



Council for Responsible Nutrition

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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: ECONOMIC IMPACT OF THE PROPOSED RULE

This is the sixth in a series of comments submitted by the Council for Responsible Nutrition regarding the above-mentioned proposed rule. These comments will address the economic impact of the proposed rule.

CRN requested and was granted additional time for submission of these comments, in order to permit us time to evaluate new information 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. Using only the information published in the *Federal Register*, we were unable to reproduce FDA's calculations and therefore prepare our own fully comparable estimates.

In the preparation of these comments, we have relied heavily upon the expertise of the firm of Glassman-Oliver Economic Consultants, Inc., specifically the analytical talents of Neil Grossman, Senior Research Analyst, and the analysis and policy guidance of Stephen Stockum, Ph.D., Senior Vice President at Glassman-Oliver. Dr. Stockum was formerly a staff economist and economic advisor at the Federal Trade Commission.

While these comments will suggest markedly different cost and benefit estimates than those put forth by FDA in the economic analysis of the proposed rule, CRN wishes to recognize the massive achievement of the agency in grappling with this task, especially in the absence of sufficient information regarding key variables. We believe the agency's overall effort and the industry's attempt to respond would have been improved by more interaction throughout this process. We again urge FDA to consider a series of workshops to provide for further discussion and analysis of the issues, prior to finalization of a GMP rule. This regulation will markedly affect the ability of companies to produce quality products while controlling costs, and it deserves further effort on the part of all stakeholders to fully comprehend the available alternatives.

In this analysis, CRN has based all of its tables and analysis on the cost and benefit information provided in the worksheets we obtained from FDA in our FOIA request. In some cases, the spreadsheet values differ from the amounts shown in the *Federal Register* publication.

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On August 11, 2003, CRN submitted four separate comments on the purpose and scope of the rule, the importance of process control, legal aspects of the proposal, and section-by-section recommendations. On July 8, 2003, CRN submitted the first comment in this series, 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. **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.

TESTING COSTS

CRN believes FDA has grossly underestimated the costs of compliance with the proposed rule, especially the cost of testing every component of every batch. As pointed out in our earlier comments, we believe the exhaustive testing requirement proposed by the agency would be excessively costly for firms of all sizes and is unnecessary in order to ensure quality once a company has established a well-controlled processing system. While some level of finished product testing is always required, a properly controlled system justifies a reduced schedule of testing of the final product. This is consistent with well-established quality assurance theory and practice. Putting an excessive amount of resources into testing the finished product does not in fact constitute "good manufacturing practice." FDA appears to recognize this fact in several places in the

preamble where it is noted that manufacturers may choose to conduct more testing of incoming ingredients and of in-process materials rather than wait until the end of the process to detect possible errors or defects. Building quality into the product from the very beginning should not be an option -- it should be the primary focus of the GMPs. We believe the current proposal fails to capture the essence of good manufacturing practices, and thus does a disservice to firms of all sizes.

CRN's member companies are committed to producing quality products and are the leading manufacturers of national brands and private label dietary supplements. The practices observed by our member companies define "current good manufacturing practices." These companies might reasonably have expected that they would already be in compliance with any reasonable rule, but such is not the case with respect to this particular proposed rule.

For purposes of computation of estimated costs, **CRN accepts FDA's assumptions regarding the following variables:**

- the number of control points,
- the average number of ingredients per product,
- the average cost per test,
- and the percentage distribution of firms across the size range, from large to small to very small.

We note, however, that the range of values for the number of ingredients per product and the cost of individual tests is large. For companies whose products contain a large number of ingredients and for some ingredients that are very expensive to test, much larger costs will be incurred.

CRN believes FDA's assumptions are grossly inaccurate for some other variables, including:

- Number of batches produced by large firms;
- Number of tests per product required by the proposed rule; and
- Percentage of required tests currently being performed.

The mischaracterization of these three variables causes FDA to severely understate the industry cost of compliance with the agency's proposed testing requirements. **CRN's estimate of testing costs is 10 times as high as FDA's**, when based on revised estimates for these three variables derived from the experience of our large member companies. CRN's estimate for finished product testing is \$245 million, compared to FDA's estimate of \$24 million. Further discussion of each variable appears below. For reference, **Table 1** reproduces FDA's estimate of testing costs, showing the calculations and assumptions upon which the estimate is based.

FDA's assumptions lead to an estimated total testing cost of about \$24 million for all firms. Only \$702,470 of this (about 3% of the total) represents additional testing that

may be required for large firms. FDA's estimates do not include any in-process testing, which the rule would clearly require. In particular, the agency's analysis suggests that an average of 2.5 in-process tests per batch are likely to be needed, at critical control points. Also, FDA's spreadsheets provided in response to our FOIA request show that additional testing may be needed for an average of 2.5 components of herbal products and 7.5 components of vitamin products. FDA's estimates do not include costs for these tests, and these numbers do not clearly match any of the estimates regarding component testing or defect testing provided in the text of the *Federal Register* publication.

NUMBER OF BATCHES PRODUCED PER YEAR

FDA estimates that large firms produce an average of 309 batches per year. This estimate is implausibly low and suggests that the FDA survey did not achieve a representative sample, at least for large firms (14 responses). Moreover, it is illogical that the distribution of the number of batches per firm is 309, 554, and 223, for large, small and very small firms, respectively. Logic would suggest that large firms would be expected to produce many more batches than small firms. This is further supported by industry sales data. FDA estimates that about 6% of firms in this industry are "large," and data from *Nutrition Business Journal* indicate that the top 6% of firms produce 79% of the industry sales volume through mass market and natural food channels, not including direct sellers and ingredient suppliers. The number of batches produced by such firms should also be large. According to the FDA estimate, large firms would account for less than 5% of the total number of batches produced. CRN does not believe this is a credible estimate.

CRN surveyed its member companies in an attempt to provide FDA with a more appropriate basis for its calculations. Many companies were reluctant to provide information directly relating to volume of production, even on a confidential basis, but seven large firms did provide relevant detail. Among those seven leading firms, the **number of batches of finished products manufactured per year is in the range of 2000 to 6,700, with an average of 3,915.**

If the CRN figures and the FDA estimates are taken to represent the upper range and the lower range of the universe of "large" firms, then averaging these two values will provide a more realistic estimate of the number of batches of dietary supplements produced per year by large companies in the dietary supplement industry. As shown in **Table 2**, we estimate the number of batches produced by large firms to be 2,112 per year, accounting for 25% of all the batches of finished product manufactured by the industry -- a more reasonable estimate than FDA's value of five percent, but still possibly low.

Table 3 shows the effect on the cost estimates of adjusting the number of batches produced by large firms, by averaging the values obtained from FDA's survey data and CRN's survey data. Applying FDA's cost calculations to this larger number of batches increases the estimate of costs for large firms by almost 6-fold.

NUMBER OF TESTS REQUIRED PER BATCH

FDA's cost estimates are based on the assumption that only two ingredient tests are required per finished vitamin product and only 2.4 ingredient tests are required per finished herbal product. CRN questions these estimates. CRN's member companies indicate that a typical multivitamin with minerals will require at least 8 separate tests and could require as many as 16 separate assays, depending on the specific nutrients present. Although some test methodologies are capable of analyzing multiple nutrients at one time, others require separate analysis, and combined analysis is not the approved AOAC methodology. In addition to tests for dietary ingredients, testing will be required for other components of dietary supplements, for potential defects including heavy metals and microbiological quality when appropriate, and for physical specifications including hardness, thickness, disintegration time, and in some cases dissolution time. Many dietary supplements contain as many non-dietary ingredients as dietary ingredients.

One large member company indicated that for a typical multivitamin product with minerals, 27 separate tests would need to be performed in order to analyze the product for all the essential vitamins and minerals plus physical and microbiological characteristics. This is true even though some tests are capable of detecting or quantifying multiple water soluble B vitamins, fat soluble vitamins, or minerals.

In later tables, especially in **Table 8**, CRN assumes that an average of 6 tests would be required for vitamin and mineral dietary ingredients (recognizing that many products contain only one or a few nutrients), and an average of 2.4 tests would be required for herbal dietary ingredients. Herbal products would also require an average of one test for solvents. In addition, for all types of products, an average of 3 tests would be required for other components, plus 2.5 in-process tests, plus 3 tests of the final batch for quality characteristics including potential defects, purity, or strength. This amounts to an average testing load of 14.5 tests for vitamin and mineral products or 11.9 tests for herbal products.

NUMBER OF TESTS ALREADY BEING PERFORMED

The FDA survey asked whether firms were currently testing products. FDA indicates that 84% of large firms do conduct tests and that 90% of the batches produced by those firms are tested. Multiplying 84% by 90%, FDA concludes that 76% of the batches produced by large firms are already being tested sufficiently and that no additional costs for those batches will be incurred. Using the same approach for small and very small firms, FDA concludes that 58% and 34% of the batches produced by such firms, respectively, are already being tested and presumably will require no additional testing. CRN does not believe any of these assertions are correct.

When FDA says 84% of large firms do conduct tests, citing the survey, the agency combines the 73% that said they do testing with 11% who said the question was not applicable or failed to answer the question at all. CRN believes it would be more

appropriate to count these 11% as firms that do not test, and to count as positive responses only those firms that actually responded “yes” to the question. Multiplying this value (73%) by the 90% of products tested, CRN calculates that large firms test 66% of the finished product, rather than the 76% calculated by FDA. Similarly, we calculate that small and very small firms are currently testing 58% and 28% of finished product, respectively. **Table 4** illustrates the calculations provided by FDA, based on the results of the survey, and those suggested by CRN, based on the same survey.

CRN’s calculations, based on the FDA survey, indicate that 34% of the batches produced by large firms are not currently being tested. This figure is 40% greater than FDA’s estimate of 24% of large firms not already testing finished products, and accordingly the cost of additional testing for large firms would increase by 40%. See **Table 5** for these calculations. The additional testing required for very small firms would also increase. This increase is captured in our summary **Table 8**.

Even large firms that are testing 90% of their products are unlikely to be performing the exhaustive level of testing required by the proposed rule, namely testing every component of every batch of finished product. Thus, a substantial volume of additional testing is likely to be required even for such firms. While leading companies do perform finished-product testing to confirm that their quality procedures are operating effectively, virtually no company tests every component of every batch. To do so would be prohibitively expensive as well as unnecessary, since a well-controlled process can reliably ensure quality while enabling a firm to conduct a reduced level of testing. This most commonly includes testing some specifications in every batch and testing other specifications on a periodic basis. We estimate that full compliance with the rule as proposed would require at least 40% more testing than is currently being done on finished batches which are tested, and this of course will increase costs. As shown in **Table 6**, this implies that only 71% of the testing that would be required by the rule is currently being done for finished products. Some leading companies indicated that even a greater percentage of additional testing would be required by the FDA proposal. **Table 7** shows the cost implication of the additional testing requirement for large firms.

Table 8 summarizes CRN’s calculations of additional testing costs that would be required under the rule as currently proposed. We estimate that testing costs for firms of all sizes would be almost \$245 million, compared to FDA’s estimate of \$24 million. This incorporates our earlier estimates of the number of tests required by the proposed rule, including tests for dietary ingredients, other components, tests of quality, purity and strength, in-process tests, and herb solvent tests.

DEVELOPMENT OF ANALYTICAL METHODS

FDA’s economic analysis does not include an estimate for the cost of developing methods of analysis. Methods development has been an important focus of industry effort for a number of years, and such efforts are costly.

The U.S. Pharmacopeia (USP) has for over a hundred and fifty years been developing methods for nutrients and botanicals used for therapeutic purposes and is the recognized authority on analytical methods for drugs. Beginning in 1985, USP launched an initiative to develop quality standards and analytical methods for nutritional supplements (primarily containing vitamins and minerals), and in 1995 that effort was expanded to include botanical dietary supplements. In the process of these activities, it has been recognized that significant methodological challenges exist even with respect to analyzing some nutrients (such as folic acid), let alone with respect to botanical and specialty ingredients. The American Herbal Pharmacopeia has also been compiling botanical monographs that address methods of analysis, among other topics. These ongoing activities emphasize the widespread recognition of the fact that there is a continuing need for methods development in this industry.

Recognizing a need for more industry involvement in method development, the INA/MVP testing initiative was developed, originally under the sponsorship of Industrial Laboratories. The initiative has recently been incorporated into the activities of NSF International, as a feature of NSF's dietary supplement certification program. With substantial industry involvement, laboratory development costs were kept to a minimum but still amounted to \$15,000 to \$20,000 for each of 22 methods developed so far in this program, with two or three labs cooperating in the validation of each method.

AOAC is the recognized authority for analytical methodologies for foods. Numerous AOAC methods currently exist for vitamins and minerals, but not all of these have been validated for the types of matrices typical of dietary supplement products. The number of AOAC methods that currently exist for botanical ingredients is small. Recognizing the need for additional methods development, Congress recently appropriated funds for the Office of Dietary Supplements (ODS) to invest in such activities. ODS has contracted with AOAC to develop 20 new methods over the next five years, and a budget of \$1 million has been allocated to this effort, amounting to an average of \$50,000 per method. The methods to be developed will be single-laboratory-validated methods. They will not be fully validated through multilaboratory testing, as is usual for AOAC methods, although such validation is desirable and may be undertaken at a future time. AOAC has convened a working group of industry and government interested parties to assist in this effort, including the preparation of a priority list of methods to be developed. That priority list currently includes twenty (20) ingredients, and participants indicated at a recent workshop that at least five times this many could be immediately identified, if more resources were available -- and these would cover only the most commonly utilized ingredients, not the full number of ingredients likely in need of method development.

Thus, CRN believes the estimated cost of the proposed rule should include a figure for the investment required to develop scientifically valid methods of analysis for numerous ingredients. At a minimum, we believe this figure should include the cost of 100 methods at a minimum cost of \$20,000 each, or a total of \$2 million. The actual cost of method development is, we believe, more likely to be in the range of \$50,000 for each test, or twice that amount if the method were to be fully validated by multiple

laboratories. Thus, an estimate of \$2 million for method development would be highly conservative.

CAPITAL EXPENSES FOR RENOVATION OF FACILITIES

FDA indicates that the capital costs for physical plant redesign would be about \$50 per square foot, and that establishments might have to renovate 0 to 20 percent of the physical plant, with 10% being the most likely value. Based on FDA's survey results regarding the size of various plants and assuming that 10% of the plant would require renovation, these figures result in costs of over \$89,000 per company for very small firms and more than 260,000 for small and large firms. **Table 9** shows the calculation of these costs, which CRN believes will total over \$600 million for the industry as a whole, as compared to FDA's estimate of \$45 million.

The reason FDA's estimate of capital costs is so low is that the agency applies a reduction factor for which no justification is provided. The reduction factor assumes that only 18% of very small firms, 10% of small firms, and 1% of large firms will actually need any capital improvements to the facility. Based on information provided by our member companies, CRN believes application of the reduction factor is inappropriate, since most firms believe they will in fact need to improve their facilities if the rule is finalized as proposed. Therefore, CRN believes FDA's estimate that most facilities will need to renovate about 10% of their physical plant is approximately accurate and should be included in the cost estimates, without a reduction factor.

One key requirement of the proposed rule that may necessitate modification of facilities is the provision mandating "smooth, hard surfaces" on all floors, walls, and ceilings. There is no precedent for this requirement in food GMPs, and the only precedent we can identify even in drug GMPs is a provision applicable to aseptic processing of some drugs including injectable products. There is no need for smooth, hard surfaces on all ceilings in a manufacturing facility and thus virtually no company will have such surfaces throughout the plant. If FDA persists in this requirement, capital costs will naturally be affected.

EQUIPMENT COSTS

FDA estimates that the cost of new equipment needed to comply with the proposed rule would be zero to \$1000, with \$100 the most likely. The agency assumes these costs would increase as a function of the size of the physical plant and would therefore be three times as great for small companies and 20 times as great for large companies. FDA's total estimated equipment expense is therefore \$100 for very small companies, \$300 for small companies, and \$2,000 for large companies. These estimates are frankly laughable. We found it difficult to identify examples of any equipment relevant to quality assurance that could be purchased at such a low cost. Latex gloves, filter papers, and some glassware fell into this category.

A large company that already has a testing infrastructure but needs to expand its capacity may reasonably expect to incur expenses of about \$240,000. This would cover the addition of two HPLCs at a cost of \$75,000 each, an ICP at a cost of \$50,000, and a GC at a cost of \$40,000. This estimate does not include extra staffing, service agreements and repairs (about 5 to 10% of the cost of equipment), supplies necessary to operate the equipment, and reference standards.

It should be noted that equipment costs may bear especially heavily on very small companies, who may not currently have well-equipped laboratories. Thus, FDA's assumption that costs will be lower for very small companies may be directly contrary to the reality. In fact, very small companies will face larger costs if they need to establish a laboratory and do not currently have a testing infrastructure. The equipment cost alone for a new laboratory is estimated to be approximately \$300,000 for major equipment such as an HPLC, GC, AA/ICP, UV, FTIR, a dissolution apparatus, and equipment needed for performing microbiological tests. In addition, about \$20,000 in basic laboratory equipment and supplies would be needed such as glassware, chemicals, standards, hotplates and stirrers, pH meters, a fume hood, a furnace, and balances.

CONSUMER BENEFITS: REDUCED ILLNESS DUE TO FEWER RECALLS

CRN analyzed the FDA weekly enforcement reports for the decade of the 1990's. The attached **Table 10** shows 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 about 0.3 recalls per year per billion dollars in sales volume (based on a current market size of approximately \$18 billion for dietary supplements and approximately \$500 billion for conventional foods). This illustrates that these two categories of foods have a similar record for product quality and safety, to the extent that recalls are a reflection of these characteristics. (In actual fact, these calculations underestimate the number of recalls of conventional foods, since they include only FDA recalls and do not include recalls of foods regulated by the U.S. Department of Agriculture.) Drugs have a higher rate of recalls, amounting to about 0.7 recalls per billion dollars in sales volume (based on a current market size of approximately \$145 billion). Thus, it is evident that stringent GMPs (such as drug GMPs) do not of themselves result in a dramatically reduced rate of recalls.

FDA's preamble text indicates that there were, on average, 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. **Table 11** shows the number of Class I and Class II recalls of dietary supplements CRN identified from FDA's weekly enforcement reports for the period from 1990 through 1999. We identified only 52 Class I and Class II recalls for dietary supplements during this 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. For example, 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 under our FOIA request, this appears to have been an error. It seems that several lines of information were omitted from FDA's Table 8 and that these 41 Class II EMS recalls actually should have been identified as Class II recalls of dietary supplements with excessive lead content. In CRN's analysis of FDA's weekly enforcement reports, we identified only 11 class II recalls of dietary supplements relating to excessive lead content. (For comparison, we identified 45 class I and class II recalls of conventional foods due to excessive lead content during this same period.) 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.

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 for the period 1990 through 1999, 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, and did the same for the other plantain recalls, 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 should be treated as a single 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.

If the true number of Class I and Class II dietary supplement recalls for the period 1990 through 1999 is 52 as CRN calculates rather than 130 as indicated by FDA, the cost implications of those recalls and thus the benefit of avoiding those illnesses would be

drastically lowered, even if we were to accept FDA's assumptions about the 100-fold relationship between the number of recalls and the number of potential illnesses. In **Table 12** we show the calculation of the weighted average cost of illness due to Class I and Class II recalls, as tabulated by FDA.

In **Table 13** we show FDA's calculation of the cost of illness due to recalls, as compared to the CRN calculation based on the number of recalls we identified from the FDA weekly enforcement reports. The smaller number of recalls naturally leads to a smaller estimate of the annual cost of illness associated with those recalls: \$14 million as compared to FDA's estimate of \$39 million.

FDA cites a reference by Walker for the agency's assumption that each illness due to a recall is a proxy for 100 unreported illnesses. However, the same reference recognizes that under-reporting is less likely for serious illnesses than for minor illnesses. The third column of **Table 13** illustrates the effect of assuming a reporting rate of 10% rather than 1%, at least for the deaths included in the FDA analysis. This assumption would reduce the cost of illness associated with recalls to \$6 million, when applied to the CRN values in column two. When applied to the FDA values in column one, this assumption would also reduce the cost of illness associated with recalls, although this calculation is not shown in the table.

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. The current number of recalls appears to be entirely comparable, per billion dollars in sales, with the number of recalls occurring in the conventional food industry, and CRN believes it would not be realistic to project a very large change as a result of new GMPs. If the expected reduction in recalls is estimated to be 50%, that would halve FDA's estimate of the benefits to be obtained due to fewer illnesses related to recalled products. Based on the ongoing recall experience relating to conventional foods and pharmaceutical products, we believe such an estimate would be more realistic but still perhaps optimistic. **Table 13** shows the effect of a 50% projected reduction in the cost of illness due to recalls, rather than FDA's estimate of a 100% reduction.

CONSUMER BENEFITS: AVOIDANCE OF RARE CATASTROPHIC EVENT

A large fraction of FDA's estimated benefit from the GMP rule is attributable to avoiding rare catastrophic events such as the outbreak of eosinophilia myalgia syndrome (EMS) due to a change in manufacturing on the part of one manufacturer of the amino acid tryptophan. The tryptophan incident occurred in 1989, and FDA uses it to postulate a 30-year cycle of potential catastrophic events due to dietary supplements. Dietary supplements have been a fixture in the American marketplace at least since at least the 1920's, when vitamins first became commercially available as purified components, so a longer periodicity could just as easily be justified. In **Table 14** we suggest a periodicity

of 70 years rather than 30 years, with an accordingly reduced estimate of prorated annual costs of illness.

FDA comments at 68 FR 12232, “The benefits attributable to this proposed rule from preventing a rare catastrophic event are highly uncertain. We do not know if such event would, in the absence of the proposed regulation, ever occur again.”

CRN points out, in addition, that it is highly uncertain whether these or any other GMPs would have prevented the EMS outbreak. The amount of the purported impurity in the tryptophan that was associated with the outbreak was extremely small. No one would have been able to predict that such a small change in the characteristics of the ingredient could have a large effect. Since the identity of the problem component was unknown, no one would have tested for it. Since the quantity of the problem component was so small, it did not adversely impact the acceptability profile of the bulk ingredient, which was said to conform to USP criteria for tryptophan. It is also relevant that some of the tryptophan involved in the outbreak was sold in Europe, where it was solely used in prescription drugs subject to stringent GMPs. A substantial number of the EMS cases identified by the Centers for Disease Control and Prevention (CDC) were associated with the use of such pharmaceutical products. Thus, we believe it is questionable whether improved GMPs (even pharmaceutical GMPs) would have or could have prevented the EMS outbreak.

CONSUMER BENEFITS: REDUCED SEARCH TIME

FDA reasons that increased consumer assurance of quality due to the GMPs could result in a reduction in the time required for consumers to search for nutritional supplements. Accordingly, FDA hypothesizes that the value of the increased assurance of quality resulting from GMPs can be proxied by the value of the reduction in consumer shopping time.

This approach suffers from fundamental analytical flaws as well as weaknesses in the values used for certain critical variables in the computation. Also, FDA’s analysis appears to proceed from the assumption that dietary supplements are not currently covered by any GMPs, which is not the case. Dietary supplements in fact are already covered by food GMPs and CRN’s member companies are subject to inspection by FDA and state field officers, using food GMPs as the standard against which their procedures are evaluated.

To the extent that new dietary supplement GMPs increase consumer confidence in the industry’s products, CRN contends that the primary benefit will result from greater use of beneficial dietary supplements. Increased use of dietary supplements would lead to improved health and resultant savings in health costs. While it is possible that some search cost savings might occur, these savings would be trivial relative to health cost savings.

In order for either of these benefits (savings in health costs or search costs) to occur, consumers must be informed about the GMPs, and must gain confidence that these GMPs will assure product quality. The FDA does not indicate what information will be disseminated to consumers or how it will be disseminated. Indeed, the preamble indicates that the agency would specifically prohibit companies from highlighting their compliance with GMPs in product labeling. It is far from clear that consumers will be broadly informed about these changes in manufacturing standards, or what percentage of those who do learn about the GMPs will interpret the information as indicating higher product quality. Yet the FDA's computation of search cost savings implicitly assumes that all consumers will be informed about the GMPs and will interpret the FDA's action as resulting in increased industry quality. If the benefits contemplated by FDA can only be realized if consumers are educated about the regulatory changes that have occurred, the agency should make efforts to assure that the information reaches consumers appropriately.

FDA's computations regarding search costs do not include a discount factor based on the percentage of consumers who become informed about the regulation and interpret it as intended. While it seems clear that a significant proportion of consumers would not become informed or would not interpret the information appropriately, we do not have information regarding the appropriate discount factor. In any event, the estimated search cost savings are overstated to the degree that no discount factor is applied.

FDA's models multiply the estimated total shopping time by the estimated percent of that time spent "searching" (70%), then multiply the result by the estimated percent of time spent searching for "quality" (20%), then assume that this time spent shopping for "quality" would be reduced by 33% by the GMPs. No reference is offered for either of the first two assumptions (in either the *Federal Register* publication or the FOIA response), and the reference for the third one offers highly limited support. The use of these three variables lends very little statistical confidence to the conclusions drawn by these models. Indeed, FDA notes at the top of 68 FR 12234 that the hypothetical search time reduction is merely a proxy for improved quality, adding, "We anticipate little or no change in aggregate shopping time for dietary supplements."

Consumer attitudes about "quality" (FDA uses this term without any qualifier or definition throughout) clearly include concepts unrelated to the GMPs. For example, a shopper contemplating purchasing a supplement to increase energy may spend a considerable amount of time attempting to assess the relative effectiveness of the numerous products offered. This is a search for product "quality" but not the type of quality addressed by the GMPs.

Consumers currently have only a limited ability to draw inferences about manufacturing quality and thus likely spend very little time performing the futile search endeavor emphasized in the three models. While the GMPs arguably could raise the lower bound of the quality range in this industry, this cannot have much of an effect on a variable that is trivial in the first place.

This is not to say that consumers ignore quality in the dietary supplement industry, only that their quality searches must emphasize variables about which they can logically draw inferences, which largely are ones not affected by the GMPs. One means of assessing quality that consumers may undertake is to look for reputable brand names. In this context the FDA notes (68 FR 12233, with references to E25, E26 and E27) that consumers spend time assessing "the large variation in product quality" for various products. This effort is aimed at comparing relative quality across alternative brands and thus largely would not be affected by the GMPs.

Consumers may conclude that health risks will be lessened by the GMPs. However, FDA's stated intent for the search cost models is to generate a proxy for the value to consumers of increased quality. To the extent that it reflects perceived reduced health risks, this proxy double counts values already included in the reduced cost of illness associated with recalls.

Thus, we find the purported link between search costs and the proposed GMPs to be a highly dubious one, both from a logical analytical standpoint and as a computational approach employed by FDA in estimating savings, and we do not count reduced search costs as a benefit of the rule in our analysis. CRN is disappointed that FDA has resorted to such thin support as an important component of its justification for such a significant and costly industry regulation. We believe the health benefits of increased supplement use, discussed in the next section, may provide more substantial support for the proposed GMPs.

SUMMARY OF INDUSTRY COSTS AND POTENTIAL BENEFITS AS IDENTIFIED BY FDA

As shown in **Table 15**, CRN's calculations show markedly increased costs, compared to FDA's analysis. Also, we question some of the benefits relied upon by the agency to offset those costs. As shown later in this document, however, we propose another benefit that FDA could consider, in terms of reducing consumer health costs through improved nutrition and disease prevention. These benefits could accrue to consumers if they have increased confidence in dietary supplements as a result of the new GMPs and accordingly make more use of beneficial dietary supplements.

FDA's estimated benefit	\$ 216.6 million
CRN's estimated benefit	\$ 34.0 million
FDA's estimated annual costs	\$ 79.4 million
CRN's estimated annual costs	\$ 300.6 million
FDA's one-time costs	\$ 54.5 million
CRN's one-time costs	\$ 629.0 million

The agency's calculations result in a net benefit of \$82.8 million in the first year and \$137.3 million in subsequent years. CRN's calculations result in a negative benefit of (\$895.7 million) in the first year and (\$266.6 million) in subsequent years.

CONSUMER BENEFITS: REDUCED HEALTH COSTS DUE TO INCREASED USE OF BENEFICIAL DIETARY SUPPLEMENTS

CRN is cognizant of the need to arrive at a balance of costs and benefits that are likely to be associated with new GMPs. FDA's calculated benefits are all directed at avoiding problems presumably associated with dietary supplements and do not take into consideration any positive health benefits from increased use of supplements. We believe the implementation of new, stronger GMPs for dietary supplements will raise the overall quality of products available to consumers and thus engender confidence in the industry, thereby resulting in social benefits. If this effect is significant, sales of dietary supplements should increase, and some consumers who were near the margin of purchasing supplements would be induced to buy them. Others who may currently use supplements only occasionally may be induced to purchase them more frequently. Consumers who are already regular supplement users may decide to increase the number of beneficial products they incorporate into their daily health regimen. The extent to which these changes occur may depend importantly on whether improved quality and thus stronger consumer confidence is achieved without substantial increases in the price of dietary supplements available to the public.

Increased use of beneficial dietary supplements would result in social benefits in the form of improved health for consumers. If this effect were substantial, health costs would fall and other related benefits would accrue, including improved quality of life (e.g., for an elderly person who takes calcium supplements and does not suffer a hip fracture). FDA does not acknowledge this important category of social benefits in its rulemaking on GMPs for dietary supplements. Yet a considerable body of evidence supports the conclusion that the health benefits of supplement usage can be very significant. CRN's 2002 publication *Benefits of Nutritional Supplements* provides a useful overview. (Dickinson, 2002) While numerous scientific studies establish the benefits of supplementation with specific nutrients or other dietary supplements, most of these do not lend themselves to quantification for the purpose of cost-benefit analysis, and few authors actually undertake a formal economic analysis of costs and benefits. We will rely on a few conservatively selected examples to make the point that large benefits in disease reduction and accompanying reductions in health costs are achievable through even small increments in appropriate supplement use by the relevant target populations.

Some of CRN's member companies are currently engaged in research on the potential health care cost savings that may be achieved through optimal use of beneficial dietary supplements, through reduction of disease risk. Unfortunately, these efforts are not yet complete and some of the information will not be made available until it is accepted for publication in a peer-reviewed journal -- a process which takes considerable time. If new data becomes available while this GMP rule is still under consideration, we will provide it to the agency.

It has long been a goal of public health policymakers to gain control over escalating health care costs by improving overall health and therefore reducing the risk of disease, especially the chronic diseases that contribute so heavily to current health care costs. Dr. Michael McGinnis of the Robert Wood Johnson Foundation and Dr. Nancy Ernst of the National Institutes of Health recently observed that Americans suffer a heavy burden of disease that is potentially preventable and predicted that healthier dietary practices could save \$71 billion per year in medical costs, lost productivity, and the value of lives lost prematurely to major chronic diseases. (McGinnis & Ernst, 2001)

Dr. Jeffrey Blumberg of the School of Nutrition Science and Policy at Tufts University has estimated the potential health care cost savings that could be realized if improved dietary practices were adopted and if those improved habits delayed the onset of cardiovascular disease, strokes, and hip fracture by 5 years. He wrote: “A 5-yr delay in the onset of cardiovascular disease could save about \$69 billion annually. A delay in the onset of strokes by 5 yr would be associated with annual savings of \$15 billion. A 5-yr delay in the occurrence of hip fracture annually could cut the number of events by 140,000 each year and save an estimated \$5 billion annually.” (Blumberg 1997) Delaying the onset of these three conditions alone could thus potentially result in a health care cost savings of \$89 billion every year. Some specific nutrients including B vitamins, omega-3 fatty acids, and calcium have been shown to reduce the risk of cardiovascular disease, strokes, and hip fracture. Other nutrients that have been shown to have protective effects on other conditions include antioxidants (vitamin C, vitamin E, lutein) for reducing the risk of cataracts and age-related macular degeneration, but we have no cost/benefit data upon which to base economic estimates for these conditions at this time.

If stronger GMPs increase consumer confidence in dietary supplements and therefore lead to an increase in the usage of products with recognized health benefits, such as multivitamins and calcium and omega-3 fatty acids, then one could predict that more consumers would obtain those health benefits and experience a reduction in chronic disease risk. The resulting health cost savings could potentially be included in FDA’s calculation of the benefits of the GMP rule. In this discussion, CRN will focus solely on nutrient/disease relationships that FDA has already evaluated and for which FDA has already approved an NLEA health claim or a qualified health claim. Of course, there are other benefits that may accrue from increased supplementation with various nutrients, so limiting our evaluation to those for which health claims or qualified health claims are permitted will result in a highly conservative estimate. The three examples we will offer relate to:

- Calcium supplementation to reduce the risk of osteoporosis;
- B vitamin supplementation to reduce the risk of cardiovascular disease; and
- Supplementation with long chain omega-3 fatty acids to reduce the risk of coronary heart disease.

In each case, our calculations will be drawn primarily from a single article and will estimate the health cost savings that could result if **one percent of the target population**

were to begin using the relevant supplement on a regular basis. The target population is women age 75 and over for osteoporosis, men over 45 for the B vitamin benefit, and people with a history of heart disease for the omega-3 fatty acid benefit.

Using very conservative estimates, we estimate a total health benefit from reduced risk in the amount of about \$659.6 million from reduced disease risk if 1% of the target population for each of the above conditions were to begin using the relevant supplement on a regular basis (Attachment C, Table 1). Thus the benefit is easily calculated based on various assumptions about the potential fraction of the population that could be motivated to use the supplement. If 5% of each target population started using the supplement, then the potential benefit would be 5 times as high, or \$3.3 billion per year.

HEALTH BENEFITS OF CALCIUM SUPPLEMENTATION

More than six million adults in the United States have osteoporosis, leading to nearly 300,000 hip fractures annually, at a cost to the health care system of almost \$9 billion per year. Several consensus conferences convened by the National Institutes of Health have recommended high calcium intakes (1500 mg per day) for postmenopausal women who are not taking estrogen replacement therapy.

Bendich and co-workers have analyzed the potential health cost savings that could be realized in the limited population of women 75 years of age and older, if they took supplements of 1200 mg calcium and thus avoided hospitalization for hip fracture. (Bendich 1999) The estimates we have incorporated from this article are highly conservative, since they consider only women 75 and older and they consider only hip fracture, although decreasing the risk of osteoporosis would also reduce other types of fracture. Also, these estimates include only direct medical care costs incurred in the hospital and in post-hospital care.

Bendich and coauthors conclude that among women 75 and older, it would be possible to realize a 46% reduction in hospitalizations for hip fracture, resulting in 83,589 fewer hospitalizations and a savings of \$1.65 billion. Backing out the cost of supplementation with 1200 mg calcium for the 9.4 million women in this age group, the potential cost benefit nets out at \$1.2 billion. If even **one percent** of the women in this age group undertook calcium supplementation as a result of increase confidence in the products due to new GMPs and avoided hip fracture, the potential benefit would be one percent of that total, or \$12 million per year (Attachment C, Table 2). If we were to conservatively estimate that 5% of women 75 and older might be motivated to begin calcium supplementation, if new GMPs caused them to have greater confidence in the product category, the benefit in health costs averted for hip fracture would be \$60 million per year.

HEALTH BENEFITS OF B VITAMINS IN REDUCING THE RISK OF CORONARY HEART DISEASE

A high homocysteine level has been identified as a risk factor for coronary heart disease. Increased intake of B vitamins including folic acid reduces homocysteine levels, and people with lower homocysteine levels have a reduced risk of heart disease. Tice and co-workers recently evaluated the cost effectiveness of grain fortification with folic acid and of additional vitamin supplementation with folic acid and vitamin B-12 for heart disease prevention. (Tice 2001) The most cost-effective approach, beyond the existing grain fortification program, was found to be supplementing men 45 years of age and over with folic acid and vitamin B-12. The calculated benefit is shown in Attachment C, Table 2. It amounts to a health benefit of \$59.9 million per year for every one percent of men 45 years of age and over (Attachment C, Table 3). To illustrate the calculations that could be drawn from this information, it implies that if 5% of men in this age group adopted regular supplementation with folic acid and B-12, the potential benefit could be five times as large, or \$300 million per year.

HEALTH BENEFITS OF SUPPLEMENTATION WITH LONG CHAIN OMEGA-3 FATTY ACIDS

The GISSI study observed a significant reduction in risk of cardiovascular death in men who had already experienced a myocardial infarction and who subsequently received supplementation with long chain omega-3 fatty acids. (GISSI 1999) The calculation of the benefit shows a potential gain of \$587.3 million dollars per year for every one percent of MI survivors who adopts regular supplementation with omega-3 fatty acids EPA and DHA (Attachment C, Table 4). If five percent of this target population adopted such supplementation as a result of improved confidence in dietary supplements due to stronger GMPs, this figure would reach almost \$3 billion per year.

CRN CONCLUSIONS AND RECOMMENDATIONS

CRN supports the need for improved dietary supplement GMPs, but we find the FDA's current proposal to be unbalanced in terms of cost and benefit due in part to the heavy focus on exhaustive end-product testing rather than on building quality into the product through rigorous process control. A well-controlled process justifies a decreased testing burden with respect to the finished product, but such a system cannot be implemented without extensive written procedures to ensure that the process remains the same over time and that the system performs consistently in the hands of many different operators. Increased consumer confidence in dietary supplements can and should result in increased usage of beneficial supplements, with resulting improvements in health and reduced risk of disease.

CRN again urges the agency to consider convening a series of workshops to permit the industry and other stakeholders to work together with FDA to seek an optimal approach to improving dietary supplement GMPs so that a final rule can be promulgated and enforced in a manner that protects consumers, enables the industry to produce quality products at a reasonable cost, and provides FDA with the necessary framework to appropriately regulate the myriad of companies that make up the dietary supplement industry.

Sincerely,

A handwritten signature in black ink that reads "Annette Dickinson". The signature is written in a cursive style and is positioned to the left of a vertical line that extends downwards from the end of the signature.

Annette Dickinson, Ph.D.
President

References

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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®

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

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
Polyphenolics	MegaNatural® Gold Grape Seed Extract, MegaNatural® Grape Skin Extracts, MegaNatural® Rubired Grape Juice Extract, MegaNatural® Red Wine Extract
Suppliers	
Member Company	Products/Ingredients/Services
Pronova Biocare, a.s.	Omega-3 Fatty Acids - EPAX®, Triomega®, Pikasol®, Omacor®
Rhodia, Inc.	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+®

FDA-Calculated Incremental Testing Costs

	Very Small	Small	Large
a % Vitamin Products	24%	42%	69%
b % Herbal Products	76%	58%	31%
c # Vit Identity Tests	1.97	1.97	1.97
d # Herb Identity Tests	2.40	2.40	2.40
e Cost of a Test	\$61.67	\$61.67	\$61.67
f # Batches	223	554	309
g Finished Batches Currently Being Tested	34.2%	58.3%	75.6%
h <i>Batches Requiring Testing (1-g)</i>	65.9%	41.7%	24.4%
i Manufacturing Fraction	54%	63%	78%
j <i>Cost Per Firm ((a*c)+(b*d))*e*f*h*i</i>	\$11,230	\$19,907	\$7,626
k Firms In FDA Survey	110	114	14
l % of Industry in FDA Survey	15.20%	15.20%	15.20%
m <i>Industry Cost (j * k) / l</i>	\$8,128,317	\$14,932,087	\$702,470

Total Industry Cost -- All Firm Sizes	\$23,762,874
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Tests Listed in FDA's FOIA Spreadsheet but Not Included in FDA Cost Calculations

In-Process Tests	2.50
Herb Component Tests	2.50
Vit Component Tests	7.46

Source of data and calculations: FOIA response

Quantity of Batches

	Very Small	Small	Large	CRN Large
Batches Per Firm	223	554	309	2,112
Number of Firms In Industry	724	750	92	92
Number of Industry Batches	161,403	415,556	28,464	194,552
Share of Batches (FDA)	26.7%	68.6%	4.7%	-
Share of Batches (CRN)	20.9%	53.9%	-	25.2%

Data from the FOIA response was used except for the CRN number of large-firm batches, which is a average of the results for a CRN survey and the FDA survey.

FDA-Calculated Incremental Large-Firm Testing Costs
Only Number of Batches Adjusted by CRN

	FDA	Batch Estimate Adjustment
a % Vitamin Products	69%	69%
b % Herbal Products	31%	31%
c # Vit Identity Tests	1.97	1.97
d # Herb Identity Tests	2.40	2.40
e Cost of a Test	\$61.67	\$61.67
f # Batches	309	2,112
g Finished Batches Currently Being Tested	75.6%	75.6%
<i>h Finished Batches Not Currently Being Tested (1-g)</i>	<i>24.4%</i>	<i>24.4%</i>
i Manufacturing Fraction	78%	78%
j <i>Cost Per Firm ((a*c)+(b*d))*e*f*h*i</i>	\$7,626	\$52,122
k Firms In FDA Survey	14	14
l % of Industry in FDA Survey	15.20%	15.20%
m <i>Industry Large-Firm Cost (j * k) / l</i>	\$702,470	\$4,801,349
Increase in Large-Firm Cost Estimate:		583%

Source of data and calculations: FOIA response

The adjusted number of large-firm batches is a average of the results for a CRN survey (3915), a NFA survey (2750) and the FDA survey (309).

Percentage of Batches Already Being Tested

This box is part of a table from page D-28 of RTI's 5/17/00
"Survey of Manufacturing Practices in The Dietary Supplement Industry"

	<u>very small</u>	<u>small</u>	<u>large</u>
6.14 Does this plant conduct tests on any in-process materials and/or finished products?			-
1. Yes	55.81	79.94	
2. No (Skip to Question 6.21)	31.69	19.30	15.66
Not Applicable	7.14	0.00	6.54
No Answer	5.36	0.76	4.49
6.15 [If 6.14 is Yes]			
What Percentage of in-process materials and/or finished products are sampled and tested?			
In-process materials: % of batches (mean response)	48.76	58.20	91.68
Finished products: % of batches (mean response)	50.19	72.32	89.61

Percentage of firms the FDA estimates to be testing

The FDA counts as "yes" an answer of: "yes", "not applicable" or "no answer".

v.s.	55.81 + 7.14 + 5.36 =	68.31
small	79.94 + 0.00 + 0.76 =	80.70
large	73.32 + 6.54 + 4.49 =	84.35

(CRN counts as "yes" only an answer of "yes".)

FDA Estimate of the percentage of finished product tested

Multiply the percentage who test (calculated above) by the percentage of finished product batches that they reported to test.

v.s.	68.31% * 50.19% =	34.3%
small	80.70% * 72.32% =	58.4%
large	84.35% * 89.61% =	75.6%

CRN Estimate of the percentage of finished product tested

Multiply the percentage who test (in box above) by the percentage of finished product batches that they reported to test.

v.s.	55.81% * 50.19% =	28.0%
small	79.94% * 72.32% =	57.8%
large	73.32% * 89.61% =	65.7%

FDA-Calculated Incremental Large-Firm Testing Costs
Only F.B.C.B.T. Adjusted by CRN

	FDA	F.B.C.B.T. Adjustment by CRN
a % Vitamin Products	69%	69%
b % Herbal Products	31%	31%
c # Vit Identity Tests	1.97	1.97
d # Herb Identity Tests	2.40	2.40
e Cost of a Test	\$61.67	\$61.67
f # Batches	309	309
g Finished Batches Currently Being Tested	75.6%	65.7%
h Finished Batches Not Currently Being Tested (1-g)	24.4%	34.3%
i Manufacturing Fraction	78%	78%
j <i>Cost Per Firm</i> $((a*c)+(b*d))*e*f*h*i$	\$7,626	\$10,719
k Firms In FDA Survey	14	14
l % of Industry in FDA Survey	15.20%	15.20%
m <i>Industry Large-Firm Cost</i> $(j * k) / l$	\$702,470	\$987,430
Increase in Large-Firm Cost Estimate:		41%

Source of data and calculations: FOIA response

Currently-Tested Batches That Might Require Additional Testing

Although many firms are currently conducting chemical tests on batches of product, they may not be conducting every test on each batch, as the proposed GMPs would require.

FDA numbers assume that any batch that is already tested at all would not require additional tests.

A CRN survey revealed that, for the current batches already being tested, a minimum of 40% more testing would be required by the proposed GMP regulations.

Needing 40% additional testing means that only 71% of required testing is being done.

Current Testing: n
Additional testing: 40%*n
Final Testing: 1.4 n

Depth of Prescribed Testing Being Done:
 $n / (1.4n) = \mathbf{71\%}$

FDA-Calculated Incremental Large-Firm Testing Costs
Only Depth of Testing Adjusted by CRN

	FDA	Depth of Testing Adjustment by CRN
a % Vitamin Products	69%	69%
b % Herbal Products	31%	31%
c # Vit Identity Tests	1.97	1.97
d # Herb Identity Tests	2.40	2.40
e Cost of a Test	\$61.67	\$61.67
f # Batches	309	309
g Finished Batches Currently Being Tested	75.6%	75.6%
Depth of Testing	100%	71%
<i>h Finished Batches Not Currently Being Tested (1-(g * Depth of Testing))</i>	24.4%	46.0%
i Manufacturing Fraction	78%	78%
j <i>Cost Per Firm ((a*c)+(b*d))*e*f*h*i</i>	\$7,626	\$14,376
k Firms In FDA Survey	14	14
l % of Industry in FDA Survey	15.20%	15.20%
m <i>Industry Large-Firm Cost (j * k) / l</i>	\$702,470	\$1,324,329
Increase in Large-Firm Cost Estimate:		89%

Source of data and calculations: FOIA response

CRN-Calculated Incremental Testing Costs

	Very Small	Small	Large
a % Vitamin Products	24%	42%	69%
b % Herbal Products	76%	58%	31%
c # Vit Identity Tests	6.00	6.00	6.00
d # Herb Identity Tests	2.40	2.40	2.40
I Component Tests	3.0	3.0	3.0
II Quality/Purity/Strength Tests	3.0	3.0	3.0
III In-Process Tests	2.5	2.5	2.5
IV Herb Solvent Test	1.0	1.0	1.0
e Cost of a Test	\$61.67	\$61.67	\$61.67
f # Batches	223	554	2,112
g Finished Batches Currently Being Tested	28.0%	57.8%	65.7%
V Depth of Current Testing	71%	71%	71%
h <i>Batches Requiring Additional Testing (1-(g*V))</i>	80.0%	58.7%	53.1%
i Manufacturing Fraction	54%	63%	78%
j <i>Cost Per Firm ((a*c)+(b*(d+IV))+I+II+III)*e*f*h*i</i>	\$74,394	\$164,155	\$738,275
k Firms In FDA Survey	110	114	14
l % of Industry in FDA Survey	15.20%	15.20%	15.20%
m <i>Industry Cost (j * k) / l</i>	\$53,845,179	\$123,132,760	\$68,008,146
Total Industry Cost -- All Firm Sizes		\$244,986,085	

Source of data and calculations: FOIA response. CRN-updated numbers are bolded and highlighted.

Capital Renovation Cost

	Very Small	Small	Large
Square Footage Per Firm	24,674	71,354	596,000
Average Increase Necessary	10%	10%	10%
Cost Per Square Foot	\$50	\$50	\$50
CRN Cost Per Firm	\$123,370	\$356,770	\$2,831,000
Number of Firms In FDA Survey	110	114	14
% of Industry in FDA Survey	15.2%	15.2%	15.2%
CRN Industry Cost	\$89,292,925	\$267,613,477	\$260,785,059
CRN Total Industry Cost \$617,691,461			
FDA Reduction Factor	18.4%	9.8%	1.0%
FDA Cost Per Firm (<i>CRN Cost * Reduction Factor</i>)	\$22,700	\$34,963	\$26,895
FDA Industry Cost (<i>CRN Cost * Reduction Factor</i>)	\$16,429,898	\$26,226,121	\$2,477,458
FDA Total Industry Cost \$45,133,477			

Data from the FOIA response was used

CRN's numbers differ from FDA's numbers because CRN did not use the reduction factor.

Frequency of Recalls

	<u>Food</u>	<u>Supplements</u>	<u>Drugs</u>
Class I & II Recalls 1990-1999	1,493	52	997
Average Annual Recalls	149.3	5.2	99.7
Annual Sales (Billions)	\$500	\$18	\$145
Recalls per \$ Billion Sales	0.3	0.3	0.7

Sources:

Number of recalls from FDA weekly enforcement reports

Annual food sales from National Food Processors Association

Annual supplement sales from Nutrition Business Journal for 2002.

Annual drug sales from Association of Drug Stores and Drug Store News for 1999.

Class I & Class II Recalls of Dietary Supplements
1990-1999

Reason for Recall	Class I Recalls	Class II Recalls
Undeclared Ingredient/Color	1	5
Unapproved Ingredient/Color	--	1
Contaminant – Microorg.	3	2
Contaminant – Digitalis	13	--
Contaminant – Lead	--	11
Contaminant – Mercury	--	--
Contaminant – Pesticide	--	--
Contaminant – Misc.	1	--
Super-Potent	2	3
Sub-Potent	--	1
L-Tryptophan	5	--
Mispackaged/Mislabeled	--	4
Processing/GMP Violation	--	--
Physical Characteristics	--	--
Regulatory Issue	--	--
Defective Packaging	--	--
Toxins/Poisons	--	--
Illness Related	--	--
Histamine	--	--
Unapproved Drug/Claim	--	--
Non-Sterile	--	--
Other/Misc.	--	--
Total Recalls	25	27

Source: FDA weekly enforcement reports

FDA-Calculated Cost Of Illness using Recall Data

Replication of Math from FOIA Response

	<u>Number of Recalls</u>	<u>Cost of a Single Illness</u>
Class I		
Hypervitaminosis A	2	\$936
Salmonella	4	\$16,208
Klebsiella Pneumonia	1	\$759,987
Selenium Poisoning	1	\$752,420
Stannous Flouride	1	\$938
EMS	7	\$871,233 *
Botulism	1	\$425,657
Lead Poisoning	1	\$9,625
Digitalis	33	\$28,684
Ephedra	1	\$169,432
Undeclared Sulfites	1	\$529
Class II		
Salmonella	4	\$569
Selenium Poisoning	6	\$954
Stannous Flouride	1	\$938 **
Botulism	1	\$1,507
Lead Poisoning	41	\$7,650
Glass Fragments	1	\$1,846
Hypervitaminosis D	1	\$1,022
Pyridoxine (Vitamin B6)	2	\$8,868
Superpotent Zinc	1	\$285 **
Niacin	1	\$4,258
Yellow #5 Sensitivity	5	\$529 ***
Yellow #6, Red #40, Blue #2	1	\$1,178
Copper Salts	1	\$369
Lactose Intolerance	1	\$290
Iron Poisoning	1	\$374
Folic Acid Super	1	
Amino Acid	1	
Subpotent Vitamin A	1	
Nonpermitted Food Additive	1	
Coumarin	2	

Class I Weighted Average	\$59,207	*
Class II Weighted Average	\$4,785	**

* The class I weighted average as computed by the FDA and replicated by CRN only includes a FDA-selected fraction (1/1000) of the EMS value.

** The class II weighted average differs slightly from the FDA's calculated average (\$4,769) because the FDA's calculations did not include the cost of Stannous Flouride and Superpotent Zinc.

*** The value for Yellow #5 has not been adjusted by CRN, although the FDA's probability of possible outcomes sum to 150%.

Cost of Illness From Recall Data

	FDA Calculation	CRN Calculation	10% Reporting Rate for Death
Reported Class I Recalls in 10 years	60	22	22
Reported Class II Recalls in 10 years	70	25	25
Reported Class I Recalls per year	6.0	2.2	2.2
Reported Class II Recalls per year	7.0	2.5	2.5
Percent Reported	1%	1%	*
Health Cost Per Class I Recall	\$59,207	\$59,207	\$21,861
Health Cost Per Class II Recall	\$4,769	\$4,785	\$4,785
Class I Health Cost Per Year	\$35,524,129	\$13,025,514	\$4,809,448
Class II Health Cost Per Year	\$3,338,204	\$1,196,345	\$1,196,345
Total Health Cost Per Year	\$38,862,333	\$14,221,859	\$6,005,793
Percentage of Cost Averted	100%	50%	50%
Annual Benefit	\$38,862,333	\$7,110,930	\$3,002,897

* Death is reported 10%, all other severities are reported 1% of the time.

Cost of a Rare Catastrophic Event

	FDA	CRN
Cost Per Event	\$1,983,901,074	\$1,983,901,074
Frequency (Likely to Occur Approximately Once Every ___ Years)	30	70
Annual Probability of Occurrence	3.33%	1.43%
Annual Cost	\$66,130,036	\$28,341,444

Source: FOIA response EMS Spreadsheet

FDA and CRN Cost-Benefit Analyses

Annual Benefits	<u>FDA</u>	<u>CRN</u>
Reduction in Illness	\$38,862,333	\$3,002,897
Reduction in Cost of Recalling Product	\$2,628,285	\$2,628,285
Avoidance of Catastrophic Events	\$66,130,036	\$28,341,444
Increased Quality (Search-Cost Proxy)	\$109,000,000	\$0
Total	\$216,620,654	\$33,972,626

Annual Costs	<u>FDA</u>	<u>CRN</u>
Sanitation/Standard Operating Procedures	\$13,229,522	\$13,229,522
Testing	\$23,762,874	\$244,986,085
Other Production & Process Controls	\$13,921,631	\$13,921,631
Holding & Consumer Complaints	\$19,328,386	\$19,328,386
Miscellaneous	\$7,566	\$7,566
Cost to Warehouses	\$9,112,738	\$9,112,738
Total	\$79,362,717	\$300,585,928

One-Time Costs	<u>FDA</u>	<u>CRN</u>
Development of Analytical Methods	-	\$2,000,000
Capital Renovations	\$45,133,477	\$617,691,461
Other	\$6,863,890	\$6,863,890
Cost to Warehouses	\$2,484,253	\$2,484,253
Total	\$54,481,620	\$629,039,604

First-Year Cost-Benefit Analysis		
Annual Benefit	\$216,620,654	\$33,972,626
Annual Cost	\$79,362,717	\$300,585,928
One-Time Cost	\$54,481,620	\$629,039,604
Net Benefit	\$82,776,316	-\$895,652,907
Second-Year Cost-Benefit Analysis		
Annual Benefit	\$216,620,654	\$33,972,626
Annual Cost	\$79,362,717	\$300,585,928
Net Benefit	\$137,257,937	-\$266,613,303

CRN-updated numbers are highlighted.

Annual Health Benefits Of Increased Supplement Usage
Examples of Supplements Which Have FDA-Approved Health Claims

<u>Supplement</u>	<u>Medical Condition</u>	<u>Annual Benefit of Supplement Usage for an Additional One Percent of the Target Population</u>
Calcium	Hip Fractures (Osteoporosis)	\$12,432,053
B Vitamins	Heart Disease	\$59,945,356
Omega-3 Fatty Acids	Heart Disease	\$587,255,800
Total		\$659,633,210

Estimated Calcium Benefits

Medical Condition	Hip Fractures (Osteoporosis)
Demographic	Women 75+
Population Hospitalized	182,974
Predicted Reduction	46%
Preventable Hospitalizations	84,168
Per Patient Hospital Expenditure	\$19,744
Expenditure for All Preventable Hospitalizations	\$1,661,812,992
Population at Risk	9,426,000
Supplementation Cost Per Person Per Year	\$44.41
Total Supplementation Cost	\$418,607,661
Net Benefit for Entire Population	\$1,243,205,331
Annual Benefit of Supplement Usage for an Additional 1% of the Target Population	\$12,432,053

Sources:

"Supplemental Calcium for the Prevention of Hip Fracture: Potential Health-Economic Benefits," Adrienne Bendich, et al., Western Journal of Medicine (May 1997).

US Census

Estimated B Vitamins Benefits

Medical Condition	Coronary Heart Disease
Demographic	Men 45+
Gain in Quality Adjusted Life Years	30,000
Value of a QALY	\$229,950
Value of Gain in QALY	\$6,898,500,000
Population at Risk	44,552,211
Supplementation Cost Per Person	\$20.29
Total Supplementation Cost	\$903,964,361
Net Benefit for Entire Population	\$5,994,535,639
Annual Benefit of Supplement Usage for an Additional 1% of the Target Population	\$59,945,356

Sources:

"Cost-effectiveness of Vitamin Therapy to Lower Plasma Homocysteine Levels for the Prevention of Coronary Heart Disease," by Jeffrey Tice, et al., JAMA (2001).

US Census

Value of QALY derived from a day equaling \$630 (FDA Federal Register Notice, p. 12230)

Estimated Omega-3 Fatty Acids Benefits

Medical Condition	Heart Disease
Demographic	Recent Myocardial Infarction Survivors
Population at Risk	7,600,000
Estimated Death Rate 3-5 Years	20%
Estimated Annual Death Rate	5%
Annual Deaths	380,000
Observed Reduction	17%
Population w/ Preventable Deaths	64,600
Years of Life Lost Due to a Single Death	4
Value of a Year	\$229,950
Cost Due to One Death	\$919,800
Cost Due to All Preventable Deaths	\$59,419,080,000
Population at Risk	7,600,000
Supplementation Cost Per Person	\$91
Total Supplementation Cost	\$693,500,000
Net Benefit for Entire Population	\$58,725,580,000
Annual Benefit of Supplement Usage for an Additional 1% of the Target Population	\$587,255,800

Sources:

"Dietary Supplementation with n-3 Polyunsaturated Fatty Acids and Vitamin E After Myocardial Infarction: Results of the GISS-Prevenzione Trial," The Lancet, 1999.

US Census

National Vital Statistics Report, Vol. 50 (American Heart Association)

Heart Disease and Stroke Statistics, 2003 (American Heart Association)

Value of Year derived from a day equaling \$630 (FDA Federal Register Notice, p. 12230)



Council for Responsible Nutrition

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September 10, 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: ECONOMIC IMPACT OF THE PROPOSED RULE

This is an addendum to the comments submitted on September 9, 2003, by the Council for Responsible Nutrition regarding the economic impact of the above-mentioned proposed rule. This note provides some additional information and clarification on points raised in yesterday's submission, but does not modify any recommendations or conclusions contained in those comments.

EQUIPMENT COSTS

CRN's comments made the point that FDA's estimate of likely equipment costs associated with the proposed GMP rule were grossly understated. We provided some data on the cost to a small or very small company of establishing and equipping a new laboratory and on the cost to any company of expanding existing laboratory capability due to the proposed increase in testing requirements. We referenced the combined cost of major pieces of equipment but did not provide detail on typical costs of specific items. The attached table provides more detail on typical equipment costs. While we note that these costs are substantial, no line item is included in our economic analysis for overall equipment costs. Thus, our estimate of industry costs is understated to the degree that it fails to fully incorporate equipment costs.

CAPITAL EXPENSES FOR RENOVATION OF FACILITIES

We provided information on estimated capital expenses. FDA initially estimated that about 10% of a company's physical plant will require renovation, but then applied a reduction factor assuming that most companies would not in fact have to make any modifications in their facilities. CRN believes 10% is a reasonable estimate of the likely impact, and some of our member companies believe a more realistic figure would be 15 to 20%. We also believe virtually all companies will need to do some renovation, if the proposal remains unchanged. Assuming that 10% of the square footage will need modification, the capital expenses turn out to be the largest single item of cost to the industry -- more than twice the cost of all the recurring expenses for process controls including testing.

In our comments, we identified the requirement for “smooth, hard surfaces” in all portions of the facility as one of the factors contributing toward potential capital expenses. Another aspect of the proposed rule that our members have identified as potentially requiring additional capital investment is the apparently blanket requirement for temperature and humidity control, without flexibility to determine whether such controls are necessary to protect the integrity of the product.

HEALTH BENEFITS OF INCREASED SUPPLEMENT USE

CRN’s comments provided information regarding estimated health benefits of increased supplement use and relied on several economic analyses of particular nutrient/disease relationships as the basis for some very conservative estimates of potential savings to the health care system. These estimates were stated in terms of the health costs that could be avoided if **one percent of the target population** started using the relevant supplement on a regular basis, because of increased consumer confidence in the product category after implementation of new GMPs.

We wish to emphasize that our estimates are extremely conservative in several respects. First, we only provided analyses for three nutrient/disease relationships for which FDA has already approved an NLEA health claim or permitted a qualified health claim. Second, our analyses in all cases were based on the potential benefits to a very narrow segment of the population: women 75 years of age and older in the case of osteoporosis, men 45 and over in the case of B vitamins and heart disease, and people who have experienced a myocardial infarction in the case of the omega3 fatty acids. These populations were selected because the available economic analyses or the particular studies chosen as the basis for our calculations dealt only with these populations. Third, in the case of the B vitamins, the beneficial economic impact of supplement use was attenuated by the fact that the United States already has made the decision to add folic acid to enriched grain products, so the calculated benefit from supplementation is limited to the incremental impact above and beyond the effect of fortification.

For these reasons, the CRN estimates of potential benefit are highly conservative and will tend to underestimate the true benefit that may be realized. Even so, the impact is substantial. We were not able to predict what percent of the population would initiate or increase its usage of dietary supplements as a result of increased confidence in the category. It is for this reason that we provided our estimates in terms of the benefit that would be observed **for each one percent of the target population** that adopted supplementation with the relevant nutrient. One can easily apply a multiplier to this figure in order to estimate the overall effect of a given level of increased use.

As we noted in our comments, CRN member companies have additional research in progress to identify the potential health care savings that could be achieved from optimal use of dietary supplements. If that research becomes available during the time FDA is reviewing the comments on this proposed rule, CRN will submit it to the agency.

CONCLUSION

Finally, CRN would like to recognize and emphasize that the objective of this entire effort to develop GMPs is to strengthen the framework within which the dietary supplement industry operates and to permit consumers to have greater confidence in the quality of the products they are purchasing. While costs and benefits are meaningful measures of the rule's impact on the industry and on consumers, the goal is not merely to juggle cost/benefit figures but to help FDA and the industry identify the best approach to achieving quality products. CRN got the ball rolling on improved GMPs for dietary supplements back in 1995, and we want to be part of the team that sees the effort through to a successful conclusion in the relatively near future. We look forward to working with the agency in this direction.

Sincerely,

A handwritten signature in cursive script that reads "Annette Dickinson". The signature is written in black ink and is positioned to the left of a vertical line that extends downwards from the end of the signature.

Annette Dickinson, Ph.D.
President

**TYPICAL COST OF EQUIPMENT
REQUIRED FOR QUALITY ASSURANCE INCLUDING
TESTING OF DIETARY SUPPLEMENTS**

HPLC system	\$ 35,000 to 75,000
HPLC columns (many different types required)	500 to 750 each
HPLC vials	20 to 100 (per 100)
Gas chromatograph (GC) system	\$ 30,000
GC/MS (mass spectrometry) system	\$ 70,000
Atomic absorption (AA) system	\$ 40,000 to 80,000
Inductively Coupled Plasma (ICP) system	\$ 100,000 to 150,000
Gravimetric/titration systems (glassware, chemicals, reagents)	\$ 2,000 to 5,000
Disintegration system	\$ 8,000 to 12,000
Disintegration system, automated	\$ 40,000
Dissolution system	\$ 12,000 to 25,000
Hardness tester	\$ 40,000
Analytical balance	\$ 3,000 to 12,000
Digital thermometer	\$ 5,000
Computer	\$ 5,000
Printer	\$ 5,000
Hot plate/stirrer	\$ 300
Latex gloves (case of 200)	\$ 300
Box of filter papers	\$ 100