated.	
Must is used to state mandatory requirements.	
Pest means any objectionable insects or other animals including, but not limited to, birds, rodents, flies, mites, and larvae.	
Physical plant means all or parts of a building or facility used for or in connection with manufacturing, packaging, or holding a dietary ingredient or dietary supplement.	
	ADD definition of purity: Purity means having the intended identity and composition and being without significant impurities.

	ADD definition of quality: Quality means having the appropriate identity, purity, and strength for the intended purpose.
Quality control means a planned and systematic operation or procedure for preventing a dietary ingredient or dietary supplement from being adulterated.	Replace with positive language: Quality control means a planned and systematic operation or procedure for assuring the quality of dietary supplement products.
Quality control unit means any person or group that you designate to be responsible for quality control operations.	It should be clarified that the quality control function need not be performed by a distinct and separate unit.
Representative sample means a sample that consists of a number of units that are drawn based on rational criteria, such as random sampling, and intended to ensure that the sample accurately portrays the material being sampled.	
Reprocessing means using, in the manufacture of a dietary ingredient or a dietary supplement, clean, unadulterated components, dietary ingredients, or dietary supplements that have been previously removed from manufacturing for reasons other than insanitary conditions and that have been made suitable for use in the manufacture of a diet any ingredient or dietary supplement.	This definition does not permit the reprocessing of ingredients that may have been removed because of "insanitary conditions" even when there are processes available that are safe and effective in removing foreign matter, microorganisms, or chemicals that may have rendered the ingredient "insanitary." For preferable language, the food GMP definition of "rework" provides a model. CRN suggests that this provision be modified to read: "Reprocessing means using, in the manufacture of a dietary supplement, clean, unadulterated components, dietary ingredients, or dietary supplements that have been previously removed from manufacturing for reasons other than insanitary conditions or that have been successfully reconditioned so that they are suitable for use."
Sanitize means to adequately treat equipment, containers, utensils, or any other dietary product contact surface by applying cumulative heat or chemicals on cleaned food contact surfaces that when evaluated for efficacy, yield a reduction of 5 logs, which is equal to 99.999 percent reduction, of representative disease microorganisms of public health significance and substantially reduce the	Need a definition for "sanitizing agent" as well as for "sanitize." Need to clarify that the requirement for efficacy to produce a 5 log reduction applies to the capability of the sanitizing agent and not to the actual performance in the processing facility. In

health significance and substantially reduce the numbers of other undesirable microorganisms, but without adversely affecting the product or its safety for the consumer.	the processing facility, a 5-log reduction on a recently cleaned contact surface is not feasible.
	ADD definition of scientifically valid analytical method: Scientifically valid analytical method means a method that is an officially published method (for example, in AOAC or USP or the American Herbal Pharmacopeia) or that is based on scientific data or results published in, for example, scientific journals, references, or text books, or supported by proprietary research.
	ADD definition of strength: Strength is having the intended concentration, that is the amount of a dietary ingredient intended per unit of use (tablet, capsule, softgel, teaspoon, or other unit).
	ADD definition for "starting material" or "raw material," if dietary ingredients are to be covered by this rule. Starting materials for dietary ingredients may not in fact be food grade or approved as food ingredients prior to processing and should not be included in definition of "components."
Theoretical yield means the quantity that would be produced at any appropriate step of manufacture or packaging of a particular dietary ingredient or dietary supplement, based upon the quantity of components or packaging to be used; in the absence of any loss or error in actual production.	
Water activity (aw) is a measure of the free moisture in a component, dietary ingredient, or dietary supplement and is the quotient of the water vapor pressure of the substance divided by the vapor pressure of pure water at the same temperature.	
We means the United States Food and Drug Administration (FDA).	
You means a person who manufactures, packages, or holds dietary ingredients or dietary supplements.	

§ 111.5 Do other statutory provisions and regulations apply? In addition to the regulations in this part, you must comply with other applicable statutory provisions and regulations under the act related to the manufacturing, packaging, or holding of dietary ingredients or dietary supplements.	
§ 111 6 Exclusions. The regulations in this part do not apply to a person engaged solely in activities related to the harvesting, storage, or distribution of raw agricultural commodities that will be incorporated into a dietary ingredient or dietary supplement by other persons	

GMP PROPOSAL	CRN COMMENTS
Subpart B--Personnel § 111 10 What microbial contamination and hygiene requirements apply? (a) Microbial contamination. You must take measures to exclude from any operations any person who might be a source of microbial contamination of any material including components, dietary ingredients, dietary supplements, and contact surfaces used in the manufacture, packaging, or holding of a dietary ingredient or a dietary supplement. Such measures include, but are not limited to, the following: (1) Excluding any person who, by medical examination or supervisory observation, is shown to have, or appears to have an illness, open lesion, or any other abnormal source of microbial contamination, which may be expected to result in microbial contamination of components, dietary ingredients, dietary supplements, or contact, surfaces, from working in any operations until the condition is corrected; and (2) Instructing your employees to notify their supervisor(s) if they have or if there is a reasonable possibility that they have a health condition, described in paragraph (a) (1) of this section that could contaminate any components, dietary ingredients, dietary supplements, or any contact surface.	
(b) Hygienic Practices. If you work in operations during which adulteration of the component, dietary ingredients, dietary supplement, or contact surface may occur, you must use hygienic practices to the extent, necessary to protect against contamination of components, dietary ingredients, dietary supplements, or contact surfaces. The hygienic practices include, but are not limited to:	
(1) Wearing outer garments in a manner that protects against the contamination of components, dietary ingredients, dietary supplements, or any contact surface;	
(2) Maintaining adequate personal, cleanliness;	
(3) Washing hands thoroughly (and, sanitizing if necessary to protect against contamination with microorganisms) in an adequate hand-washing facility: (i) Before starting work; and (ii) At any time when the hands may have become soiled or contaminated;	

(4) Removing all unsecured jewelry and other objects that might fall into components, dietary ingredients, dietary supplements, equipment, or packaging, and removing hand jewelry that cannot be adequately sanitized during periods in which components, dietary ingredients, or dietary supplements are manipulated by hand. If hand jewelry cannot be removed, it must be covered by material that is maintained in an intact, clean, and sanitary condition and that effectively protects against contamination of components, dietary ingredients, dietary supplements, or contact surfaces;	
(5) Maintaining gloves used in handling components, dietary ingredients, or dietary supplements in an intact, clean, and sanitary condition. The gloves must be of an impermeable material;	
(6) Wearing, where appropriate, in an effective manner, hairnets, caps, beard covers, or other effective hair restraints;	
(7) Not storing clothing or other personal belongings in areas where components, dietary ingredients, or dietary supplements or any contact surfaces are exposed or where contact surfaces are washed;	
(8) Not eating food, chewing gum, drinking beverages and using tobacco products in areas, where components, dietary ingredients, dietary supplements, or any contact surfaces are exposed, or where contact surfaces are washed; and	
(9) Taking any other precautions necessary to protect against the contamination of components, dietary ingredients, dietary supplements, or contact surfaces with microorganisms, filth, or any other extraneous materials, including, but not limited to, perspiration, hair, cosmetics, tobacco, chemicals, and medicines applied to the skin.	
§ 111.12 <u>What personnel qualification requirements apply?</u> (a) You must have qualified employees to manufacture, package, or hold dietary ingredients or dietary supplements; and (b) Each person engaged in manufacturing, packaging, or holding must have the training and experience to perform the person's duties.	CRN suggests the following preferred language: "Each person engaged in the manufacture of a dietary product should have the education, training, and experience (or any combination thereof) needed to perform the assigned functions."

§ 111.13 What supervisor requirements apply? (a) You must assign qualified personnel to supervise the manufacturing, packaging, or holding of dietary ingredients and dietary supplements. (b) You and the supervisors you use must be qualified by training and experience to supervise.	

GMP PROPOSAL	CRN COMMENTS
Subpart C--Physical Plant § 111.15 What sanitation requirements apply to your physical plant? (a) Physical plant facilities (1) You must maintain your physical plant in a clean and sanitary condition; and (2) You must keep your physical plant in repair sufficient to prevent components, dietary ingredients, dietary supplements or contact surfaces from becoming contaminated	
(b) Cleaning compounds, sanitizing agents, and pesticides. (1) You must use cleaning compounds and sanitizing agents that are free from microorganisms of public health significance and safe and adequate under the conditions of use.	
(2) You must not use or hold toxic materials in a physical plant in which contact surfaces, components, dietary ingredients, or dietary supplements are manufactured or exposed, unless those materials are necessary: (i) To maintain clean and sanitary conditions; (ii) For use in, laboratory testing procedures; (iii) For maintaining or operating the physical plant or equipment; or (iv) For use in the plant's operations.	
(3) You must identify and hold toxic cleaning compounds, sanitizing agents, pesticides, and pesticide chemicals in a manner that protects against contamination of components, dietary ingredients, dietary supplements, or contact surfaces.	
(c) Pest control. (1) You must not allow animals or pests in any area of your physical plant. Guard or guide dogs are allowed in some areas of your physical plant if the presence of the dogs will not result in contamination of components, dietary ingredients, dietary supplements, or contact surfaces; (2) You must take effective measures to exclude pests from the physical plant and to protect against	

contamination of components, dietary ingredients, dietary supplements, and contact surfaces on the premises by pests; and (3) You must not use insecticides, fumigants, fungicides or rodenticides, unless you take precautions to protect against the contamination of components, dietary ingredients, dietary supplements, or contact surfaces.	
(d) Water supply. (1) You must provide water that is safe and of adequate sanitary quality, at suitable temperatures, and under pressure as needed, in all areas where water is necessary for: (i) Manufacturing dietary ingredients or dietary supplements; (ii) Making ice that comes in contact with components, dietary ingredients, dietary supplements or contact surfaces; (iii) Cleaning any surface; and (iv) Employee bathrooms and hand-washing facilities. (2) Water that contacts components, dietary ingredients, dietary supplements, or any contact surface must at a minimum comply with the National Primary Drinking Water regulations prescribed by the Environmental Protection Agency under 40 CFR part 141 and any state and local government requirements; (3) You must have documentation or otherwise be able to show that water that contacts components, dietary ingredients, dietary supplements, or any contact surface meets the requirements in paragraph (d) (2) of this section.	See text of specific CRN comments process controls, for suggestions related to defining water quality.
(e) Plumbing. The plumbing in your physical plant must be of an adequate size and design and be adequately installed and maintained to: (1) Carry sufficient amounts of water to required locations throughout the physical plant; (2) Properly convey sewage and liquid disposable waste from your physical plant; (3) Avoid being a source of contamination to components, dietary ingredients, dietary supplements, water supplies, or any contact surface, or creating an unsanitary condition; (4) Provide adequate floor drainage in all areas where floors are subject to flooding-type cleaning or where normal operations release or discharge water	

or other liquid waste on the floor; and (5) Not allow backflow from, or cross connection between, piping systems that discharge waste water or sewage and piping systems that carry water used for manufacturing dietary ingredients or dietary supplements, for cleaning contact surfaces, or for use in bathrooms or hand-washing facilities.	
(f) Sewage disposal. You must dispose of sewage into an adequate sewage system or through other adequate means.	
(g) Bathrooms. You must provide your employees with adequate, readily accessible bathrooms. The bathrooms must be kept clean and must not become a potential source of contamination to components, dietary ingredients, dietary supplements, or contact surfaces. You must: (1) Keep the bathrooms in good repair at all times; (2) Provide self-closing doors; and (3) Provide doors that do not open into areas where components, dietary ingredients, dietary supplements, or contact surfaces are exposed to airborne contamination except where alternate means have been taken to protect against contamination (such as double doors or positive airflow systems).	
(h) Hand-washing facilities. You must provide hand-washing facilities that are adequate, convenient, and furnish running water at a suitable temperature. You must do this by providing: (1) Hand-washing and, where appropriate, hand-sanitizing facilities at each location in your physical plant where good hygienic practices require employees to wash or to sanitize or both wash and sanitize their hands; (2) Effective hand-cleaning and sanitizing preparations; (3) Air driers, sanitary towel service, such as disposable paper towels, or other suitable drying devices; (4) Devices or fixtures, such as water control valves, designed and constructed to protect against recontamination of clean, sanitized hands; (5) Signs that are easy to understand and are posted throughout the physical plant that direct employees handling components, dietary ingredients, dietary supplements, or contact surfaces to wash and, where appropriate, to sanitize their hands before they start work, after each absence from their duty station, and when their hands may have become soiled or contaminated;	

and (6) Trash bins that are constructed and maintained in a manner to protect against recontamination of hands and contamination of components, dietary ingredients; dietary supplements, or any contact surface.	
(i) Trash disposal. You must convey, store, and dispose of trash to: (1) Minimize the development of odor; (2) Minimize the potential for the trash to attract, harbor, or become a breeding place for pests; (3) Protect against contamination of components, dietary ingredients, dietary supplements, any contact surface, water supplies, and grounds surrounding your physical plant; and (4) Control hazardous waste to prevent contamination of components, dietary ingredients, dietary supplements, and contact surfaces.	
(j) Sanitation supervisors. You must assign one or more employees to supervise overall sanitation. These supervisors must be qualified by training and experience to develop and supervise sanitation procedures.	
§ 111.20 What design and construction requirements apply to your physical plant? Any physical plant you use in the manufacture, packaging, or holding of dietary ingredients or dietary supplements must: (a) Be suitable in size, construction, and design to facilitate maintenance, cleaning, and sanitizing operations;	Some of these provisions are not relevant to closed, continuous systems used by manufacturers of some dietary ingredients. If manufacturers of dietary ingredients are covered by these GMPs, then there needs to be language indicating that some of these requirements are only needed "when applicable."
(b) Have adequate space for the orderly placement of equipment and holding materials as is necessary for maintenance, cleaning, and sanitizing operations and to prevent contamination and mixups of components, dietary ingredients, and dietary supplements during manufacturing, packaging, or holding;	
(c) Permit the use of proper precautions to reduce the potential for mixups or contamination of components, dietary ingredients, dietary supplements, or contact surfaces, with microorganisms, chemicals, filth, or other-extraneous material. Your physical plant must have and you must use separate or defined areas of adequate size or other control systems, such as	

computerized inventory controls or automated systems of separation, to prevent contamination and mixups of components, dietary ingredients, and dietary supplements during the following operations: (1) Receiving, identifying, holding, and withholding from use, components, dietary ingredients, dietary supplements, packaging, and labels that will be used in or during the manufacturing, packaging, or holding of dietary ingredients and dietary supplements; (2) Separating, as necessary, components, dietary ingredients, dietary supplements, packaging, and labels, that are to be used from components, dietary ingredients, dietary supplements, packaging, or labels that are awaiting material review and disposition decision, reprocessing, or are awaiting disposal after rejection; (3) Separating the manufacturing, packaging, and holding of different product types including, but not limited to, different types of dietary ingredients, dietary supplements and other foods, cosmetics, and pharmaceutical products; (4) Performing laboratory analyses and holding laboratory supplies and samples; (5) Cleaning and sanitizing contact surfaces; (6) Packaging and label operations; and (7) Holding dietary ingredients or dietary supplements.	
(d) Be designed and constructed in a manner that prevents contamination of components, dietary ingredients, dietary supplements, or contact surfaces. The design and construction must include, but not be limited to: (1) Floors, Walls, and ceilings that are of smooth and hard surfaces that can be adequately cleaned and kept clean and in good repair; (2) Fixtures, ducts, and pipes that do not contaminate components, dietary ingredients, dietary supplements, or contact surfaces by dripping or condensate;	In (d)(1), OMIT phrase "that are of smooth and hard surfaces." Smooth hard surfaces are not needed in all parts of the plant. This requirement appears to be based on drug GMPs for aseptic processes and is inappropriate as an overall requirement for all aspects of dietary supplement manufacturing facilities. Also, for continuous or closed processing systems, a specific requirement relating to walls and ceilings is not necessary. The cost of installing smooth hard ceilings in parts of the facility where they are not needed would be substantial and unnecessary.
(3) Adequate ventilation or environmenta1 control equipment such as air flow systems, including filters, fans, and other air-blowing equipment, that minimize	

odors and vapors (including steam and noxious fumes) in areas where they may contaminate components, dietary ingredients, dietary supplements, or contact surfaces; (4) Fans and other air-blowing equipment located and operated in a manner that minimizes the potential for microorganisms and particulate matter to contaminate components, dietary ingredients, dietary supplements, or contact surfaces; (5) Equipment that controls temperature and humidity; and	
(6) Aisles or working spaces between equipment and walls that are adequately unobstructed and of adequate width to permit all persons to perform their duties and to protect against contamination of components, dietary ingredients, dietary supplements, or contact surfaces with clothing or personal contact.	
(e) Provide adequate light in: (1) All areas where components, dietary ingredients, or dietary supplements are examined, processed, or held; (2) All areas where contact surfaces are cleaned; and (3) Hand-washing areas, dressing and locker rooms, and bathrooms.	
(f) Use safety-type light bulbs, fixtures, skylights, or other glass that is suspended over exposed components, dietary ingredients, or dietary supplements in any step of preparation, unless otherwise constructed in a manner that will protect against contamination of components, dietary ingredients, or dietary supplements in case of glass breakage.	
(g) Provide protection by any effective means against contamination of components, dietary ingredients, and dietary supplements in bulk fermentation vessels, including consideration of: (1) Use of protective coverings; (2) Placement in areas where you can eliminate harborages for pests over and around the vessels; (3) Placement in areas where you can check regularly for pests, pest infestation, filth or any other extraneous materials; and (4) Use of skimming equipment.	
(h) Use adequate screening or other protection against pests, where necessary.	

GMP PROPOSAL	CRN COMMENTS
Subpart D--Equipment and Utensils § 111.25 What requirements apply to the equipment and utensils you use? (a) (1) You must use equipment and utensils that are of appropriate design, construction, and workmanship to enable them to be suitable for their intended use and to be adequately cleaned and properly maintained. Equipment and utensils include, but are not limited to, the following: (i) Equipment used to hold or convey; (ii) Equipment used to measure; (iii) Equipment using compressed air or gas; iv) Equipment used to carry out processes in closed pipes and vessels; and (v) Equipment used in automatic, mechanical, or electronic systems.	These provisions should only apply to equipment that may impact a product's identity, purity, quality, strength and composition. Equipment and utensils used in the manufacturing, handling and storage of dietary supplement ingredients and dietary supplements are, in many instances, similar or identical to those used to perform that same operation in the food industry. It is inconsistent to postulate that their use in the supplement industry poses a greater risk solely on the basis of the type of product made with them. Since no greater risk exists, we would suggest that this section be changed to reflect wording currently found in 21 CFR 110.40.
(2) You must use equipment and utensils of appropriate design and construction so that use will not result in the contamination of components, dietary ingredients, or dietary supplements with: (i) Lubricants; (ii) Fuel; (iii) Coolants; (iv) Metal or glass fragments; (v) Filth or any other extraneous material; (vi) Contaminated water; or (vii) Any other contaminants.	Replace with provisions from section 110.40 of the food GMP:
(3) All equipment and utensils you use must be: (i) Installed and maintained to facilitate cleaning the equipment, utensils, and all adjacent spaces;	

(ii) Corrosion-resistant if the equipment or utensils contact components, dietary ingredients, or dietary supplements; (iii) Made of nontoxic materials; (iv) Designed and constructed to withstand the environment of their intended use, the action of components, dietary ingredients, or dietary supplements, and, if applicable, cleaning compounds and sanitizing agents; and (v) Maintained to protect components, dietary ingredients, and dietary supplements from being contaminated by any source.	
(4) Equipment and utensils you use must have seams that are smoothly bonded or maintained to minimize accumulation of component, dietary ingredient, or dietary supplement particles, dirt, filth, organic material, or any extraneous materials or contaminants to minimize the opportunity for growth of microorganisms.	
(5) Each freezer and cold storage compartment you use to hold components, dietary ingredients, or dietary supplements: (i) Must be fitted with an indicating thermometer, temperature-measuring device, or temperature-recording device that shows the temperature accurately within the compartment; and (ii) Must have an automatic device for regulating temperature or an automatic alarm system to indicate a significant temperature change in a manual operation.	
(6) Instruments or controls used in the manufacturing, packaging, or holding of a dietary ingredient or dietary supplement, including but not limited to, instruments or controls you use to measure, regulate, or record temperatures, hydrogen ion concentration (pH), water activity, or other conditions that control or prevent the growth of microorganisms or other contamination must be: (i) Accurate and precise; (ii) Adequately maintained; and (iii) Adequate in number for their designated uses.	
(7) Compressed air or other gases you introduce mechanically into or onto a component, dietary ingredient, dietary supplement, or contact surface or that you use to clean any contact surface must be treated in such a way that the component, dietary ingredient, dietary supplement, or contact surface is not contaminated.	

(b)(l) You must calibrate instruments and controls you use in manufacturing or testing a component, dietary ingredient, or dietary supplement. (2) You must calibrate before first use; and (i) As specified in writing by the manufacturer of the instrument and control, or (ii) At routine intervals or as otherwise necessary to ensure the accuracy and precision of the instrument and control.	Calibration is necessary only for those instruments needed to prevent adulteration and ensure that specifications for identity, purity, quality, strength and composition are met. Some instruments are used only for operational efficiency or cost control and have no direct bearing on product quality. Options: refer to "instruments and controls you use to generate data required by the master manufacturing record or specifications." Another option would be to require the quality control unit to prepare a critical instrument list for the instruments that require calibration.
(c) You must: (1) Establish a written procedure for calibrating instruments and controls you use in manufacturing or testing a component, dietary ingredient, or dietary supplement and document that the written procedure was followed each time a calibration is performed, or (2) Document, at the time of performance that the instrument and control calibration established in accordance with this section was performed.	It is surprising that the only FDA-proposed written procedures are for calibration. This emphasis on calibration appears disproportionate. CRN members believe written procedures should be required for numerous other processes and procedures, as elsewhere in these comments.
(d) You must identify the following for calibrating instruments and controls in any written procedure or at the time of performance: (1) The instrument or control calibrated; (2) The date of calibration; (3) The reference standard used including the, certification of accuracy of the known reference standard and a history of recertification of accuracy; (4) The calibration method used including appropriate limits for accuracy and precision of instruments and controls when calibrating; (5) The calibration reading or readings found; and (6) The recalibration method used if accuracy or precision or both accuracy and precision limits for instruments and controls were not met; and (7) The initials of the person who performed the calibration.	The requirements for calibration are unduly prescriptive and should not be necessary given the requirement for written procedures.
(d) You must repair or replace instruments or controls that cannot be adjusted to agree with the reference standard.	

(e)(I) You must maintain, clean, and sanitize as necessary, all equipment, utensils, and any other contact surfaces that are used to manufacture, package, or hold components, dietary ingredients, or dietary supplements. Equipment and utensils must be taken apart as necessary for thorough maintenance, cleaning, and sanitizing. (2) You must ensure that all contact surfaces used for manufacturing or holding of low-moisture components, dietary ingredients, or dietary supplements are in a dry and sanitary condition at the time of use. When the surfaces are wet-cleaned, they must be sanitized, when necessary, and thoroughly dried before subsequent use.	There should be written procedures for cleaning and maintaining equipment and utensils.
(3) If you use wet processing during manufacturing, you must clean and sanitize all contact surfaces, as necessary, to protect against the introduction of microorganisms into components, dietary ingredients, or dietary supplements. When cleaning and sanitizing is necessary, you must clean and sanitize all contact surfaces before use and after any interruption during which the contact surface may have become contaminated. If you use contact surfaces in a continuous production operation or in back-to-back operations involving different batches of the same dietary ingredient or dietary supplement, you must clean and sanitize the contact surfaces as necessary.	
(4) You must clean surfaces that do not touch components, dietary ingredients, or dietary supplements as frequently as necessary to protect against contaminating components, dietary ingredients, or dietary supplements.	
(5) Single-service articles (such as utensils intended for one-time use, paper cups, and paper towels) must be: (i) Stored in appropriate containers; and (ii) Handled, dispensed, used, and disposed of in a manner that protects against contamination of components, dietary ingredients, dietary supplements, or any contact surface.	
(6) Cleaning compounds and sanitizing agents must be adequate for intended use and safe under condition of use;	
(7) You must store cleaned and sanitized portable equipment and utensils that have contact surfaces in a location and manner that protects them from contamination.	
(f) You must keep calibration records as required by this section in accordance with § 111.125.	

§ 111.30 What requirements apply to automatic, mechanical, or electronic equipment? (a) When you use automatic, mechanical, or electronic equipment to manufacture, package, label, and hold a dietary ingredient or dietary supplement, you must: (1) Design or select equipment to ensure that dietary ingredient or dietary supplement specifications are consistently achieved and (2) Determine the suitability of your equipment by ensuring that your equipment is capable of operating satisfactorily within the operating limits required by the process.	Should only apply to equipment that impacts identity, purity, quality, strength, and composition.
(b) For any automatic, mechanical, or electronic equipment you use, you must: (1) Routinely calibrate, inspect, or check to ensure proper performance. Your quality control unit must approve these calibrations, inspections, or checks; (2) Make and keep written records of equipment calibrations, inspections, or checks; (3) Establish and use appropriate controls, to ensure that your quality control unit approves changes in the master manufacturing record, batch control records, packaging operations and label operations, or changes to other operations related to the equipment that you use and that only authorized personnel institute the changes; (4) Establish and use appropriate controls to ensure that the equipment functions in accordance with its intended use. These controls must be approved by your quality control unit; and (5) Make and keep backup file(s) of software programs and of data entered into your computer system. Your backup file (e.g., a hard copy of data you have entered, diskettes, tapes, microfilm, or compact disks) must be an exact and complete record of the data you entered. You must keep your backup software programs and data secure from alterations, inadvertent erasures, or equipment loss.	
(c) You must keep automatic, mechanical, or electronic equipment records required by this section in accordance with § 111.125.	

GMP PROPOSAL	CRN COMMENTS
Subpart E--Production and Process Controls § 111.35 What production and process controls must you use? (a) You must implement a system of production and process controls that covers all stages of manufacturing, packaging, labeling, and holding of the dietary ingredients and dietary supplements. (b) Your production and in-process control system must be designed to ensure that the dietary ingredient or dietary supplement is manufactured, packaged, and held in a manner that will prevent adulteration of the dietary ingredient or dietary supplement. The production and in-process control system must include all requirements of this subpart and must be reviewed and approved by the quality control unit.	Add to paragraph (a): Written procedures for these production and process controls must be established and followed. Rationale: Without written procedures, there is not an adequate basis for controlling the production process or for employee training and supervision.
(c) You must use a quality control unit in your manufacturing, packaging, and label operations for producing the dietary ingredient or dietary supplement to ensure that these operations are performed in a manner that prevents adulteration and ensures that the dietary ingredient or dietary supplement meets specifications for identity, purity, quality, strength, and composition.	Avoid implication that a separate unit is necessarily required. Change language to: "You must establish a quality control function in your .....(etc.)"
	Insert new paragraph dealing with requirements for "dietary ingredients." For example: Any "dietary ingredient" as defined in section 201(ff) of the act must have been marketed in the United States prior to October 15, 1994, or must comply with the statutory requirements for a "new dietary ingredient" as set forth in section 413 of the act.
(d) Any substance, other than a "dietary ingredient" within the meaning of section 201(ff) of the Federal Food, Drug; and Cosmetic Act (the act), the intended use of which results or may reasonably be expected to result, directly or indirectly, in its becoming a component or otherwise affecting the characteristics of the dietary ingredient or dietary supplement must be: (1) Authorized for use as a food additive under section 409 of the act; or (2) Authorized by a prior sanction consistent with §	OMIT subsection (d). There is no counterpart for this provision in other food GMPs or even in drug GMPs. This is covered by the general provision in 111.5 that other applicable laws and regulations must be observed. At a maximum, this section might state: Other substances used in dietary

170.3(l) of this chapter; or (3) If used as a color additive, subject to a listing that, by the terms of that listing, includes the use in a dietary supplement; or (4) Generally recognized as safe (GRAS) for use in a dietary ingredient or dietary supplement. Any claim that a substance is GRAS, other than a dietary ingredient within the meaning of section 201(ff) of the act, must be supported by a citation to the agency's regulations or by an explanation for why there is general recognition of safety of the use of the substance in a dietary ingredient or dietary supplement; and (5) Must comply with all other applicable statutory and regulatory requirements under the act	supplements must comply with the statutory and regulatory provisions of the act. NOTE: It is not feasible to require that the starting materials used by bulk ingredient manufacturers be GRAS or approved food additives. Many raw materials are not in fact food grade substances or approved food ingredients until after processing. Thus, this section should not refer to "any substance," if it is to apply to dietary ingredient manufacturers. CRN is urging that the rule apply only to manufacturers of finished dietary supplement products. Another possibility is to add a definition for "raw material" or "starting material" in addition to the definition for "component," if dietary ingredient manufacturers are covered by the rule. If this is done, the "component" definition would also need to be modified to indicate that starting materials for dietary ingredients are not covered by the definition of "component."
(e) You must establish a specification for any point, step, or stage in the manufacturing process where control is necessary to prevent adulteration. Specifications must be established for: (1) The identity, purity, quality, strength, and composition of components, dietary ingredients, or dietary supplements that you receive; (2) The in-process controls in the master manufacturing record where control is necessary to ensure the identity, purity, quality, strength, and composition of dietary ingredients or dietary supplements; (3) The identity, purity, quality, strength, and composition of the dietary ingredient or dietary supplement that you manufacture; and (4) The dietary ingredient or dietary supplement labels and the packaging that may come in contact with dietary ingredients and dietary supplements. The packaging must be safe and suitable for its intended use and comply with all other applicable statutory and regulatory requirements under the act and must not be reactive or absorptive so as to affect the safety of the dietary ingredient and dietary supplement.	Modify to refer to a positive rationale, such as: You must establish a specification for any point....where control is necessary to assure production of a quality product. Specifications must be established for:

(f) You must monitor the in-process control points, steps, or stages to ensure that specifications established under paragraph (e) of this section are met and to detect any unanticipated occurrence that may result in adulteration;	
(g) You must ensure, through testing or examination, that each specification that you established under paragraph (e) of this section is met. Specific testing requirements are as follows: (1) You must test each finished batch of the dietary ingredient or dietary supplement produced before releasing for distribution to determine whether established specifications for identity, purity, quality, strength, and composition are met provided that there are scientifically valid analytical methods available to conduct such testing. (2) For any specification for identity, purity, quality, strength, or composition for which you document cannot be tested on the finished batch of a dietary ingredient or dietary supplement, because there is no scientifically valid analytical method available for such testing, then you must: (i) Perform testing on each shipment lot of components, dietary ingredients or dietary supplements received to determine whether such specification is met; and (ii) Perform testing in-process in accordance with the master manufacturing record where control is necessary to ensure the identity, purity, quality, strength, and composition of dietary ingredients or dietary supplements, and (3) Your quality control unit must determine when finished batch testing cannot be completed for any specification on the identity, purity, quality, strength, and composition of dietary ingredients or dietary supplements.	A well-controlled process plus one identity test should be permitted to substitute for a requirement to test each batch for all specifications. See CRN comments on Process Control for detail on what constitutes a qualified process. Acceptance of a Certificate of Analysis, plus one identity test, should be acceptable where the vendor's reliability has been verified and where it has been established that the Certificate Analysis is based on appropriate testing by the vendor.
(h) You must use an appropriate test or examination to determine whether your specifications are met. An appropriate test is one that is a scientifically valid analytical method.	Need definition for "scientifically valid." See CRN suggestion in section on definitions.
(i) You must: (1) Establish corrective action plans for use when an established specification is not met; (2) Review the results of the monitoring required by this section and conduct a material review of any component, dietary ingredient, dietary supplement, packaging or label for which you establish a specification that is not met, or any unanticipated occurrence that adulterates or could result in adulteration of the component, dietary ingredient, dietary supplement, packaging, or label; and	Written procedures should be established and followed for reprocessing batches or start-up materials that do not conform to specifications.

(3) Make a material disposition decision for any component, dietary ingredient, dietary supplement, packaging, or label: (i) If a component, dietary ingredient, dietary supplement, packaging, or label fails to meet specifications; (ii) If any step established in the master manufacturing record is not completed; (iii) If there is any unanticipated occurrence during the manufacturing operations that adulterates or may lead to adulteration of the component, dietary ingredient, dietary supplement, packaging, or label; (iv) If calibration of an instrument, or control suggests a problem that may have caused batches of, a dietary ingredient or dietary supplement to become adulterated; or (v) If a dietary ingredient or dietary supplement is returned.	
(4) For any deviation, or unanticipated occurrence which resulted in or could lead to adulteration of the component, dietary ingredient, dietary supplement, packaging, or label (i) You must reject the component, dietary ingredient, dietary supplement, packaging, or label unless the quality control unit determines that in-process adjustments are possible to correct the deviation or occurrence; (ii) You must not reprocess a rejected component, dietary ingredient, or dietary supplement unless approved by the quality control unit; and (iii) You must not reprocess any component, dietary ingredient or dietary supplement if it is rejected because of contamination with microorganisms or other contaminants, such as heavy metals;	Good to give QC the authority to determine whether adjustments are possible to correct a deviation. Same principle should be applied to reprocessing and returns. Should allow reprocessing if there is a scientifically valid procedure for removing the contaminant.
(5) Have your quality control unit review and approve any material review and disposition decision described in paragraphs (i) (2) and (i) (3) of this section.	
(j) The person who conducts the material review and makes the disposition decision must, at the time of performance, document every material review and disposition decision in paragraph (i) of this section. The documentation must be included in the appropriate batch production record and must: (1) Identify the specific deviation from the specification or the unanticipated occurrence; (2) Describe your investigation into the cause of the	

deviation from the specification or the unanticipated occurrence; (3) Evaluate whether or not the deviation from the specification or unanticipated occurrence has resulted in or could lead to adulteration; (4) Identify the action(s) taken to correct and prevent a recurrence of the deviation or the unanticipated occurrence; and (5) Discuss what you did with the component, dietary ingredient, dietary supplement, packaging, or label.	
(k) You must test or examine components, dietary ingredients, and dietary supplements for those types of contamination that may adulterate or may lead to adulteration. You must use an appropriate scientifically valid method for the test or examination. The types of contamination include, but are not limited to, the following: (1) Filth, insects, or other extraneous material, (2) Microorganisms; and (3) Toxic substances.	Written procedures should be established and followed for describing the tests or examinations needed to assure purity, composition, and quality of the finished product. Also, it should be recognized that tests performed by suppliers may be accepted as equivalent to testing by any qualified laboratory, provided the reliability of the vendor has been verified and the vendor has supplied a certificate of analysis based on actual testing of the lot of materials.
(l) Tests in accordance with this section must include at least, one of the following: (1) Gross organoleptic analysis; (2) Microscopic analysis; (3) Chemical analysis; or (4) Other appropriate test.	
(m) You must record results of all testing and examinations performed in accordance with this section. If a test or examination is performed on a batch production you must record the test or examination result in the batch production record in accordance with § 111.50(c) (10). Your records must document whether the testing and examination demonstrates that specifications are met.	
(n) For any specification that is not met, you must conduct a material review and disposition decision under paragraph (i) of this section.	
(o) You must make and retain records, in accordance with § 111.125, to ensure that you follow the requirements of this section. The records must include, but are not limited to:	

(1) The specifications established; (2) The actual results obtained during the monitoring operation; (3) Any deviation from specifications and any unanticipated occurrences; (4) Any corrective actions taken; (5) The disposition decisions and follow-up; and (6) The identity of the individual qualified by training and experience who investigated any deviation from specifications) or unanticipated occurrence and the identity of the individual from the quality control unit who reviewed the results of that investigation.	
	ADD provisions relating to expiration dating: (1) Dietary supplements should bear an expiration date (or shelf life date) when needed to support quantitative claims made in labeling. Such date shall be supported by data and rationale to reasonably assure that the product meets established specifications at the expiration date. (2) Appropriate accelerated stability studies or data from similar product formulations may be used for an initial determination of shelf life. Product shelf life shall be confirmed and may be extended on the basis of real time studies on product stored under labeled storage conditions.

GMP PROPOSAL	CRN COMMENTS
§ 111.37 What requirements apply to quality control? (a) You must use a quality control unit to ensure that your manufacturing, packaging, label, and holding operations in the production of dietary ingredients and dietary supplements are performed in a manner that prevents adulteration and misbranding, including ensuring that dietary ingredients and dietary supplements meet specifications for identity, purity, quality, strength, and composition.	This section should refer to a quality control function rather than implying that a separate unit is necessarily required. For example: "You must have and utilize a quality control function to ensure that.....(etc)."
(b) Your quality control unit must do the following: (1) Approve or reject all processes, specifications, controls, tests, and examinations, and deviations from or modifications to them, that may affect the identity, purity, quality, strength, and composition of a dietary ingredient or dietary supplement; (2) Determine whether all components, dietary ingredients dietary supplements, packaging, and labels conform to specifications; (3) Approve or reject all components, dietary ingredients, dietary supplements, packaging and labels; (4) Review and approve all master manufacturing records and all modifications to the master manufacturing records; (5) Review and approve all batch production-related records which include, but are not limited to, cross referencing receiving and batch production records, approval of a material review and disposition decision, approval for reprocessing, and reject all components, dietary ingredients packaging, and labels; approve all master manufacturing records and the master manufacturing records; approval for releasing for distribution; (6) Review and approve all processes for calibrating instruments or controls; (7) Review all records for calibration of instruments, apparatus, gauges, and recording devices; (8) Review all records for equipment calibrations, inspections, and checks; (9) Review and approve all laboratory control processes, and testing results; (10) Review and approve all packaging and label records which include, but are not limited to, cross-referencing receiving and batch production records, approval for repackaging and relabeling, and	

approval for releasing for distribution;	
(11) Collect representative samples of: (i) Each shipment lot of components, dietary ingredients, dietary supplements, packaging, and labels received to determine whether the component, dietary ingredient, dietary supplement, packaging, or labels meet specifications; (ii) In process materials at points, steps, or stages, in the manufacturing process as specified in the, master manufacturing record where control is necessary to ensure the identity, purity, quality, strength, and composition of dietary ingredients or dietary supplements; (iii) Each batch of dietary ingredient or dietary supplement manufactured to determine, before releasing for distribution, whether the dietary ingredient or dietary supplement meets its specifications for identity, purity, quality, strength, and composition; and (iv) Each batch of packaged and labeled dietary ingredients or dietary supplements to determine that you used the packaging specified in the master manufacturing record and applied the label specified in the master manufacturing record.	Reserve samples of in-process materials are not commonly retained, and the cost of this additional requirement is not included in the economic analysis. In-process materials are not in finished form and are not presumed to be stable in their in-process form. Also, there are issues of storage, safety, and stability that would have a direct impact on the ability and need to retain in-process samples. There should not be a requirement to retain in-process samples.
(12) Keep the reserve samples for 3 years from the date of manufacture for use in appropriate investigations including, but not limited to, consumer complaint investigations to determine, for example, whether the dietary ingredient or dietary supplement associated with a consumer complaint failed to meet any of its specifications for identity, purity, quality, strength, and composition. The reserve samples must: (i) Be identified with the batch or lot number; and (ii) Consist of at least twice the quantity necessary for tests.	Retention time for reserve samples of finished product should be reasonably related to the shelf life of the product. CRN suggests a retention time of 3 years after the date of manufacture or 1 year after the end of the shelf life (expiration date).
(13) Perform appropriate tests and examinations of: (i) Components, dietary ingredients, dietary supplements, packaging, and labels received to ensure that they meet specifications; (ii) Dietary ingredient and dietary supplement batch production at points, steps, or stages identified in the master manufacturing record where control is necessary to prevent adulteration;	

(iii) Dietary ingredients and dietary supplements that you manufacture to ensure that they meet specifications; and (iv) Packaged and labeled dietary ingredients and dietary supplements to ensure that you used the packaging specified in the master manufacturing record and you applied the label specified in the master manufacturing record.	
(14) Review and approve all material review and disposition decisions; and	
(15) Approve the reprocessing or distribution of returned dietary ingredients or dietary supplements.	
(c) Your quality control unit must establish and maintain documentation at the time of performance that it performed the review, approval, or rejection requirements of this section by recording the following: (1) Date the required review, approval, or rejection was performed; and (2) Signature of the person performing the requirement.	
(d) You must keep quality control records in accordance with § 111.125.	

GMP PROPOSAL	CRN COMMENTS
§ 111.40 What requirements apply to components, dietary ingredients, dietary supplements, packaging, and labels you receive? (a) For components, dietary ingredients, or dietary supplements you receive, you must: (1) Visually examine each container or grouping of containers in a shipment for appropriate content label, container, damage, or broken seals to determine whether the container condition has resulted in contamination or deterioration of, the, components, dietary ingredients, or dietary supplement;	ADD: Written procedures should be established and followed for the receipt, identification, examination, handling, sampling, testing, and approval or rejection of raw materials. NOTE: It should be noted that quality requirements for received dietary ingredients and other components should apply equally to materials received from foreign suppliers as to materials received from domestic suppliers. There is potential for domestic suppliers to be disadvantaged, if foreign suppliers are not held to equally high standards.
(2) Visually examine the supplier's invoice, guarantee, or certification to ensure that the components, dietary ingredients, or dietary supplements are consistent with your purchase order and perform testing, as needed, to determine whether specifications are met.	Allows reliance on C of A for ensuring received materials are consistent with purchase order, but requires testing for meeting specifications. Need to describe conditions under which a verified C of A can be relied upon instead of re-testing. See separate CRN comments on process controls.
(3) Quarantine components, dietary ingredients, or dietary supplements until your quality control unit reviews the suppliers invoice, guarantee, or certification and performs testing, as needed, of a representative sample to determine that specifications are met. If specifications are not met, you must conduct a material review and make a disposition decision. Your quality control unit must approve and release the components, dietary ingredients, and dietary supplements from quarantine before you use them;	Supplier comment: Not feasible to quarantine incoming material in a continuous extraction and purification operation, such as one that could be built adjacent to a soy crushing or vegetable oil refinery to receive a continuous side stream flow from that operation. In such operations, quarantine and QC approval occurs later in the process after the material has been isolated and concentrated in a stable matrix suitable for holding. CRN has recommended that this GMP rule apply only to finished product manufacturers, but if it applies to suppliers, then consideration must be given to the concern expressed in this section.

(4) Identify each lot of components, dietary ingredients, or dietary supplements in a shipment in a manner that allows you to trace the shipment to the supplier, the date received, the name of the component or dietary supplement, and the status (e.g., quarantined, approved, or rejected) and to trace the shipment lot to the dietary ingredient or dietary supplement manufactured and distributed. You must use this unique identifier whenever you record the disposition of each shipment lot received; and	
(5) Hold components, dietary ingredients, or dietary supplements under conditions that will protect against contamination, deterioration, and avoid mixups.	
(b) For packaging and labels you receive, you must: (1) Visually examine each container or grouping of containers in a shipment for appropriate content label, container damage, or broken seals to determine whether the container condition has resulted in contamination or deterioration of the packaging and labels; (2) Quarantine packaging and labels until your quality control unit tests or examines a representative sample to determine that specifications are met. You must conduct at least a visual identification on the containers and closures. If specifications are not met, you must conduct a material review and make a disposition decision. Your quality control unit must approve and release packaging and labels from quarantine before you use them; (3) Identify each shipment lot of packaging and labels in a manner that allows you to trace the shipment lot to the supplier, the date received, the name of the packaging and label and the status (e.g., quarantined, approved, or rejected) and to trace the shipment lot to the dietary ingredient or dietary supplement manufactured and distributed. You must use this unique identifier whenever you record the disposition of each shipment lot received; and (4) Hold packaging and labels under conditions that will protect against contamination, deterioration, and avoid mixups.	ADD: Written procedures must be established and followed for receipt, storage, handling, sampling, examination and testing if necessary of labeling and packaging materials. Instead of "quality control unit," refer to "persons exercising your quality control function."
(c) (1) The person who performs the component, dietary ingredient, dietary supplement, packaging, or label requirements of this section must document, at the time of performance, that the requirements were followed. The documentation must include, but not be limited to: (i) The date that the components, dietary ingredients, dietary supplements, packaging, or	

labels were received; (ii) The signature of the person performing the requirement; (iii) Any test results; and (iv) Any material review and disposition decision you conducted in accordance with §111.35(i) and disposition of any rejected material under S 111.74. (2) You must keep component, dietary supplement, packaging, and label receiving records in accordance with § 111.125.	

GMP PROPOSAL	CRN COMMENTS
§ 111.45 What requirements apply to establishing a master manufacturing record? (a) You must prepare and follow a written master manufacturing record for each type of dietary ingredient or dietary supplement that you manufacture and for each batch size to ensure uniformity from batch to batch. The master manufacturing record must: (1) Identify specifications for the points, steps, or stages in the manufacturing process where control is necessary to prevent adulteration; and (2) Establish controls and procedures to ensure that each batch of dietary ingredient or dietary supplement manufactured meets those specifications.	Instead of "uniformity", goal should be to "ensure that specifications are met from batch to batch."
(b) The master manufacturing record must include the following information: (1) The name of the dietary ingredient or dietary supplement to be manufactured and the strength, concentration, weight, or measure of each dietary ingredient for each batch size;	
(2) A complete list of components to be used;	
(3) An accurate statement of the weight or measure of each component to be used;	
(4) The identity and, weight or measure of each dietary ingredient that will be declared on the Supplement Facts label and the identity of each ingredient that will be declared on the ingredients list of the dietary supplement in compliance with section 403(s) of the Federal Food, Drug, and Cosmetic Act;	
(5) A statement that explains any intentional excess amount of a dietary ingredient;	
(6) A statement of theoretical yield of a manufactured dietary ingredient or dietary supplement expected at each point, step, or stage of the manufacturing process where control is needed to prevent adulteration, and the expected yield when you finish manufacturing the dietary ingredient or dietary supplement, including the maximum and minimum percentages of theoretical yield beyond which a deviation investigation of a batch is performed and material review is conducted and disposition decision is made;	Supplier comments: Accurate yield information is irrelevant for quality control in continuous operations where a component may be present as a dilute constituent in a complex matrix of very large volume. In some instances, 5000 bushels of an agricultural commodity is needed to produce 1 kg of product intended as a dietary ingredient. THUS: section should be modified to exclude continuous processes, suppliers of dietary ingredients are to be covered by this rule. CRN has

	urged that the rule apply only to manufacturers of finished products.
(7) A description of packaging and a copy of the label to be used; and	
(8) Written instructions including, but not limited to, the following: (i) Specifications for each point, step, or stage in manufacturing the dietary ingredient or dietary supplement necessary to prevent adulteration; (ii) Sampling and testing procedures; (iii) Specific actions necessary to perform and verify points, steps, or stages, necessary to meet specifications and otherwise prevent adulteration, including, but not limited to, one person weighing or measuring a component and another person verifying the weight or measure and one person adding the component and another person verifying the addition; (iv) Special notations and precautions to be followed; and (v) Corrective action plans for use when a specification is not met.	
(c) You must have the quality control unit review and approve each master manufacturing record and any modifications to a master manufacturing record.	
(d) You must keep master manufacturing records in accordance with § 111.125.	

GMP PROPOSAL	CRN COMMENTS
§ 111.50 What requirements apply to establishing a batch production record? (a) You must prepare a batch production record every time you manufacture a batch of a dietary ingredient or dietary supplement and the batch production record must include complete information relating to the production and control of each batch.	
(b) Your batch production record must accurately follow the appropriate master manufacturing record and you must perform each step in producing the batch. (c) The batch production record must include, but is not limited to, the following information:	
(1) The batch, lot, or control number,	
(2) Documentation at the time of performance, showing the date on which each step of the master manufacturing record was performed, and the initials of the persons performing each step, including but not limited to: (i) The person responsible for weighing or measuring each component used in the batch; and (ii) The person responsible for adding the component to the batch.	This is not realistic for continuous operations, but seems to be written for batch processes and should only be applicable to finished dietary supplement manufacturers.
(3) The identity of equipment and processing lines used in producing the batch;	
4) The date and time of the maintenance, cleaning, and sanitizing of the equipment and processing lines used in producing the batch;	Equipment cleaning records are typically retained in an equipment log and should not be included in the batch record.
(5) The shipment lot unique identifier of each component, dietary ingredient, dietary supplement, packaging, and label used;	For suppliers of dietary ingredients, this would be difficult to comply with for continuous processes. The use of "where applicable" may be appropriate, if FDA elects to make the GMPs applicable to suppliers of dietary ingredients. CRN recommends that only finished product manufacturers be covered by the rule.
(6) The identity and weight or measure of each component used;	See comment on immediately previous section, above.

(7) The initials at the time of performance or at the completion of the batch of the person responsible for verifying the weight or measure of each component used in the batch;	
(8) The initials at the time of performance or at the completion of the batch of the person responsible for verifying the addition of components to the batch;	
(9) A statement of the actual yield and a statement of the percentage of theoretical yield at appropriate phases of processing;	Suppliers comments: yield information is irrelevant for quality control in continuous operations where components intended for eventual use as dietary ingredients may be present as dilute constituents in a complex matrix of very large volume. Section should be modified to exclude continuous processes, if suppliers of dietary ingredients are to be covered by this rule. CRN has recommended that the rule apply only to finished product manufacturers.
(10) The actual test results for any testing performed during the batch production;	Test results are typically retained in lab records and should not be included in detail in the batch record. Also, the word "actual" should be eliminated. In electronic systems or when testing is done by an outside laboratory, the original (actual) record of the test results may not be available to the manufacturer. For test results obtained in-house, original records are typically kept as part of master laboratory records but may be cross-referenced in batch records.
(11) Documentation that the dietary ingredient and dietary supplement meets specifications;	
(12) Copies of all container labels used and the results of examinations conducted during the label operation to ensure that the containers have the correct label;	
(13) Any documented material review and disposition decision in accordance with § 111.35(j); and	
(14) Signature of the quality control unit to document batch production record review and any approval for reprocessing or repackaging.	

(d) The quality control unit must review in accordance with § 111.37 (b) (5) the batch production record established in paragraph (c) of this section. (1) If a batch deviates from the master manufacturing record, including any deviation from specifications, the quality control unit must conduct a material review and make a disposition decision and record any decision in the batch production record. (2) The quality control unit must not approve and release for distribution any batch of dietary ingredient or dietary supplement that does not meet all specifications.	QC must have authority to decide whether to release a batch if there is only a minor deviation from specs (for a measure such as tablet thickness, for example) that is not significant to overall product quality. Thus, subparagraph (2) should be omitted. The previous subparagraph already requires review and a disposition decision, and the following paragraph already requires documentation of the outcome of the review.
(e) The quality control unit must document in accordance with § 111.37(c) the review performed in accordance with paragraph (d) of this section and it must be documented at the time of performance. The review and documentation must include, but is not limited to, the following: (1) Review of component, dietary ingredient, and dietary supplement receiving records including review of testing and examination results; (2) Identification of any deviation from the master manufacturing record that may have caused a batch or any of its components to fail to meet specifications identified in the master production record; (3) Records of investigations, conclusions, and corrective actions performed in accordance with paragraph (d) of this section; and (4) The identity of the person qualified by training and experience who performed the investigation in accordance with paragraph (d) of this section.	
(f) You must not reprocess a batch that deviates from the master manufacturing record unless approved by the quality control unit. You must not reprocess a dietary ingredient or dietary supplement if it is rejected because of contamination with microorganisms of public health significance or other contaminants, such as heavy metals;	QC should have authority to decide whether reprocessing is appropriate. Reprocessing should be allowed if there is a valid procedure for correcting the defect.
(g) Any batch of dietary ingredient or dietary supplement that is reprocessed must meet all specifications for the batch of dietary ingredient or dietary supplement and be evaluated and approved	

dietary supplement and be evaluated and approved by the quality control unit before releasing for distribution. The results of the reevaluation by the quality control unit must be documented in the batch production record; and	
(h) You must collect representative reserve samples of each batch of dietary ingredient or dietary supplement and keep the reserve samples for 3 years from the date of manufacture for use in appropriate investigations including, but not limited to, consumer complaint investigations to determine whether, for example, the dietary ingredient or dietary supplement associated with a consumer complaint failed to meet any of its specifications for identity, purity, quality, strength, and composition.	This requirement must be modified to take the shelf life of the product into consideration. Especially if manufacturers of dietary ingredients are to be covered by the rule, then it must be recognized that many dietary ingredients do not have a shelf life as long as 3 years. It makes no sense to put a sample into reserve for 3 years if it has a shelf life of only 1 year. Any analysis performed on such a sample would be meaningless. CRN recommends that the rule apply only to finished product manufacturers, but even so the retention requirement should be related to shelf life. One option is to require retention for 3 years from the date of manufacture or for one year beyond the expiration date.
(i) You must keep batch production records in accordance with § 111.125.	

GMP PROPOSAL	CRN COMMENTS
§ 111 60 What requirements apply to laboratory operations? (a) You must use adequate laboratory facilities to perform whatever testing and examinations are necessary to determine that components, dietary ingredients, and dietary supplements received meet specifications; that specifications are met during in-process, as specified in the master manufacturing record; and that dietary ingredients and dietary supplements manufactured meet specifications.	
(b)(I) You must establish and follow laboratory control processes that are approved by the quality control unit. Laboratory control processes must include, but are not limited to, the following: (i) Use of criteria for selecting appropriate examination and testing methods; (ii) Use of criteria for establishing appropriate specifications; and (iii) Use of sampling plans for obtaining representative samples of: (A) Components, dietary ingredients, and dietary supplements received to determine. whether specifications are met; (B) In-process materials during the batch manufacturing when testing or examination is required in the master manufacturing record; (C) Each batch of dietary ingredient or dietary supplement manufactured to determine that the, dietary ingredient or dietary supplement meets specifications; (D) Packaging and labels received to determine that he materials meet specifications; and (E) Each batch of packaged and labeled dietary ingredients or dietary supplements to ensure that the label specified in the master manufacturing record has been applied. (iv) Use of criteria for selecting standard reference materials used in performing tests and examinations; (v) Use of appropriate test method validations; and (vi) Use of test methods and, examinations in accordance with established criteria, (2) The person who conducts thee testing and examination at the time of performance, must	

document that laboratory examination results. (3) You must keep laboratory examination and testing records in accordance with § 111.125.	
(c) You must verify that the laboratory examination and testing methodologies are appropriate for their intended use.	
(d) You must identify and use the appropriate validated testing method for each established specification for which testing is required to determine whether the specification is met.	Should refer to "scientifically valid" method rather than "validated" method.

GMP PROPOSAL	CRN COMMENTS
§ 111.65 What requirements apply to manufacturing operations? (a) You must design or select manufacturing processes to ensure that dietary ingredient or dietary specifications are consistently achieved.	
(b) You must conduct all manufacturing operations in accordance with adequate sanitation principles.	
(c) You must take all the necessary precautions during the manufacture of a dietary ingredient or dietary supplement to prevent contamination of components, dietary ingredients, or dietary supplements. These precautions include, but are not limited to:	
(1) Performing manufacturing operations under conditions and controls that protect against the potential for growth of microorganisms and the potential for contamination;	This language does not take into consideration some processes that involve fermentation. It also does not take into account that some processes may include a "proven kill step" for removing undesirable microorganisms. As an alternative, consider the language of the food GMP in 110.80 (b)(2): "Performing manufacturing operations under such conditions and controls as are necessary to minimize the potential for the growth of **undesirable** microorganisms, or for the contamination of the product;"
(2) Washing or cleaning components that contain soil or other contaminants;	
(3) Using water that meets the National Primary Drinking Water regulations or, where necessary, higher sanitary quality and that complies with all applicable Federal, State, and local regulations for water that is used in the manufacturing operation. If you reuse water that was used to wash components to remove soil or contaminants, the reused water must be safe and of adequate sanitary quality so that it does not become a source of contamination;	
(4) Performing chemical, microbiological, or other testing as necessary to prevent the use of contaminated components, dietary ingredients, and dietary supplements;	
(5) Sterilizing, pasteurizing, freezing, refrigerating controlling hydrogen-ion concentration (pH), controlling humidity, controlling water activity (A_w), or	

using any other effective means to remove, destroy, or prevent the growth of microorganisms and prevent decomposition;	
(6) Holding components, dietary ingredients, and dietary supplements that can support the rapid growth of microorganisms of public health significance in a manner that prevents the components, dietary ingredients, and dietary supplements from becoming adulterated;	
(7) Identifying and holding any components, dietary ingredients, or dietary supplements, for which a material review and disposition decision is required, in a manner that protects the components, dietary ingredients, or dietary supplements against contamination and mixups;	
(8) Performing mechanical manufacturing steps (such as cutting, sorting, inspecting, shredding, drying, grinding, blending, and sifting) by any effective means to protect the dietary ingredients or dietary supplements against contamination. Such steps must include consideration of: (i) Cleaning and sanitizing contact surfaces; (ii) Using temperature controls; and (iii) Using time controls.	
(9) Using effective measures to protect against the inclusion of metal or other foreign material in components, dietary ingredients, or dietary supplements. Compliance with this requirement must include consideration of the use of: (i) Filters or strainers; (ii) Traps; (iii) Magnets; or (iv) Electronic metal detectors.	
(10) Segregating and identifying all containers for a specific batch of dietary ingredients or dietary supplements to identify their contents and, where necessary, the phase of manufacturing; and (11) Identifying all processing lines and major equipment used during manufacturing to indicate their contents including the name of the dietary ingredient or dietary supplement and the specific batch or lot number and, when necessary, the phase of manufacturing.	Supplier comments: In continuous bulk operations for manufacturing dietary ingredients, the batch or lot number often is not identified until after the materials has been blended and moved into a storage bin. Section should be modified to exclude continuous processes, if suppliers of dietary ingredients are to be covered by the rule. CRN has urged that only finished product manufacturers be covered.

(d) You must conduct a material review and make a disposition decision in accordance with § 111.35(i) for any component, dietary ingredient, or dietary supplement that fails to meet specifications or that is or may be adulterated. If the material review and disposition decision allows you to reprocess the component, dietary ingredient, or dietary supplement, you must retest or reexamine the component, dietary ingredient, or dietary supplement to ensure that it meets specifications and is approved by the quality control unit.	