VII. Analysis of Impacts

A. Introduction

FDA has examined the economic implications of this proposed rule as required by Executive Order 12866. Executive Order 12866 directs agencies to assess all costs and benefits of available regulatory alternatives and, when regulation is necessary, to select regulatory approaches that maximize net benefits (including potential economic, environmental, public health and safety, and other advantages; distributive impacts; and equity). Executive Order 12866 classifies a rule as significant if it meets anyone of a number of specified conditions, including: Having an annual effect on the economy of $100 million, adversely affecting a sector of the economy in a material way, adversely affecting competition, or adversely affecting jobs. A regulation is also considered a significant regulatory action if it raises novel legal or policy issues. FDA has determined that this proposed rule, if it were to become a final rule, would be a significant regulatory action as defined by Executive Order 12866.

The Small Business Regulatory Enforcement Fairness Act of 1996 (Public Law 104-121) defines a major rule for the purpose of congressional review as being likely to cause one or more of the following: an annual effect on the economy of $100 million; a major increase in costs or prices; significant adverse effects on

competition, employment, productivity, or innovation; or significant adverse effects on the ability of U. S.-based enterprises to compete with foreign-based enterprises in domestic or export markets. In accordance with the Small Business Regulatory Enforcement Fairness Act, OMB has determined that this proposed rule, when final, will be a major rule for the purpose of congressional review.

FDA has examined the economic implications of this proposed rule as required by the Regulatory Flexibility Act (5 U.S.C. 601-612). If a rule has a significant economic impact on a substantial number of small entities, the Regulatory Flexibility Act requires agencies to analyze regulatory options that would lessen the economic effect of the rule on small entities. FDA finds that this proposed rule would have a significant economic impact on a substantial number of small entities.

We carry out the cost-benefit analyses required for significant rules in the Preliminary Regulatory Impact Analysis, in section VII.B of this document. We perform the Initial Regulatory Flexibility Analysis of the effects on the proposed rule on small businesses in section VII.C of this document.

B. Preliminary Regulatory Impact Analysis

1. The Need for the Proposed CGMP Regulations

The proposed CGMP regulations are needed because establishments that manufacture, package, and hold dietary

ingredients and dietary supplements may not have sufficient market incentives to use controls to prevent the adulteration and misbranding of dietary ingredients or dietary supplements, including incentives to ensure their identity, purity, quality, strength, and composition (product quality). Manufacturing, packaging, and holding practices that ensure product quality can be costly, so establishments may not adopt them unless required to do so by regulation. Without the proposed regulations consumers of dietary supplements cannot be assured that all establishments are manufacturing dietary supplements in a way that ensures that these products are not adulterated or misbranded.

Manufacturing, packaging, and holding practices can compromise safety if they fail to prevent biological, chemical, and physical contamination, or if the wrong dietary ingredients are used that present an unreasonable risk of illness or injury. Strength (which is the amount of a specific dietary supplement or dietary ingredient in each tablet or capsule) that differs from label statements, missing or extra ingredients, and inconsistency across units of the product are other problems caused by poor manufacturing practices. Products may also be held in insanitary or environmentally inappropriate conditions, or may be physically damaged if stored improperly. Some poor manufacturing practices, such as the use of ingredients that are undeclared, of incorrect

strength, or missing altogether result in a misbranded product. The proposed CGMP regulations would establish minimum requirements to ensure that manufacturing, packaging, and holding practices ensure the identity and quality of components, dietary ingredients, and dietary supplements.

Consumers today rely on manufacturer's assurances, existing regulations and statutes (for example, section 402(a)(3) and (a)(4) of the act), and recourse to the legal system to ensure that products are not defective. Brand names convey some information to consumers about a firm's manufacturing practices. Some private organizations, such as the National Nutritional Foods Association and the USP design minimum product standards or manufacturing requirements. The current act contains some provisions that prevent using putrid substances and insanitary manufacturing practices. In addition, either the threat of litigation or consumers seeking compensation for defective products and adverse health events may create incentives for establishments to adopt good manufacturing practices.

Actions by manufacturers, primarily voluntary quality controls, do not provide sufficiently protective industry-wide minimum requirements for manufacturing, packaging, and holding of dietary ingredients and dietary supplements. Without the proposed regulations, survey evidence shows that products in the dietary supplement market are sorted somewhere between two types:

- Higher-priced products with brand names or industry certification that follow several of the good manufacturing practices proposed here;
- Lower-priced products that contain no private certification or respected brand name and that follow few of the good manufacturing practices that are proposed here.

Without the proposed rule, the current practices do not provide all consumers with safe manufacturing practices or reliable product quality throughout the industry.

The market for dietary supplements is full of information; consumers of dietary supplements must sort through information and misinformation about the properties of these products from magazines, brochures, popular books, television, and a host of other sources. However, the information from these sources deals most often with the claims for the products themselves, not with the steps taken by establishments to protect against contamination or to ensure quality. Private quality control fails to provide industry-wide minimum good manufacturing practices for the following reasons:

- Establishments do not have incentives to disclose information about their own practices, because disclosure that some consumers may perceive to be harmful or undesirable would reduce the demand for

their products. Establishments therefore have incentives to withhold information from consumers.

- Businesses normally do not advertise differences in manufacturing practices. They seldom have access to competitors' proprietary information, and they may fear that advertising based on differences in practices would discredit the entire industry.
- Without public disclosure of product quality and adverse health events, the link between manufacturing practice and health hazard is difficult to establish. The link is probabilistic, requires data pooling across products and establishments (in order to establish cross sectional variation), and can be interpreted in a variety of ways.
- Because many consumers already mistakenly believe that the Federal Government guarantees safety, businesses have weak incentives to adopt good manufacturing practices, which are costly. In one recent survey of the nations consumers, 34 percent report that they believe that the government regulates dietary supplements to ensure safety and that products do what they claim to do. (For details of the survey, see Ref. E3.) If people believe that good manufacturing practices are already followed, manufacturers may

believe they gain little from voluntarily adopting them.

Information about manufacturing practices for dietary supplements is imperfect and costly to produce, so well-informed people should be willing to pay for improvements in the quality of information. An important benefit of the proposed regulations will be to reduce variation in manufacturing practices and ensure minimum quality for dietary supplement products. Reducing the variation in product quality by creating industry-wide minimum requirements reduces the information consumers now attempt to get through costly and uncertain sources in order to make purchasing decisions.

2. Regulatory Options

FDA considered several regulatory options for dealing with current manufacturing, packaging, and holding practices that may not ensure product quality. The options considered include: (a) No new regulatory action, (b) fewer requirements for vitamins and minerals, (c) more restrictive regulations than the proposed CGMP regulations, (d) HACCP without the other elements of CGMP regulations, (e) final product testing only, (f) regulations for high-risk products or hazards only, and (g) the proposed rule.

a. No new regulatory action. Under this option, consumers would probably rely on the following as protection against defective products:

- Possible enforcement action by FDA under, for example, section 402(a)(3) and (a)(4) of the act, regarding adulterated foods that consist of filthy, putrid, or decomposed substances or foods that have been prepared, packed, or held under insanitary conditions so that they may become contaminated or may be rendered injurious to health;
- Publicity from private consumer groups or health agencies on the risks from products not manufactured using CGMP regulations, manufacturers assurances, and the voluntary adoption of some or all provisions of the proposed regulations;
- Current or enhanced State and local enforcement activity to bring about a reduction of potential harm from contaminated or poor quality dietary supplements; or
- Litigation or the threat of litigation by consumers who allege harm from consumption of the dietary supplement.

We believe that there are compelling reasons not to rely on these alternatives alone.

If public and private health agencies, consumer groups, competitors, trade organizations or other third parties publicized the risks from products not manufactured using private good manufacturing practices, then consumers would decide for themselves on the risks of contaminated or poor quality products. The weakness of this alternative is that third-party organizations cannot easily discover many of the problems caused by poor manufacturing practices because manufacturers are reluctant to voluntarily share information to third parties about their manufacturing practices.

Actions by manufacturers, such as by voluntarily introducing good manufacturing practices, occur when the expected private economic benefits of the actions exceed the private costs. Voluntary adoption of good manufacturing practices will occur when it is profitable to do so. Many establishments appear to be adopting some publicly available good manufacturing practice models in order to meet the demand for safer and more uniform products. NNFA is implementing a good manufacturing practice certification program. The USP sets standards for strength, purity, disintegration, and dissolution for individual and combination vitamins and minerals. Also, Consumerlab.com is introducing a certification label, CL, to show when ingredients meet their minimum requirements. However, 36 percent of recently surveyed dietary supplement establishments do not follow any good

manufacturing practice models for their products (Ref. E2). The breakdown of survey results shows that 48 percent of very small firms, 27 percent of small firms and 11 percent of large firms do not follow a good manufacturing practice model. The survey results also show that 32 percent of vitamins and mineral establishments, 39 percent of amino acid/protein/animal extract establishments, 41 percent of herbal and botanical establishments, and 59 percent of establishments not already classified, do not follow a good manufacturing practice model.

Without industry-wide uniform requirements, some establishments may follow different practices but convey the message that they follow good manufacturing practices. In short, people who want to discriminate between establishments that use good practices and those that do not would not have sufficient information to do so. Another reason for our skepticism about universal voluntary adoption of good manufacturing practices is that good practices appear to be taken for granted by many consumers. Indeed, some consumers already believe that the Federal Government regulates the manufacturing practices of the industry, so firms lack an inventive to provide additional assurance (Ref. E3).

Current or enhanced State and local regulations could bring about a reduction of potential harm from contaminated supplements. This alternative has the advantage that State and

local governments can exercise more discretion when responding to local manufacturing conditions or consumer health practices than the Federal Government. Because most of the industry engages in interstate commerce, however, Federal regulations are appropriate. Also, Federal regulations would apply uniformly across the country, whereas State and local regulations might impose different standards on establishments that supply supplements across State and local boundaries.

Litigation or the threat of litigation may help to bring about the goals of the proposed rule. The potential of costly litigation from the harm caused by deficient manufacturing practices creates an incentive for manufacturers to reduce the risks from defective products. However, we do not believe that litigation or the threat of litigation has created the incentives for all manufacturers to implement the manufacturing practices that we believe are necessary to avoid adulterated or misbranded products. As discussed earlier, not all surveyed dietary supplement manufacturers reported that they followed good manufacturing practices. Furthermore, in some cases it is difficult and costly to demonstrate to the courts that the harm to plaintiffs was actually the result of poor manufacturing practices, making recourse to the courts sometimes impractical.

In the absence of the proposed CGMP regulations, the burden of monitoring manufacturing practices would fall more heavily on

consumers, despite the difficulties consumers face in monitoring manufacturers. Moreover, the proposed CGMP regulations are preventative and should ensure that problems are identified and dealt with during manufacturing, packaging, and holding, rather than after someone has consumed an unsafe product and experienced an adverse effect.

b. Fewer requirements for vitamins and minerals. FDA could require more controls from establishments that manufacture, package, or hold plant or animal derived dietary ingredients such as amino acids, proteins, herbals, botanicals and other products not classified as vitamin and mineral manufacturers, packagers, or holders. The plant or animal derived dietary ingredients are probably characterized by greater variation in product quality than synthetically derived dietary ingredients. Under this option, the segment of the industry that manufacture, package, or hold products that are the most likely to have difficultly manufacturing or maintaining uniform product quality dietary ingredients would be required to follow the proposed testing and other production and process control requirements. Manufacturers of vitamins and minerals would be required to follow the sanitation, holding, and consumer complaint provisions only, they would not have to adopt manufacturing controls to ensure that products did not contain too much or too little of a vitamin or mineral.

Plant or animal ingredients are likely to experience greater natural variation in product quality than synthetic compounds, so they may require the higher minimum standard of regulation contained in the proposed regulation. The advantage of this option is that fewer establishments will be affected as much; approximately 723 establishments classified as manufacturers, packagers or holders of products other than vitamins and minerals, rather than the 1,566 establishments estimated to be covered by the proposed regulation (see table 2 of this document). The compliance costs would therefore be lower. The disadvantage is that vitamin and mineral manufacturers also potentially manufacture products of variable quality, so the expected benefits from more consistent product quality would be reduced. Moreover, if dietary supplements contain too little of a vitamin or mineral consumers may not receive the intended health benefits, and if the dietary supplements contain too much of a vitamin or mineral they may experience illness or injury.

We estimate that the benefits of this option would be approximately proportional to the ratio of recalled products that were classified as vitamins and minerals to all recalled dietary supplements products. Approximately 50 percent of the recalled products were vitamins and minerals so we estimate that this option would generate no more than $109 million in benefits. We assumed that the costs of this option would be proportional to

the fraction of establishments that would be required to follow all of the proposed provisions and those that follow the reduced requirements with the total costs estimated for this proposal as shown in table 17 of this document. The estimated mean cost of the proposed regulation is $86 million (see table 19 of this document). The fraction of establishments required to follow all the provisions is .46 (= 723/1566). The fraction of establishments that would have reduced testing is .54 (= 843/1566). Testing is approximately 36 percent of the total costs. We estimate the total costs from this option to be $69 million ($86 million x .46 + $86 million x .54 x (1 - .36)).

c. More restrictive CGMP regulations than the proposed regulations. One option is to propose (or finalize) more restrictive rules than the proposed CGMP regulations. Under this option, CGMP regulations could provide consumers with additional safeguards. Several of the largest manufacturers of dietary supplements now voluntarily comply with some of these additional safeguards (Ref. E2). The most significant additional provisions that would be required under this option are product quality testing for each incoming shipment lot of components and dietary ingredients, inprocess testing for contaminates at critical control points and mandatory written procedures for all of the various provisions of the proposed regulation.

The advantage of this option is that the additional requirements provide safeguards that the essential safety and quality provisions are being followed. The disadvantage of this option is that it is more costly than the proposed rule, and we are not aware of any information that would show any additional verifiable health benefits.

d. HACCP without the other elements of CGMP regulations. The agency could propose a requirement that manufacturers implement a HACCP (or HACCP like) system for the manufacturing of dietary supplements without the other elements of the proposed CGMP regulations. A critical control point is where production controls can be applied to reduce or eliminate hazards (including biological, chemical, or physical contamination) that may make dietary supplements unsafe.

The advantage of an industry-wide HACCP program is that HACCP does not require manufacturers to follow detailed uniform requirements in order to achieve desirable outcomes. Manufacturers themselves determine for their specific products and processes how they will best eliminate, reduce, or control hazards in the manufacturing of dietary supplements.

We have not designed a hypothetical HACCP system for the dietary supplement industry. For the purpose of generating estimates of costs and benefits, we assumed that a HACCP regulation for a dietary supplement manufacturer would be likely

to encompass sanitation prerequisites that are met, writing a HACCP plan, and monitoring critical control points. The benefits and costs of the HACCP plan would be generated by controls for a narrower set of hazards in the manufacturing, packaging, and holding processes than those covered by this proposal, and would not include the other benefits and costs generated by the proposed rule especially the reduced consumer search costs, because uniform product quality would not necessarily be assured. The advantage of HACCP as an option to prevent product contamination is that it does not specify detailed manufacturing requirements. The disadvantage is that in the absence of uniform controls there would not be uniform minimum product quality across the industry and consumers would not derive the same benefits from lower search costs.

e. Require final product testing only. FDA could propose that manufacturers test their finished products for identity, purity, quality, strength, and composition but not include any of the other mandatory provisions of the proposed regulation. The advantage of this option is that it would be the least costly option of those considered. Many firms already test some of their finished products, reducing the impact of this option. Approximately 69 percent of manufacturing plants conduct finished product testing and almost 65 percent of all finished batches in the industry are already tested using physical, chemical,

microbiological, visual or organoleptic testing techniques (Ref. E2). The problem with this option is that finished product testing alone cannot ensure product quality for some types of products. Not every finished product currently has a test that confirms identity, purity, quality, strength, or composition, especially for multiingredient products. Tests may not have been developed, or they may not be completely reliable, or they may not be capable of evaluating every type of product defect. Also, potentially lower cost alternatives to finished product testing--such as incoming component lot testing, inprocess testing, or both--might be available and desirable to firms as a means to protect the public. Moreover, finished product testing alone is not sufficient to prevent products with microbiological or chemical contamination from being discovered because it is possible that false negatives might occur, as when there is "hotspot" contamination within a batch. Preventative controls must be imposed to achieve that goal. Finally, finished product testing alone also will not facilitate trace backs when defective products are discovered in the marketplace, nor will it facilitate responsible investigations of consumer complaints. The estimated cost of this option is lower than that of the other options, but it does not generate the full range of benefits provided by the proposed rule.

f. Regulate only high-risk products. FDA could propose CGMP regulations that would cover only high-risk products. The advantage of this option is that it would impose lower costs than the proposed rule, but (if all risky products could be identified and regulated) generate the same level of benefits. Only those establishments that manufacture high-risk products or have high-risk hazards would incur the costs of adopting CGMP regulations. High-risk might be defined as those products most likely to be contaminated, or suffer other product defects. There are two problems with this option. Adverse event reporting is not mandatory, so significant underreporting is expected. Also, it is possible that the confirmed illnesses and other problems linked to particular dietary supplements may be those most easily traced, rather than those with the highest risk. High levels of identified problems may not be closely correlated with high levels of risk. In other words, problems associated with the known defective products may or may not be correlated with the highest risk. Without more data and risk assessments, it would be difficult to distinguish what risks may be associated with particular dietary supplements. We therefore have no basis upon which to begin a full evaluation of what the high-risk products are or may be.

3. Coverage of the Proposed Rule

The proposed rule would cover establishments that manufacture, package, hold dietary ingredients or dietary supplements. Tables 2, 3, and 4 of this document list the estimated number of covered manufacturers, packagers, dietary ingredient suppliers, holders, and other establishments. Table 2 of this document shows the number of covered establishments by product type and size. A small business, based on the Small Business Administration definition, is any firm with 500 or fewer employees. For purposes of analysis, we defined very small establishments as having fewer than 20 employees. Table 3 of this document shows the number of establishments categorized as manufacturers, ingredient suppliers, repackers or relabelers, holders whose primary business is dietary ingredients or dietary supplements, and other (although not including other holders and distributors). Table 4 of this document shows our estimate of the number of general warehouses and wholesalers that hold dietary supplements.

Table 2.--Covered Establishments by Product Type and Size From Dietary Supplement Enhanced Establishment Database (DS-EED)

Product Type	Very Small	%	Small	%	Large	%	Unknown	%	Total
Vitamins and Minerals	252	29.8	223	26.5	78	9.2	290	34.5	843
Amino Acids, Proteins	21	31.0	16	23.0	6	6.9	27	39.1	69
Herbals and botanicals	148	42.6	46	13.2	5	1.1	150	43.1	348
Supplements not already classified	93	30.4	66	21.6	20	6.5	127	41.6	306
Total	514	32.8	351	22.4	106	6.8	594	38.0	1,566

Table 3.--Covered Establishments by Type of Operation From DS-EED

Establishment Type	Number of Establishments	Percent of Establishments
Manufacturer	1,228	78.4
Dietary ingredient supplier	106	6.7
Repacker; relabeler	26	1.7
Holder	114	7.3
Establishments not already classified	92	5.9
Total	1,566	100.0

Table 4.--Covered Establishements That Hold Dietary Supplements

Type of Holders	Source and SIC Code		Number of Establishments
Grocery Wholesalers or Drug Wholesalers	Dunn and Bradstreet	5122, 5141	25,527
Food or Drug Warehouse	Dunn and Bradstreet	N/A	738
Miscellaneous Food or Drug Warehouse	Dunn and Bradstreet	4225, 4226, 5912, 5499, 5411, 5122, 5141, 5149, 5399, 5311, and 5331	238
Dietary Supplement	DS-EED		114
Total			26,617

We consulted several sources to estimate the number of establishments reported in tables 2, 3, and 4 of this document. The number shown in tables 2 and 3 of this document, 1,566, is

the estimated number of establishments in the DS-EED that manufacture, repackage, supply dietary ingredients, or hold dietary supplement products in the United States. RTI developed the DS-EED using FDA's Official Establishment Inventory (OEI) and supplemented that source with information from trade organizations, trade shows, and electronic databases (Refs. E1 and E2).

The number of establishments in the DS-EED that hold dietary supplements is not the total number of holders covered by the proposed regulation. The holding establishments in the DS-EED identified holding dietary supplements as their primary business. To estimate the total number of establishments that could hold dietary ingredients or dietary supplements but do not consider dietary supplements as their primary business, we performed three searches of firms that are listed with Dun and Bradstreet's Dialog database. We first looked for a count of firms that had standard industrial classification (SIC) codes for wholesalers of groceries or drugs. Next we looked for a count of firms that met the description of warehouses of groceries or drugs (no SIC codes were used). Finally, we looked for a count of any firms that had both warehouse SIC codes and miscellaneous drug stores, food stores, sundries, and general merchandise (SIC 4225, 4226, 5912, 5499, 5411, 5122, 5141, 5149, 5399, 5311, and 5331). The results are shown in table 4 of this document. We concluded that the total number of establishments in this category that could hold dietary ingredients or dietary supplements and would be covered

by the regulation was approximately the sum of the numbers counted in the three searches, or 26,617.

The number of establishments that hold dietary ingredients or dietary supplements includes retailers that sell dietary supplements to consumers, and transporters of dietary ingredients and dietary supplements. We made no effort to determine the number of such holders, because the proposed requirements do not apply to retailers and transporters. We believe that retailers and transporters may voluntarily adopt provisions related to the holding of these products and thus there may be changes in the marketplace with accompanying costs and benefits. However, we expect that the only retailers and transporters that will voluntarily adopt the proposed requirements are those that expect the private benefits of adoption will exceed the private costs.

4. Baseline Practices

a. Consumer baseline practices. Baseline consumer and manufacturer practices, governed by current market forces and existing government regulations, give rise to the current risks associated with the manufacturing of dietary supplements. When determining baseline manufacturing practices, it is necessary to estimate both the practices that are used now, as well as the likely changes in manufacturing practices that will occur even in the absence of new regulations. The risks to consumers from these products can be associated with a combination of consumption habits, the contamination of the products, or both. Contamination may be caused by current manufacturing practices.

Consumption is influenced by the price and quality of dietary supplements, set by the interaction of market participants. Finally, changes in practices of either consumers or manufacturers caused by new regulatory requirements will give rise to changes in risks, as estimated by changes in costs and benefits.

The consumption of dietary supplements has grown in recent years. Consumers report that they are using a wider range of product types, and that they are using dietary supplements for more reasons than they were in the past.

Table 5 of this document illustrates the rapid sales growth of the dietary supplement industry from 1994 to 2000. Panel A of table 5 of this document shows annual sales of three general categories of dietary supplements, a measure of the market size of the supplement industry. Annual increases in sales of herbals and botanicals were the greatest, averaging 18 percent per year, while annual increases in sales of supplements that were neither vitamins and minerals nor herbals and botanicals increased less, averaging 11 percent per year. The lowest annual sales increases were for vitamins and minerals, averaging 8 percent per year. For all dietary supplements combined, sales increased an average of 12 percent a year since 1994 (not shown on the table).

While the sales growth shown in table 5 of this document, Panel A, is impressive, only part of this apparent growth represents increased use. Population growth and rising prices also contributed to the apparent growth. The real (growth

inflation-adjusted) increase in dietary supplement prices is estimated by subtracting the inflation rate from the rate of price increases of dietary supplements (Ref. E4). As shown in table 5 of this document, Panel B, between 1995 and 1997 the real price of vitamins and minerals and supplements other than vitamins and minerals all increased. Rising real price indicates that demand is growing rapidly.

Table 5 of this document, Panel C, shows estimated annual increases in per capita consumption of dietary supplements.[1] As shown in table 5 of this document, Panel C, the estimated per capita consumption of the different categories of dietary supplements has increased since 1994.

For the consumption estimates in table 5 of this document, we averaged dietary supplement use over the entire U.S. population, 275 million. In table 6 of this document, we included estimated average supplement use for the population of supplement users, 160 million (Ref. E13). The three panels in table 6 of this document show the annual consumption per supplement user and the annual change in consumption per supplement user for vitamins and minerals, herbals and botanicals, and supplements other than vitamins and minerals and

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[1]An index measuring per capita consumption of dietary supplements can be derived using the following equation: $PCC_t = [1{,}000 \times Sales_t]/[POP \times P_t]$, where, t = year index; PCC_t = per capita consumption (# of unit sales); Sales = millions of dollars of sales; POP_t = thousands of U.S. residents; P_t = average price of supplement. In the formula, we measure consumption as the number of dietary supplement units (bottles, packages, etc.) sold per U.S. resident for a given year.

herbals and botanicals. Table 6 of this document also shows that during this period the proportion of consumers using supplements increased faster than the average consumption for the total population. The surprising implication of this result is that consumption per user has apparently declined since 1994.

One limitation of the estimates in table 6 of this document is that prevalence of supplement use is based on the proportion of U.S. adults consuming supplements, while the per capita consumption figures are based on the entire U.S. population. Nonetheless, we do not have any reason to believe that the estimated trend in consumption per user is biased. This trend, expressed as the percentage change in consumption per user, is negative for all segments of the dietary supplement industry since 1994. The large and rising number of consumers accounts for the growing size of the dietary supplement industry.

Table 5.--Growth in Market Size and Per Capita Consumption
Of Dietary Supplements, 1994-2000

Panel A							
Nominal Market (Millions of Current Dollars)							
	1994	1995	1996	1997	1998	1999	2000
Vitamins	3,960	4,220	4,780	5,190	5,550	5,940	6,360
Growth rate		6.57%	13.27%	8.58%	6.94%	7.03%	7.07%
Minerals	700	800	900	1,070	1,160	1,250	1,350
Growth rate		14.0%	13.0%	19.0%	8.0%	8.0%	8.0%
Herbals and Botanicals	2,070	2,530	2,990	3,530	4,170	4,840	5,520
Growth rate		22.22%	18.18%	18.06%	18.13%	16.07%	14.05%
Supplements other than vitamins/minerals and botanicals	2,070	2,290	2,620	2,890	3,180	3,490	3,840
Growth rate		10.63%	14.41%	10.31%	10.03%	9.75%	10.03%
Total	8,080	9,840	11,290	12,680	14,060	15,520	17,070
Growth rate		12.0%	15.0%	12.0%	11.0%	10.0%	10.0%
Panel B							
Prices							
	1994	1995	1996	1997	1998	1999	2000
Consumer price index-units	148.5%	152.5%	157.0%	160.5%	163.2%	166.7%	
Inflation rate	2.56%	2.76%	2.957%	2.23%	1.68%	2.14%	2.39%
Vitamins and minerals							
Average nominal price (IRI)	$6.20	$6.50	$6.87	$7.34	$7.54	$7.78	$8.05
Nominal price increase	2.69%	4.84%	5.69%	6.84%	2.72%	3.18%	3.43%
Real price increase	5.25%	2.08%	2.74%	4.61%	1.04%	1.04%	1.04%
Supplements other than vitamins and minerals							
Average nominal price	$6.20	$6.50	$6.87	$7.34	$7.70	$8.11	$8.56
Nominal price increase	5.80%	4.84%	5.69%	6.84%	4.85%	5.31%	5.56%
Real price increase	3.24%	2.08%	2.74%	4.61%	3.17%	3.17%	3.17%
Panel C							
Per Capita Consumption (Number of Units Sold Per U.S. Resident)							
	1994	1995	1996	1997	1998	1999	2000
Vitamin/mineral sales	2.45	2.47	2.62	2.64	2.72	2.80	2.87
% Growth		0.69%	6.19%	0.66%	3.12%	2.74%	2.55%
Herbals sales	1.28	1.48	1.64	1.80	2.00	2.19	2.34
% Growth		15.48%	10.79%	9.45%	11.60%	9.17%	7.03%
Supplements other than vitamins and minerals and herbals sales	1.28	1.34	1.44	1.47	1.53	1.58	1.63
% Growth		4.53%	7.26%	2.26%	3.95%	3.23%	3.25%

Table 6.--Comparison of Consumption Per Person With Consumption Per User: Evidence That the Dietary Supplement Market Is Becoming Broader Not Deeper

A. Vitamins and Minerals							
Average Growth	1994	1995	1996	1997	1998	1999	1994-2000
Per capita consumption (units per U.S. resident)	2.45	2.47	2.62	2.64	2.72	2.80	
% Growth		0.69%	6.19%	0.66%	3.12%	2.74%	2.68%
Consumption prevalence		47.70%	54.0%	61.0%	70.0%	79.0%	
Reference		Ref. E6	Ref. E6	Ref. E6	Ref. E6	Ref. E7	
% Growth			13.44%	13.44%	13.44%	13.44%	13.44%
Consumption per user (units)		5.18	4.85	4.30	3.91	3.54	
% Growth			-6.39%	-11.27%	-9.10%	-9.43%	-9.05%
B. Herbals and Botanicals							
Average Growth	1994	1995	1996	1997	1998	1999	1994-1999
Per capita consumption (units per U.S. resident)	1.28	1.48	1.64	1.80	2.00	2.19	
% Growth		15.48%	10.79%	9.45%	11.60%	9.17%	11.30%
Consumption prevalence	8.20%	12.10%	12.10%	12.10%	28%	49%	
Reference	Ref. E8	Ref. E8	Ref. E8	Ref. E9	Ref. E10	Ref. E7	
% Growth		47.56%	0.00%	0.00%	131.40%	75.00%	50.79%
Consumption per user (units)	15.64	12.24	13.56	14.84	7.16	4.47	
% Growth		-21.74%	10.79%	9.45%	-51.77%	-37.62%	-18.18%
C. Supplements Other than Vitamins and Minerals and Herbals and Botanicals							
Average Growth	1994	1995	1996	1997	1998	1999	1994-1999
Per capita consumption (units per U.S. resident)	1.28	1.34	1.44	1.47	1.53	1.58	
% Growth		4.53%	7.26%	2.26%	3.95%	3.23%	4.24%
Consumption prevalence	5.1%	8.8%	11.2%	14.2%	18.1%	23.0%	
Reference	Ref. E8	Ref. E8	Ref. E8	Ref. E8	Ref. E8	Ref. E7	
% Growth		72.55%	27.15%	27.15%	27.15%	27.14%	36.23%
Consumption per user (units)	25.15	15.24%	12.85	10.34	8.45	6.86	
% Growth		-39.42%	-15.64%	-19.58%	-18.25%	-18.81%	-22.34%

b. Manufacturer's baseline practices. FDA contracted with RTI to conduct a survey of the dietary supplement industry to learn about both baseline (existing) manufacturing practices and the existing standards used for manufacturing dietary ingredients and dietary supplements (Ref. E2). A sample of 966 dietary supplement establishments from the DS-EED database was selected from an estimated eligible population of 1,566 firms in the

industry. The sample was stratified by manufacturer's product type and the size of firm in the industry. Stratification helps ensure that estimates of the subpopulations are more precise. Establishments that were stratified by manufacturer's product type were classified as primarily: (1) Vitamins and minerals; (2) amino acids, proteins, or animal extracts; (3) herbals and botanicals; or (4) all other product types not already classified. The product type strata were further stratified by four size categories: (1) Very small, (2) small, (3) large, and (4) unknown. This categorization generated 16 sampling strata.

The contractor, RTI, sent each of the 966 firms in the sample a lead letter on FDA letterhead and a one-page brochure to explain the purpose of the survey, the value of the establishment's participation, and the agency's confidentiality procedures. Following the mailing, RTI placed telephone calls to each establishment to screen for eligibility and to recruit eligible establishments for the mail survey. To be eligible for the survey, establishments had to currently manufacture, repackage, supply dietary ingredients, hold, import or export dietary supplements for human consumption. Almost 50 percent of the establishments sampled were not eligible for the survey because they were no longer in operation at the listed address or did not handle any dietary supplements or ingredients for human consumption.

To achieve the highest possible response rate, RTI operated a toll-free help line and attempted to contact each establishment up to eight times before assigning a disposition of nonresponse. RTI also attempted up to two refusals conversions, which are attempts to persuade firms that declined to answer the survey to respond. The survey was conducted over a 10-week period, November 29, 1999, to February 4, 2000. There were a total of 238 completed surveys, resulting in a final disposition of: (1) An overall eligibility rate of close to 50 percent, and (2) a response rate of 50 percent.

Determining baseline practices is necessary in order to determine the new activities that are likely to take place as a result of implementation of this proposed rule. Each of the new activities potentially brought about by the proposed rule has both a marginal (or incremental) cost and a marginal (or incremental) benefit. These incremental costs and benefits of likely new activities form the basis of our economic analysis of the proposed rule.

The survey asked establishments a series of questions about existing practices; we used the responses to estimate how many establishments in the industry already operated in accordance with the requirements of the proposed regulation. One key assumption in this analysis is that no firms are expected to stop CGMPs and no firms are expected to start good manufacturing

practices in the absence of this rule. The universe for the survey includes the establishments discussed in section VII.B.3 of this document. If firms start good manufacturing practices in the absence of this rule, both the costs and benefits of the rule would be less than we estimate. If firms were to stop in the absence of the rule, both the costs and benefits would be more than we estimate. We lack information about the trend in the industry, so we assumed that the survey reflects both the current and future practices in the industry. We request comment or information about the industry trend in adopting good manufacturing practices.

i. Stratification. The survey was stratified by product type and establishment size. Stratification ensures that samples are representative of the industry population.[2] The subdivisions of the population of interest here were establishment size (by the number of employees) and product type, because these characteristics are likely to influence whether an establishment already has adopted the practices that would be required by the regulation. The DS-EED includes nine product types: (1) Vitamins and minerals; (2) herbals and botanicals; (3) herbal and botanical extracts; (4) amino acids; (5) proteins; (6) animal extracts; (7) tea like products; (8) concentrates, metabolites,

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[2]Stratification is a subdivision of the population of establishments in the dietary supplement industry by a unique characteristic such as product type or number of employees.

or constituents; and (9) supplements not already classified (all other supplements). Establishments may produce more than one product type; establishments with multiple product types were, however, only classified in one category. For stratification and reporting purposes, we defined the following four mutually exclusive categories of dietary supplements:

1. Vitamins and minerals (includes establishments that may also manufacture, package, or hold herbals and botanicals, amino acids, proteins, or animal extracts but predominately manufacture vitamins and minerals);
2. Amino acids, proteins, and animal extracts (includes establishments that also manufacture, package or hold herbals and botanicals, including extracts; excludes establishments already classified as vitamins and minerals);
3. Herbals and botanicals, including extracts (excludes establishments already classified as "vitamins and minerals" or "amino acids, proteins, or animal extracts"); and
4. Supplements not already classified (all other product types).

We further stratified each of the four product categories into four size categories, very small, small, large, and unknown-

-resulting in 16 sampling strata. We classified each establishment into one mutually exclusive industry category (manufacturer, dietary ingredient supplier, repacker/relabeler, holder, or establishment not already classified). Establishments that manufacture supplements and also supply, repack, or hold dietary supplements or ingredients were classified as manufacturers.

ii. Size stratification. The Small Business Administration classifies companies as "small" based on the size of the entire company, including both parent and subsidiaries. If firms that manufacture dietary supplements have 500 or fewer employees, they are classified as small. Because the DS-EED data on size are only for specific establishments and not parent firms, we had to obtain parent company information on employment or revenue to correctly classify each establishment as part of a small or large company. To obtain parent company data for establishments in the survey universe, we sent *info*USA[3] the DS-EED data records (N = 2,004) and requested the name, address, primary SIC, employment size (in ranges), and revenue (in ranges) of parent company firms with establishments in the survey universe. *Info*USA matched 1,219 of the 2,004 records in the DS-EED to their U.S. database of 10.3

[3] *Info*USA is a publicly held company that creates proprietary business databases. Their database includes such information as: Company name, address, phone number, fax number, estimated sales, volume, number of employees, type of business (SIC code or yellow page heading), key contact names, and titles.

million businesses. Of the 1,219 matched records, 31 records were found to be duplicates of another record and were removed, leaving 1,188 matched records and 1,566 total records in the sampling frame. The nonmatched records did not match because: (1) They were recently established businesses, (2) they were out of business, or (3) they had recently changed their names or addresses. Because data on revenue or employment size were not available for the nonmatched records, we created an "unknown" stratum for these establishments. The survey of practices collected information on employment that allowed us to classify some of these establishments by size for the analysis.

Of the 1,188 matched records, 180 were linked to parents. The parent company data for these 180 establishments were merged with the survey universe. The remaining 1,008 records did not link to an ultimate parent company. For these records, the establishment and parent company were the same entity, so we used establishment level data to classify size. We classified each of the establishments in the survey universe as part of very small, small, or large businesses based on the employment size or annual revenues of each establishment's parent company. If an establishment or its parent company had 500 or fewer employees or sales less than $20 million (if data on employment were not available), then the establishment was classified as small. An

establishment was classified as very small if the number of employees was less than 20.

iii. Survey response. Table 7 of this document presents the number of establishments surveyed, stratified by the four product types and by size. Although the sample allocation was designed to yield 400 completed surveys, we received only 238 completed mail surveys. The number of respondents was fewer than expected because the number of establishments that were ineligible was greater than we expected and because some establishments did not respond to the survey after agreeing to participate. Ineligible establishments are those that no longer produce dietary supplements because they have gone out of business or changed product lines, or they have moved and could not be located. Despite receiving fewer responses than planned, the confidence level for the final results allowed us to make meaningful inferences regarding the industry. For example, 65 percent of the establishments surveyed responded that they followed published good manufacturing practice models; the 95 percent confidence interval was 56 to 72 percent. By size category, 52 percent of very small, 73 percent of small, and 89 percent of large establishments responded that they followed published good manufacturing practice models (Ref. E2). Although we do not suggest that these percentages are precise, they do tell a plausible story of the current use of good manufacturing

practice models in the supplement industry: The use of good manufacturing practice models appears to be widespread but far from universal, with use more likely the larger the establishment.

Table 7.--Number of Completed Surveys by Sampling Strata

Product Type	Size				
	Very Small	Small	Large	Unknown	Total
Vitamins and minerals	19	39	13	1	72
Amino acids, proteins	8	7	0	5	20
Herbals and botanicals, including extracts	58	25	0	30	113
Supplements not already classified	14	13	2	4	33
Total	99	84	15	40	238

The mean survey results reflect the degree of uncertainty associated with each practice. The use of a survey for this economic analysis often required the use of the survey answers from more than one question to assess the impact of each proposed provision. For example, answers to questions about testing herbals might have been combined with questions about whether the firms manufactured herbals. Some highlights of the survey are:

- Plant characteristics: Manufacturers account for 62 percent of the total firms and 36 percent of manufacturers produce vitamins and minerals as their primary product.
- Use of published good manufacturing practice model: 65 percent of all firms follow some type of good manufacturing practice model, primarily food good manufacturing practices; 28 percent follow the NNFA

good manufacturing practices and 31 percent follow FDA's drug good manufacturing practice requirements.

- Personnel: 67 percent of all establishments maintain records of personnel education, training, or experience.
- Quality control: 85 percent of all establishments have a unit or person responsible for quality control. Almost 80 percent of all manufacturers conduct at least some type of identity tests on incoming components and dietary ingredients and 96 percent of these firms also conduct some type of contamination test; 63 percent conduct some type of potency test. Nearly 70 percent conduct tests on inprocess materials or finished products. Of these firms, 97 percent conduct identity tests, 94 percent conduct contamination tests and 72 percent conduct potency tests. Asked whether firms hold reserve samples of each finished batch, 75 percent answered yes. Of the plants that have production processes, 70 percent use production and process controls that identify the points, steps, or stages in the manufacturing process to prevent adulteration. Almost 68 percent of all incoming ingredient or component lots are tested now and almost 70 percent of

inprocess or finished product batches are tested in some manner.

- Warehousing: 70 percent of warehouses have temperature controls and 22 percent have humidity controls.
- Consumer complaints: Only 19 percent report incidents to FDA.

5. Baseline Risk

The current number of illnesses caused by poor manufacturing practices requires data linking illnesses directly to poor practices. Without direct evidence on the number of illnesses caused by poor manufacturing practices, we had to use an indirect approach. There are two indirect ways to estimate the number of illnesses caused by defective products:

- We could take the number of reported cases and multiply by a factor to account for underreporting.
- We could take the number of defective products and multiply by the probability of illness for the given defect.

In an ideal analysis, we would estimate the baseline both ways and then compare them. For the analysis of illnesses from poor manufacturing practices, however, we did not have sufficient data to perform either type of baseline estimate.

We looked at many sources for information, including medical and other literature on adverse events, information from

poison control centers, reports to the agency, popular newspaper and magazine articles, and surveys of users. The literature review was conducted using Medline, Healthstar, Aidsline, Cancerlit, and OldMedline (Ref. E12). We found evidence of many adverse events associated with dietary supplements. For example, one recent survey found that 12 percent of consumers (about 11.9 million) who have used an herbal remedy claim to have suffered from side effects or other adverse reactions (Ref. E13). The American Association of Poison Control Centers received 6,914 reports on dietary supplements in 1998 (Ref. E14). In a recent survey, 46 percent of respondents answered that people get sick from dietary supplements "often" or "sometimes" (Ref. E3). In addition, the agency has received many voluntary reports of illnesses caused by dietary supplements (Ref. E15). The vast majority of the illnesses described in the sources we consulted, however, are reported as associated with the ingredients used in the products themselves, not with poor manufacturing processes. We have no direct evidence on what fraction of illnesses can be attributed to manufacturing processes. The anecdotal evidence implies that many illnesses could have been caused by poor manufacturing processes, but with a few exceptions, no evidence explicitly links illnesses to these manufacturing processes.

The agency's recall records are more useful than the reports on illnesses, because the class 1 and class 2 recalls all involve

defective products that could have caused illness if ingested. The major public health events that have been linked to poor manufacturing processes show up in the list of dietary supplements recalled. Although the recall data cannot be linked directly to illness data, we have found anecdotes, surveys, and some medical literature on illnesses that could be caused by avoidable manufacturing mistakes. We have recall data that show that manufacturing mistakes exist, so we can construct a possible link between manufacturing mistakes and potential illnesses or injuries. The number of illnesses associated with a recall is both variable and uncertain, and could be anything from zero to quite large. We concluded that one illness would not be an implausibly high average for a recall, so we assumed that a recalled product could be a proxy for a single reported illness associated with a defective product. We ask for comments on this assumption.

Because there are no well established systems for the notification of adverse health events related to dietary supplements, and some significant barriers to reporting, we assume that unreported illnesses caused by poor manufacturing practices are substantially greater than reported illnesses. We relied on Ref. E16 to estimate a more precise relationship between reported and unreported rates. Based on empirical data for drug and vaccine reporting rates among other studies, the

author of Ref. E16 determined that for dietary supplements, reported illnesses represent at best approximately 1 percent of total illnesses (Ref. E16). A similar multiplier of 100 linking known cases of foodborne illness to total incidence is often used. We assume that reporting adverse health events due to poorly manufactured dietary supplements would occur at the same proportion as adverse health events caused for other reasons by dietary supplements. We show the sensitivity of benefits to the choice of multiplier below, in the uncertainty and sensitivity analysis of our results.

The outbreak of eosinophilia-myalgia syndrome (EMS) resulting from contaminated L-Tryptophan resulted in the recall of the contaminated products. In part based on this example, we assume that product recalls can indicate when there are adverse health events. We also assume that the reported class 1 and class 2 recalls that have occurred over the last 10 years represent the number and type of recalls that will occur in the future but for the implementation of this regulation. From 1990 through 1999, the agency received reports on an annual average of 13 class 1 and class 2 recalls of dietary supplements. If each recall is a proxy for a reported illness, then the total number of unreported illnesses per year is approximately 1,300. Obviously, to the extent that products are successfully recalled, illnesses will be avoided. Our assumption is that the recall occurs because at

best one person on average has been made ill. We recognize that our procedure generated highly uncertain estimates of the number of illnesses. The use of recalls to estimate reported and unreported illnesses probably generated a distribution of illnesses below the "true" distribution, because many illnesses occur that are not linked to recalls and are never reported. We were not able to determine even the approximate size of the underestimation from this procedure.

We estimated the monetary value of the health benefits from CGMP regulations by multiplying the number of illnesses prevented by the health costs associated with an illness. The health benefits associated with preventing an illness come from: (1) Preventing the loss of productivity, (2) the reduction in pain and suffering, and (3) the reduction in expenditures on medical treatment. We measured lost productivity indirectly with measures of functional state, which includes measures of physical function. We estimated the losses caused by pain and suffering with a symptom-problem index. We used direct measures of medical costs, such as payments to physicians and hospitals.[4]

Table 8 of this document contains summaries of our measures of the health effects potentially caused by known instances of defective products associated with poor manufacturing processes.

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[4]The cost of a hospital day is from the Health Care Financing Agency's Indicator Tables. It is the amount per patient day in 1997, adjusted to 1999 dollars. See Ref. E17.

We estimated the health loss per day for the different levels of illness severity by summing the lost productivity (as measured by functional state) and the loss from pain and suffering (as measured by the symptom-problem index[5]). These losses per day can be interpreted as the difference between a day of normal health, where normal is defined as the population's health not affected by these products, and a day of suffering from the health conditions caused by these defective products. The numerical scale is a relative baseline that rests on the notion of a quality-adjusted life day (QALD). The QALD for a day of normal health equals 1; the QALD for death equals 0. The loss of QALDs per illness equals the daily loss multiplied by the number of days the illness lasts. We converted QALDs to dollars by multiplying the index numbers by the value of a statistical life day and adding the direct medical costs.

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[5]Functional Status Code is a measure of lost mobility (MOB), physical activity (PAC) and social activity (SOC). Lost MOB might mean an inability to drive a car. Lost PAC might mean walking with physical limitations. Lost SOC might mean self-care is not possible. Symptom-problem health utility index is a weighted measure of the cost of each symptom. For example, a sick or upset stomach has a utility weight of .290.

Table 8.--Summary of Health Effects Based on Potential Illness Associated With Recalls Between 1990 and 1999

Problem	Class of Recall	No. of Recalls	Outcomes	Frequency of Illness (percent)	Quality Adjusted Life Day	Duration of Illness (days)	Medical Cost ($) Per Event	Health Cost ($) Per Event
Hypervitaminosis A	1	2		100	0.472	3	$84	$936
Salmonella	1	4	Mild	93.8	0.473	2	0	534
			Moderate	5	0.473	5	800	2,223
			Severe	1.2	0.563	17	9,100	14,859
			Reactive arthritis (short term)	2	0.42	25	100	6,438
			Reactive arthritis (long term)	1	0.42	5,223	400	1,320,252
	2	4	Death	0.04			9,100	5,009,100
Klebsiella pneumonia	1	1	Severe	85			6,235	10,650
			Death	15			6,235	5,006,325
Selenium poisoning	1	1	Low doses	50	0.482	3	84	954
			Severe	35	0.482	3	2,578	4,448
			Death	15			2,578	5,002,578
Stannous fluoride	1	1	Acute	100	0.473	3	84	938
	2	1			0.473	3	84	938
Eosinophilia-myalgia syndrome	1	7	Mild	47	0.482	5,223	1,176	1,515,863
			Moderate	50	0.482	60	84	17,484
	2	41	Severe	10			14,964	27,394
Glass fragments	2	1	Dental injury, simple	50	0.231	1	139	
			Dental injury, complicated	12			3,741	
			Oral emergency	12			3,741	6,428
			Tracheo-esophageal obstruction	25				290
			Esophageal perforation	1			14,964	23,343
Hypervitaminosis D	2	1		100	0.473	3	168	1,022
Pyridoxine (vitamin B6)	2	2		100	0.482	30	168	8,868
Super-potent zinc	2	1	Mild	50				285
			Moderate	40				596
			Severe	10			1,247	3,347
Niacin	2	1		100			84	4,258
Yellow #5 (undeclared)	2	5	Mild allergic reaction	90	0.44	2	0	529
			Severe allergic reaction	10			2,494	3,346
			Contact dermatitis	50			84	1,205
Yellow #6, red #40, blue #2 (undeclared)	2	1	Abdominal cramps	10	0.473	3	84	938
			Contact dermatitis	90			84	1,205
Copper salts	2	1		100	0.473	1	84	369
Digitalis	1	33	Mild	94.9	0.473	3	84	938
			Severe (heart block)	5			1,247	455,883
			Death	0.1				5,000,000
Ephedra (undeclared)	1	1	Cardiovascular	14			1,415	3,530
			CVS w/chronic	2			2,591	457,227
			Nervous system	14	0.47	2	1,331	1,900
			NS w/chronic	2			2,507	455,597
			Liver impairment	4			168	4,342
			Exfoliative dermatitis	7			84	1,206
			Other	54	0.29	1	0	174

Table 8.--Summary of Health Effects Based on Potential Illness Associated With Recalls Between 1990 and 1999 (Continued)

Problem	Class of Recall	No. of Recalls	Outcomes	Frequency of Illness (percent)	Quality Adjusted Life Day	Duration of Illness (Days)	Medical Cost ($) Per Event	Health Cost ($) Per Event
			Death	3			$2,507	$5,002,507
Lactose (undeclared) intolerance	2	1	Mild	100	0.48	1	0	290
Iron poisoning	2	1	Mild	100	0.48	1	84	374
Sulfites (undeclared)	1	1	Mild allergic reaction	100	0.44	2	0	529

We used the transformed value of statistical life to estimate the value of QALD. For the most likely value of a statistical life day, we used $630. We derived this value from a widely-used estimate of the value of a statistical life: $5 million. The $5 million estimate is based on calculations matching labor market risks with wages for risky jobs. Workers in risky jobs tend to receive increased wages to compensate them for (usually) small increases in the probability of death. The implicit value of a statistical life is the increased wage divided by the increased probability of death. The advantage of valuing statistical lives with this method is that it reflects the observed willingness of workers, and by inference, of the whole population of adults, to accept small risks to their lives in a real world risk-dollar tradeoff.

We turn the estimated value of a statistical life into a value of a statistical life day by first assuming that the workers have a remaining life expectancy of 36 years (Ref. E18). Using a 3 percent social rate of time preference, the present value of 36 years is 21.83 years. The social rate of time

preference is the average long-term real rate of interest, with no premiums for risk and other factors that affect interest rates. Most analysts use the average real rate on long-term treasury bonds (3 to 5 percent in recent years) to represent the social rate of time preference. The discounted expected days lost for a statistical death is 21.83 x 365 = 7,968. Therefore, the value of a statistical day is $5 million/7,968, which is approximately $630. We use this value to estimate the public health benefits from preventing illness.

In addition to lost productivity and pain and suffering, illness caused by supplement contamination leads to direct medical costs. Direct medical costs include the cost of medicine, hospitalization, and visits to physicians and other professionals. We included all estimated medical costs, not just out-of-pocket expenses. These full medical costs often are missed because most medical care is covered by health insurance that separates the bearer of the medical cost (society) from the bearer of the utility losses (the ill person).

The total costs of illnesses caused by the contamination of dietary supplements from poor manufacturing practices would be the costs per illness (classified by severity) multiplied by the number of illnesses (classified by severity). For chronic illnesses, the utility losses and medical costs stretch indefinitely into the future. We used a real discount rate of 7

percent to calculate the present value of chronic medical expenditures and utility losses. OMB suggests using a real discount rate of 7 percent to analyze the costs and benefits of regulations. This rate approximates the marginal rate of return on an average investment in the private sector in recent years. We used a different discount rate for the social rate of time preference (3 percent) and the discount rate of future medical costs (7 percent). Medical costs, like all expenditures, reflect the foregone benefits from alternative investments. The pure social rate of time preference can differ from the return on private investments.

6. Benefits and Costs

Changes in current practices by manufacturers, or consumers, or both, cause incremental (marginal) benefits and costs. There are several possible reactions manufacturers might have to the proposed regulatory requirements:

- Stop producing dietary supplements and possibly go out of business.
- Move production to a foreign country where compliance with these regulations is more difficult to enforce.
- Comply with part or all of the proposed regulation.

Consumers will likely be confronted with higher priced dietary supplements but also products that are, on average, more uniform and higher quality. To the extent that the latter is unknown to

consumers, they will probably reduce consumption of dietary supplements, perhaps in some cases substituting them with alternative products such as foods.

The benefits from the proposed regulation and the regulatory options result from reducing contamination and adopting practices that will result in consistently high quality dietary supplements. Creating industry-wide minimum requirements for good manufacturing practices should reduce the occurrence of product defects, which in turn should reduce the number of illnesses and deaths. Defective products can cause isolated cases of illnesses, but also rare catastrophic events such as the outbreak of eosinophilia myalgia syndrome (EMS) that resulted from the consumption of contaminated L-Tryptophan. That outbreak caused 38 deaths and over 1,500 illnesses.

The provisions that require establishments to maintain consumer complaint files related to manufacturing practices will generate additional health benefits. The use of these files by manufacturers and the agency will help identify dietary supplements that were manufactured or contaminated in ways that could cause a significant or unreasonable risk of illness or injury. These records may reduce the likelihood of catastrophic events, because a cluster of illness complaints could be identified, and preventive action taken before the number of illnesses reached catastrophic levels.

Improved product quality will also reduce the number of products recalled. Certain manufacturing practices, such as more frequent finished product quality testing, help establishments to identify problems before the products are released for consumption. If defective products are caught before they are released, they will not be recalled.

Creating minimum requirements should also generate benefits for consumers by reducing the variation in product quality. Creating verifiable minimum manufacturing requirements reduces the private effort necessary to distinguish products manufactured, packaged, and held using good practices from those using poor practices. Reducing the effort needed to find products with the identity, purity, strength, quality, and composition, among other characteristics, creates a potentially substantial, though implicit, benefit for consumers.

The benefits from the proposed rule, then, are from:

- Reduced health costs caused by the reduced number of illness;
- Fewer product recalls, and;
- Greater assurance of consistent and better quality products.

a. Reduced illnesses. The proposed regulation would improve the safety of dietary supplements, which would reduce the number of illnesses and the probability of deaths caused by

manufacturing problems. The proposed rule would also improve product safety through the provisions requiring records and investigations of consumer complaints related to manufacturing practices. We assumed that the proposed rule would reduce both sporadic illnesses and catastrophic outbreaks. We estimated the reduction of sporadic or annual illnesses by using the agency's recall records as evidence of possible illnesses; class 1 and class 2 recalls of dietary supplements all involved adulterated products that could have caused illness if ingested. We estimated the reduction of illnesses from preventing catastrophic events by using the public health effects of the outbreak of EMS that resulted from consumption of contaminated L-Tryptophan.

i. Reduced illnesses estimated from recall data. For annual illnesses, we used this formula for estimating the benefits from fewer illnesses:

Marginal health benefits =
baseline (or current) number of illnesses caused by poor manufacturing practices x
expected reduction in the number of illnesses brought about by the proposed regulation x
health cost saved per prevented illness.

We estimated the annual expected health benefits for the proposed rule by taking the values in table 8 of this document and weighing them by their incidence in the table. We computed

the expected health benefits from preventing a single illness (of any type) associated with a class 1 recall as a weighted average of all potential illnesses (see table 8 of this document), with the potential illness divided by the total number of class recalls.

The following formulas show how we calculated the average health benefits of preventing a single illness associated with a class 1 recall.

$\$health_{ij} = (QALD \times days \times \$ \text{ per } QALD)_{ij} + \$ medical_{ij}$

$EB_j = \sum_i (f_{ij} \times \$health_{ij})$

$EB\ [c1] = \sum_j (w_j \times EB_j)$

$w_j = r_j / (\sum_j r_j)$

where:

$\$health_{ij}$ = health costs of severity level i of illness j;

QALD = quality adjusted life day;

$ per QALD = dollar value of a statistical day;

$ medical = direct medical costs;

Eb_j = expected health benefit from preventing a single case of illness j;

f_{ij} = frequency of severity i of illness j ($\sum f_{ij} = 1$);

m = number of levels severity for illness j;

EB [c1], EB [c2] = expected benefits from preventing an average illness associated with a class 1 recall or a class 2 recall;

w_j = weight of illness j;

r_j = number of product recalls for hazard j;

n = number of hazards or potential types of illness.

We then repeated the procedure for class 2 recalls and the associated illnesses in table 8 of this document. Table 9 of this document shows the average value of preventing a single illness associated with class 1 and class 2 recalls.

We estimated the annual marginal health benefits as the health benefits per illness for each class of recall multiplied by the estimated number of recalls.

Health Benefits =

(EB[c1] x estimated annual number of class 1 illnesses prevented) +

(EB[c2] x estimated annual number of class 2 illnesses prevented).

To estimate the number of illnesses prevented, we started with the average annual number of products recalled for the decade 1990 to 1999--six class 1 and seven class 2. As discussed above, we then assumed that these recalled products represented proxies for about 1 percent of all illnesses caused by these problems leading to the recalls. With that assumption, we get

600 illnesses from class 1 recalls and 700 illnesses from class 2 recalls (see table 9 of this document)[6].

Table 9 of this document shows the estimated value of the health benefits from the proposed rule using class 1 and 2 recall data.

Table 9.--Health Benefits Using Recall Data

Total number of illnesses prevented, recall base	1,300
Total number of illnesses associated with class 1 recalls	600
Total number of illnesses associated with class 2 recalls	700
Dollar estimate of health benefit for preventing an illness associated with a class 1 recall	$60,000
Dollar estimate of health benefit for preventing an illness associated with a class 2 recall	$5,000
Dollar estimate of annual health benefits, recall base	$39 million

ii. Health benefits from preventing a rare catastrophic event. We estimated the marginal health benefits from reducing the probability of a catastrophic event as follows:

Marginal health benefits =

Change in probability of rare catastrophic event caused by poor manufacturing practices brought about by the proposed regulation x the number of illnesses caused by the rare event x health cost saved per illness.

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[6] We used a probability distribution to represent the uncertainty associated with the number of illnesses. We modeled the number of illnesses prevented for each class as the average number of recalled products plus a negative binomial distribution representing unknown cases. The negative binomial distribution estimates the number of failures (unknown cases) that will occur before some number of successes (known cases) for a given probability of success. In the negative binomial distribution, we assumed that the number of recalled products were reported cases and that the probability of reporting equaled 1 percent (Ref. E16). The result is that the mean estimated number of illnesses is 100 times the reported number of recalls.

In 1989, there was a widespread outbreak of EMS resulting from consumption of contaminated L-Tryptophan. More than 1,500 cases (175 acute illnesses and 1,287 chronic illnesses) and 38 deaths were identified in 50 states (Refs. E21 and E22). The outbreak prompted a recall of all dietary supplements that contained more than 100 mg per daily dose, which later was expanded to almost all products containing L-Tryptophan. We used the public health cost of this event as an estimate of the cost of a future rare catastrophic event associated with dietary supplements.

EMS is characterized by severe myalgia and elevated eosinophils counts. Some of the most common symptoms are fatigue, weakness, fever, and arthralgia. Although a repeat of the EMS outbreak is not expected, it is an example of the rare, catastrophic events that should be prevented or mitigated by the proposed CGMP regulation. The testing provisions of the proposed regulation should reduce the probability that contaminated ingredients would be released to the public. The provisions for keeping complaint files and investigating complaints would allow more rapid identification of a major health event; the defective products could be identified and withdrawn well before the event claimed as many victims as L-Tryptophan.

To estimate the benefits from preventing reduction in the probability of a rare catastrophic event occurring, we first

estimated the period between now and the last rare catastrophic event, 1989, and we needed to make baseline assumptions about the likely time interval between events. The last catastrophic event occurred over 13 years ago, so we assumed that the lower bound would be 50 years. For lack of data, we then assumed a uniform probability distribution between these two bounds, which leads to a rough estimate of once in 30 years. We do not know how likely rare events are, nor do we actually know the likelihood of reducing these events by the proposed regulation. There can be no conclusive empirical support for the likelihood of a future event because the past may not predict the future in the absence of a stable frequency distribution that reflects a statistically significant number of similar events. All we know is that such an event occurred at least once in the recent past, and remains a possibility. We recognize that our lack of information about such events creates significant uncertainty about the social costs of these events and the health benefits from reducing their impact. Our estimate is meant to convey the potential or hypothetical enormity of such an event, not the certainty of such an event. We would like comments regarding our estimate of such an event.

The health cost of the EMS outbreak was large because of the number, severity, and duration of the cases. One followup study (Ref. E21) found 88 percent of EMS patients were still

symptomatic 21 to 64 months after onset. The symptoms associated with EMS also frequently lead to activity limitations. Another study of victims (Ref. E22) found that 74 percent of symptomatic EMS sufferers were limited in their functions 12 months after the onset of illness.

To find the health cost of the outbreak, we estimated the cost of the following health outcomes: Death, acute illness only, chronic illness with no activity limitation, chronic illness with mild activity limitation, chronic illness with moderate limitation, and chronic illness with severe limitations. To determine the cost for each of these health outcomes, we multiplied the lost quality-adjusted life days over the duration of the illness by the value of a life day. For medical costs, we estimated the cost of hospitalization for the EMS patients who required hospitalization (32 percent of all victims), by assuming 3 days per hospital stay. We used $1,284 as the cost per day of time spent in a hospital (Ref. E17). We assumed that chronic sufferers visited the doctor once a year at a cost of $84 per visit. We estimated the total cost of the event to be about $2 billion. Most of the cost of the outbreak comes from the deaths and severe chronic illnesses. Table 10 of this document shows the values used in the calculation. Note that the categories are not mutually exclusive. The average age of victims was about 50, so the value of statistical life was adjusted accordingly. If

the event occurs about once in 30 years in the absence of the proposed rule, then the expected average annual cost would be about $66 million.

Table 10.--Health Benefits From Preventing Rare Catastrophic Event

	Number	Costs per case
Hospitalization	480	$3,741
Death	38	$4,214,301
Acute Illness	175	$8,760
Chronic illness not limited	380	$1,091,849
Mild chronic illness, limited	190	$1,349,002
Moderate chronic illness, limited	307	$1,601,539
Severe chronic illness, limited	409	$1,602,844
Visits to physicians	1,287	$1,539

The benefits attributable to this proposed rule from preventing a rare catastrophic event are highly uncertain. We do not know if such an event would, in the absence of the proposed regulation, ever occur again. The EMS outbreak may have been a unique event, although the recent severe public health effects associated with aristolochic acid in Europe show that such similar events remain possible (Ref. E23). We also do not know that if another catastrophic event occurred, the health effects would be as large as for L-Tryptophan. Some of the smaller clusters associated with dietary supplements could represent small events potentially prevented by the proposed CGMP regulations (Ref. E15).

We included reducing the likelihood of a catastrophic public health event as a benefit of the rule because the battery of checks and controls that would be required under the proposed regulation would reduce the likelihood of such an event occurring again. In particular, the requirement that establishments keep records of consumer complaints should lead to early

identification and prevention of potential catastrophic events related to manufacturing practices.

Our estimate of the health benefits associated with this proposal is based on two models that estimate future illnesses and deaths prevented by this proposed rule: Illnesses caused by sporadically adulterated products and predicted by recall data; and rare catastrophic outbreaks of illnesses, as predicted by one previous event in the United States and corroborated by one in Europe. The frequency and magnitude of a rare catastrophic event is largely hypothetical. In contrast, sporadic illnesses are small but frequent events that happen routinely. Small sporadic events are characterized by significant underreporting primarily because of the difficulty linking an illness with the cause of an illness. Determining the cause of an illness in small sporadic events is made even more difficult because only the most serious illnesses are likely to be reported and because of the difficulty of linking the cause of an illness with poor manufacturing practices. Catastrophes are large but infrequent events that create hundreds of illnesses with reporting that is close to complete because the public health system typically devotes considerable care in identifying the origin and magnitude of the problem. Adding these two models should not lead to double counting the health benefits. Double counting would most likely occur if a recalled product caused both sporadic illnesses and a

catastrophic number of illnesses and the public health system accurately recorded the full number of both sporadic and catastrophic illnesses.

b. Fewer products recalled. Implementation of the proposed regulation would reduce the number of adulterated products distributed to the public, which would reduce the number of products recalled. Manufacturing practices, such as testing of finished products and better recordkeeping, will increase the ability of establishments to identify problems before products are released for distribution. If adulterated products are caught before they are distributed, they will not be recalled.

To estimate the direct benefits from fewer recalled adulterated dietary supplements, we estimated the baseline number of annual recalls of dietary supplements due to contamination before the proposed regulation. From 1990 to 1999, FDA received reports on an average of 20 recalls per year (Ref. E12). The average figure reported here includes class 3 recalls. The number of units of dietary supplements for each recalled product varied, so we used a distribution per recalled product of 1,000 units to 34,000 units (Ref. E12). Product price also varied, with most prices falling between $5 per unit and $9 per unit; we used a most likely price of $7.70 per unit. We also included an adjustment for the goodwill lost by the establishment as a result of the recall. Studies of changes in market valuations of firms

after recalls indicate that the value of lost customer goodwill, based on the decline of the share price of publicly traded stocks from recalls is often as large as the cost of the recall itself (Ref. E24). We multiplied the direct cost of the recall by two in order to include the lost goodwill. The result is an estimated savings of about $3 million per year.

We based the estimated benefits from fewer recalled products on our recall data. If there were private recalls due to contaminated supplements that were not included in our data, the benefits from reduced recalls may be understated.

c. Reduced hypothetical search costs as a measure of the benefit from increased assurance of quality. Consumers incur a cost if they purchase products but do not get the quality of product they anticipated. Determining the cost they incur is difficult, because we cannot look at the price of poor quality products and conclude that consumers paid too much, even when they did not get the quality they anticipated. We cannot disentangle the price consumers are paying, from the price they should be paying, because we assume consumers expect some unknown number of their products may not meet their expectations but purchase them anyway. In other words, we cannot rule out the possibility that the purchase price already incorporates the expectations of consumers that some products will be "lemons." Because we cannot look into the minds of consumers to determine

their expectations or their willingness to pay for these products, we can only estimate the benefits from more uniform quality by estimating the changes in behavior that would occur if consumers were aware of the change in quality brought about by the proposed rule. In other words, we assume that if the quality attributes of dietary supplements were observable, then consumers would spend time searching for those attributes, as they do for other goods. We measured this benefit as a reduction in the hypothetical search costs for product quality, meaning the identity, quality, purity, strength, and composition claimed on the label.

The hypothetical measure of quality starts by assuming the existence of a baseline amount of search necessitated by the existence of poor manufacturing practices. Our hypothetical consumers must search for products made with good manufacturing practices, because they cannot take such practices for granted when purchasing dietary supplements. Although the search we use as a measure of the benefits from improved quality is hypothetical, the values we use in estimating our search model are based on data and inferences about real searches for other products.

To get the products they want, people search across the range of market alternatives. Several recent articles have noted the large variation in product quality for different goods and

services (Refs. E25, E26, and E27). Searching takes time and resources that could be used for other purposes, so a regulation that reduces search provides measurable benefits to consumers. To reduce the effort devoted to searching, consumers of dietary supplements should therefore be willing to pay some amount. We lack, however, a measure of what they would be willing to pay, partly because some consumers may not know that dietary supplements may contain more or less (or something not even expected) of what they think they are buying. Indeed, if consumers of dietary supplements could determine the quality of these products by merely examining the product or the label, the market alone would be sufficient to ensure that firms responded to consumer preferences for product quality. Consumers would search for those brands that are more likely to have the desired quality, and manufacturers would most likely adopt sufficient quality controls to satisfy consumer preferences. The market response is weak now because only some consumers know that product quality problems exist, and even these consumers must rely on imperfect information. If there were uniform quality control practices throughout the industry that ensured against product quality defects, consumers would not have to search for the products that they believe are free from contamination or have the identity, purity, strength, quality, and composition they want. Consumers could more reasonably assume that all

products are free from contamination and have the identity, purity, strength, quality, and composition stated on the label.

We faced the problem of trying to measure what people would pay for more uniform products quality if they knew that manufacturing quality requirements did not already exist. To estimate what people would pay, we start with the hypothetical behavior of people aware of the lack of uniform product quality; we call these hypothetical people the "sophisticated consumers."

Sophisticated consumers spend time searching for signals about the quality of dietary supplements. The proposed CGMP regulations would reduce the amount of search (by some uncertain amount) carried out by these consumers. The benefits of the rule, however, would not be confined to sophisticated consumers. We also expect "naive consumers" to enjoy the benefits. Naive consumers would incur the costs of additional search once the correct or adverse information about quality is available, suffer from worry or an illness from taking poor quality products, or incur the cost of paying for products that do not meet their needs (Ref. E28). Once good practices are in place they would avoid these costs. Naive consumers are those who fail to search for quality or search little not because they do not care but because they do not know that quality varies as much as it does. In other words, they lack the information that problems exist; if they know about the problems, they would search or be willing to

pay more to ensure that supplements they consume meet minimum quality standards. Although these naive consumers may not change their behavior in response to the proposed CGMP regulation, they would nonetheless enjoy the benefits. The naive consumers, of course, also represent real consumers of dietary supplements. The total benefits of the quality standards part of the proposed rule will be the implicit value of the gain in product quality enjoyed by all consumers.

The problem is to measure that gain based on hypothetical searches. We needed to use data from searches in other markets, because we found no information on direct or indirect searching for minimum dietary supplement quality standards. For the sophisticated consumer, we assumed that the value of search time should be approximately the same as the willingness to pay for an attribute of the good. Sophisticated consumers will hypothetically search until the expected benefit of continued searching is less than the expected cost of continued searching. The total cost of search time will, on average, be no more than the expected cost of the additional quality desired. Search time includes the time spent: Reading product labels and other literature about the product, comparing one product with other products, examining the product itself (sometimes carefully), thinking about the product, and second guessing final decisions. It might also include the time actually shopping for the product:

Finding the locations where the product is sold, driving there and back, waiting in checkout lines, and walking up and down the aisles.

We used information on shopping times for a range of products to derive an estimate for the hypothetical search time for dietary supplements. We assumed that some fraction of shopping time is pure search time, although we also recognize that search time includes more than the search for product quality. Some search time, for example, is for price, efficacy, and other attributes. The reduction in search time for the sophisticated consumer would therefore be at most a fraction of total search time for dietary supplements. The measure of time saved then is:

Reduced search time due to CGMP regulation =

shopping time x

fraction of shopping time spent searching x

fraction of search time associated with searches for quality x

fraction of search time associated with searches for quality that would be eliminated if CGMP rule guaranteed minimum quality.

We took the estimated reduction in hypothetical search time for the sophisticated consumer and applied it to all consumers to get an estimate of the implicit benefits of establishing minimum

quality standards. This estimated saving in hypothetical search time is not a forecast of reduced shopping time; it is a proxy measure of the benefit from reduced variance and improved mean product quality. We anticipate little or no change in aggregate shopping time for dietary supplements.

We converted the time measure into a monetary measure by multiplying the time reduction for sophisticated consumers by the average wage rate. The benefits measure reduced search time associated with improved quality assurance:

Quality assurance benefits =
reduction in search time (in hours per year) per
sophisticated consumer x
average wage rate per hour x
total number of consumers.

The shopping time model is an indirect approach to measuring benefits in a market with asymmetric information; it is not a prediction about how shopping behavior will change in that market. Indeed, we believe that most of the beneficiaries of this part of the rule will never recognize that they are beneficiaries.

Standardization imposes minimum requirements on manufacturing, which in turn should reduce the variance of product quality. The reduction in product quality variation should reduce the amount of information sophisticated consumers

need to acquire before purchasing dietary supplements (Ref. E29). People need not rely as much on such indicators as brand names, price, place of purchase, articles in consumer magazines, or advertising to determine the likelihood that dietary supplements meet minimum quality standards.

Although no studies deal with dietary supplements directly, the literature on consumer search for other commodities provides insights that increase our understanding of the search costs for supplements (Refs. E30 and E31). Duncan and Olshavsky (Ref. E32) surveyed buyers of television sets and found that 88 percent of respondents performed some type of search activity before purchase. In a study (Ref. E33) of consumer search for microwave ovens, the average buyer of a new microwave oven was willing to search for four alternative products. Search for groceries has been characterized as a two-stage process (Ref. E34). First, people engage in prestore activities, such as reading advertisements, writing shopping lists, clipping coupons, and comparing stores. Second, people engage in search activities at the store, including price and product comparison and search for items with coupons. Most people devote time to search activities for all but the most routine purchases.

To estimate the reduction in hypothetical search costs from the proposed rule, we started with estimates of the time consumers spend in search for groceries and other household

purchases (including durable goods). We assumed that the search time for these products was related to shopping time. Because search costs include the costs of evaluating magazine articles or brochures, the costs of obtaining a friend's advice, and the costs of instore product comparisons, our estimates will not correspond precisely to the actual costs of search for these products (Ref. E35). We believe, however, that the measure will be a reasonable approximation. Although search time often takes place outside of measured shopping time, measuring search time as some proportion of total shopping time should generate a plausible if not a precise estimate.

We generated three models of search time for dietary supplements, based on three separate studies of shopping time:

- Drug Store
- Use of Time
- Grocery Store

We used three models based on different assumptions because using a range of studies reduced the likelihood of systematic bias in our analysis.

The drug store model. The drug store study recorded the amount of time people spent looking at an item on the shelf before making a purchase (Ref. E36). Customers, on average, spent 3.75 minutes studying a product before purchasing it. Although there are quality standards in place for over-the-

counter drugs and not for dietary supplements, we assumed that this represented a measure of the amount of time the sophisticated consumer might spend searching for a product with the desired quality.

The use of time model. The Americans' Use of Time Project (Ref. E37) used time diaries to study how adults spent all of their time. The study collected data from over 3,500 adults on use of time. Data from these time diaries reveal that adult Americans spent about 364 minutes per week shopping for personal consumption items, such as groceries and other household products.

The grocery store model. In the grocery store study, hidden observers tracked and recorded shopping time in the store (Ref. E38). The study found that people on average spent about 21 minutes shopping in the grocery store. By combining estimated time per trip with the Food Marketing Institute's (Ref. E10) finding that consumers average about 2.2 grocery shopping trips per week, we generated an estimate of search time for all grocery store purchases of 46.2 (= 2.2 x 21) minutes per week.

For each of the models, we needed to make assumptions to convert shopping time for other commodities into search time for dietary supplements. Table 11 of this document shows the assumptions and information used in each model.

Table 11.--Three Models of Search Time: Assumptions Used in Simulations

Drug Store Model		
Variable	Value or Distribution	Source and Notes
Search time in minutes per item	3.75	Ref. E30
Number of products per person per year	6.57	Ref. E4
Average wage rate	$15.65 per hour, or $0.26 per minute	Ref. E42
Population	273 million	Ref. E19
Fraction of search time devoted to searching for quality	0.2 (based on uniform distribution, 0.1 to 0.3)	Based on number of attributes consumers search for
Use of Time Model		
Variable	Value or Distribution	Source and Notes
Weekly shopping time for all items in minutes	346	Ref. E37
Fraction percent of budget spent on supplements	$15.5 billion/$6,250 billion	Ref. E4 and E19
Average wage rate	$15.65 per hour, or $0.26 per minute	Ref. E42
Adult population	205 million	Ref. E19
Ratio of search time to shopping time	0.7 (based on uniform distribution, 0.4 to 1.0)	Based on descriptions of shopper behavior
Fraction of search time devoted to searching for quality	0.2 (based on uniform distribution 0.1 to 3.0)	Based on number of attributes consumers search for
Potential reduction in search time attributable to CGMP regulations	33% most likely (could be between 15 and 50%)	Based on likelihood of problem and likelihood that search will decline proportionally, and the expert opinion of pharmacists
Grocery Store Model		
Variable	Value or Distribution	Source and Notes
Weekly shopping time for groceries in minutes	46.2	Ref. E38
Ratio of supplement expenditures to grocery expenditures	$15.5 billion/$710 billion	Ref. E38
Average wage rate	$15.65 per hour, or $0.26 per minute	Refs. E4 and E19
Adult population	205 million	Ref. E19
Ratio of search time to shopping time	0.7 (based on uniform distribution, 0.4 to 1.0)	Based on descriptions of shopper behavior
Fraction of search time devoted to searching for quality	0.2 (based on uniform distribution, 0.1 to 0.3)	Based on the number of attributes that consumers search for
Potential reduction in search time attributable to CGMP regulations	33% most likely (could be between 1% and 50%)	Based on likelihood of problem, the likelihood that search will decline proportionally, and the expert opinion of pharmacists

The drug store data generated a direct estimate of search time. In the drug store model we assumed that the time spent standing in front of the drug product could be used to estimate

the time searching for dietary supplements. We then used data on the number of products purchased per person and the total U.S. population to generate an estimate of annual search time for dietary supplements.

To estimate the time spent searching for supplements from the use-of-time study, we assumed that the share of all shopping time devoted to supplements would be proportional to the share of a consumer's budget spent on supplements. We recognize that it could well be higher if supplements require more search than the average commodity. According to an industry source and FDA projections, consumers spent about $15.5 billion on dietary supplements in 1999 (see table 5 of this document). Consumers spent about $6,250 billion on all personal consumption in 1999, which means that dietary supplements accounted for about 0.24 percent of those expenditures. Personal consumption expenditures included in this estimate are food, alcoholic beverages, housekeeping supplies (such as laundry and postage), household furnishings and equipment (such as furniture and appliances), apparel (includes footwear), personal care products and services, reading materials, tobacco products, and smoking supplies. Annual shopping time per person for dietary supplements would therefore be about 44.6 minutes per year (= ($15.5 billion/$6,250 billion) x 346 minutes per week x 52 weeks). We converted shopping time to search time by assuming that search time equaled

40 to 100 percent of shopping time. Total search time equaled search time per adult multiplied by 205 million adults. We assumed that all adults would perform search, although we recognize that not all adults consume dietary supplements and not all search is conducted by adults. Children might search for these products also. The opportunity cost for children, as measured by their wage rate is much less then for adults, so we assumed their search time could be ignored. We used the total adult population rather than just the adult consumers of dietary supplements, because the shopping time studies are for all adults.

We estimated search time in the grocery store model with assumptions similar to those in the use-of-time model. We assumed that the ratio of search time for supplements to search time for groceries would equal the ratio of expenditures on supplements to expenditures on groceries. Estimates from the 1998 Consumer Expenditure Survey (Ref. E39) (adjusted for changes in prices between 1998 and 1999) reveal that consumers spent approximately $710 billion on grocery store purchases in 1999. Grocery store purchases included food, alcoholic beverages, housekeeping supplies, personal care products, tobacco products, and smoking supplies. Annual shopping time per person for dietary supplements would therefore be about 52.5 minutes per year (= ($15.5 billion/$710 billion) x 46.2 minutes per week x 52 weeks).

We again converted shopping time to search time by assuming that search time equaled 40 to 100 percent of shopping time. Like the estimate from the use of time model, this value was then multiplied by 205 million adults.

We used these three models based on different assumptions because we wanted to explore a range of studies to avoid systematic bias in our analysis. We recognize that the three estimated annual search times for dietary supplements do not represent the search for quality alone. Consumers search for a variety of features; only part of every search will be devoted to quality. We assumed that 10 to 30 percent of pure search time involves quality searches. Estimating the impact of CGMP regulations on consumers' search time is difficult, since no previous studies have analyzed the changes in search time following the adoption of CGMP regulations or from increases in product quality standardization. However, a consistent finding from the literature is that search time should decline following a decrease in the variation in product quality (Refs. E35 and E40). In the absence of previous empirical studies, we assumed that the proposed rule would reduce the hypothetical search time for quality "the search time of sophisticated consumers" by 1 to 50 percent, with 33 percent the most likely value. A survey of pharmacists reported their belief that 30 percent of their customers place manufacturing quality as a top priority in

selecting one herbal over another (Ref. E41). We also used evidence from product tests that indicated that up to 33 percent of products were missing key ingredients or contained unwanted ingredients (Refs. E25, E26, and E27). If the proposed rule guarantees that products will contain what the label claims, then perhaps search time for quality will decline by that percentage.

To estimate the value of the possible reduction in searching for quality, we multiplied our estimated time saving by the average wage rate, which is an estimate of the value of time. The average hourly wage rate for U.S. workers was $15.65.[7] We ran computer simulations of all three models. The results for the three models are shown in table 11 of this document.

d. Other benefits. The proposed regulation could also reduce the total time and effort that all covered establishments expend to monitor ingredient suppliers and holders of their products. Because all ingredients and holders would be subject to the same uniform minimum requirements, variation in their practices would decline, so firm monitoring of upstream and downstream vendors could decline.

The provision that requires establishments to maintain complaints files would allow a manufacturer to more readily be able to identify a product that causes a significant or

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[7] Personnel Employment, Hours, and Earnings. Series ID: EES00510006 Seasonally Adjusted, Industry: Goods-producing Data Type: Average hourly earnings of production workers, Employment Cost Index, Bureau of Labor Statistics.

unreasonable risk of illness or injury. The manufacturer can then take necessary steps to prevent any additional adverse health impact. We have attempted to quantify this benefit for preventing catastrophic events, but not for reducing smaller risks. FDA adverse event reports, however, imply that many such small events occur, and the proposed rule could prevent some of them (Ref. E15).

In addition, if the same adverse events show up in complaints received by different firms selling products with the same or similar manufacturing problems, no one firm selling such products may recognize the need to investigate the complaints especially if the risk is relatively low. Because we would have access to complaint files, our review would be more likely than any individual firm's review to identify the need to investigate the complaint because of a reasonable possibility of a relationship between the manufacturing process of a dietary supplement and the adverse event.

e. Total measured benefits. The total measured benefits from the proposed rule are the sum of the value of health benefits, the value of the reduced number of product recalls, and the reduction in hypothetical search costs. Table 13 of this document shows the total benefits.

Table 12.--Three Models to Estimated Search Cost Savings

Baseline Model	Cost Savings
Drug store model	$108 million
Use of time model	$101 million
Grocery store model	$119 million
Average of three baseline models	$109 million

Table 13.--Summary of Annual Benefits

Benefits	Mean
Fewer illnesses (from table 8)	$39 million
Fewer illnesses (from table 10)	$66 million
Fewer product recalls (from table 9)	$3 million
Reduced consumer search (from table 12)	$109 million
Total benefits	$218 million

7. Costs

The same changes in practices that produce benefits also have costs, the opportunity costs of not doing what consumers and manufacturers are now doing. The proposed regulation would require dietary supplement establishments to adopt some new practices in order to manufacture, package, and hold their products. The costs incurred for those who choose to comply will be for personnel, grounds and physical plant, equipment and instrumentation controls, quality control and laboratory operations, production and process controls, handling consumer complaints, and holding. In some cases, establishments would need to make capital improvements to the physical plant, add or replace equipment or controls, perform additional maintenance, keep records, carry out tests, or execute a variety of additional tasks that they may not have previously performed. We estimated the additional costs of production associated with the proposed

rule and the leading regulatory options, using the survey (Ref. E2) to estimate baseline manufacturing practices.

a. Description of the costs. To estimate costs for the dietary supplement industry, we initially divided the industry into four product categories and three size categories. Because the survey showed that there were only a few establishments in some categories, we consolidated the size and product into three size categories. The size categories were:

- Very small (fewer than 20 employees)
- Small (20 to 499 employees)
- Large (500 or more)

Although this consolidation glosses over the important differences across products, the purpose is to estimate the broad average costs of the rule.

For each category, we constructed a cost model that included every provision of the CGMP regulations that the proposed rule requires or recommends. We then attached a cost to each provision that had an activity associated with it. Most provisions did not have costs attached to them, mainly because they were either descriptive or the costs were included elsewhere. For the rule as a whole, we estimated the marginal, or additional costs for over 70 provisions of the proposed rule.

We expressed the cost as cost per unit, with the unit being either the establishment, the number of employees, or the annual

number of batches produced. The costs of this proposed rule included the following general activities: Sanitation, production and process controls, holding and distributing, and consumer complaints.

b. Costs of general activities. i. Sanitation. Sanitation includes both one-time capital improvements and ongoing efforts. Some provisions of the proposed regulation may require establishments to perform one-time capital improvements to their physical plant facilities.

The proposed regulation would also require, if not already in place, physical plant owners to install new or additional plumbing systems to carry additional water or sewage, additional toilet or hand washing facilities, additional facilities for trash disposal, or new signs to instruct employees. The proposed regulations might also require establishments to add space in order to keep equipment and materials father apart, which will help to prevent contamination or mixups. Other possible capital expenditures (among many other possible requirements) include:

- Replacing floors, walls, or ceilings with smooth, hard surfaces;
- Changing fixtures, ducts, or pipes that might be a source of contamination by dripping or condensation;

- Adopting ventilation control systems including filters, fans, or other air-blowing equipment to prevent odors or vapors;
- Additional lighting to ensure that equipment, contact surfaces, or other areas where supplements are examined, processed, or held can be adequately seen.

Sanitation also requires that equipment utensils must be of suitable design, construction, and workmanship to enable them to be adequately cleaned and maintained. To meet this requirement, some establishments may need to provide additional maintenance or additional cleaning and sanitation for their equipment and utensils. Also, freezers and cold storage compartments used to slow or arrest the growth of microorganisms must be fitted with thermometers to accurately show the temperature within the compartments. Instruments and devices used in manufacturing must be accurate, adequately maintained, and adequate in number. To meet this requirement establishments might have to purchase new equipment, replace old equipment, or provide additional maintenance to existing equipment.

ii. Production and process controls. Production and process controls are the main preventive mechanism to ensure the identity, purity, quality, strength, and composition in the proposed rule. Establishments must implement a system of production and process controls that covers all stages of

processing, from the receipt and acceptance of components, dietary ingredients, dietary supplements, packaging, and labels through the release for distribution and holding of the dietary ingredients and dietary supplements. Establishments must identify points, steps, or stages in the manufacturing process where control is necessary to prevent adulteration. Establishments must also establish specifications for the identity, quality, purity, strength, and composition of components, dietary ingredients, or dietary supplements. Establishments must monitor the points, steps, or stages in the batch production, as specified in the master manufacturing record, where control is necessary to prevent adulteration. Establishments must establish specifications for packaging to ensure that containers or closures that come into contact with dietary ingredients or dietary supplements are not reactive or absorptive and are composed of substances that are safe for use in or on food.

Establishments that have not already done so must establish a quality control unit with one or more individuals that have with the authority and responsibility to review the results of monitoring, make decisions on the disposition of materials, and identify whether actions taken to correct any deviations are appropriate. The quality control operation must ensure that

components, dietary ingredients, and dietary supplements conform to specifications.

iii. Holding and distributing. Establishments must hold and distribute dietary ingredients and dietary supplements under appropriate conditions of temperature, humidity, and light so that the identity, quality, purity, strength, and composition of the dietary ingredients and dietary supplements are not affected. Establishments must also identify and hold components, in-process materials, and dietary supplements under conditions that will protect them against mixups and physical, chemical, and microbial contamination. Packaging materials must also be protected against deterioration. Establishments that do not now perform these requirements and the other provisions associated with holding will incur a compliance cost.

iv. Consumer complaints. The quality control unit must review all consumer complaints involving the failure of a dietary supplement to meet any of its specifications, or the failure to meet any other requirements under proposed part 111, including those specifications and other requirements that, if not met, may result in possible illness or injury. In addition, the quality control unit must investigate such a consumer complaint where there is a reasonable possibility of a relationship between the consumption of a dietary supplement and an adverse event. The complaint and report of the investigation results should be

reported to FDA when there is a possibility of a serious adverse event.

c. Major costs by type of activity. Within these four categories (sanitation, production and process controls, holding and distributing, consumer complaints), the major costs of the proposed rule are recordkeeping (except for sanitation), capital costs for physical plant and equipment, finished product quality testing (part of production and process controls only), labor costs for certain required tasks, and some other costs that were not easily classified.

i. Recordkeeping. We used a study of a medical device CGMP regulation to estimate the costs of recordkeeping (Ref. E44). We request comments on the applicability of a study of the medical device CGMP's to dietary supplements.

The compliance cost of recordkeeping is the sum of both the initial design and printing of the recordkeeping documents and the recurring costs of maintaining the records. The cost of training personnel to use mandatory records is a recurring cost that depends on how frequently records are modified, the frequency of personnel turnover, and how complicated the tasks are that are being recorded. The recurring costs are measured by the workers' wage rate, which we assumed is $15.65 per hour based on the average manufacturing wage, multiplied by the expected labor hours necessary to perform a written or electronic record

and the time necessary for management to review the records to see the actions are documented accurately. For electronic records, the recurring time is the time necessary to ensure that the equipment is serviced and maintained properly.

ii. Capital costs for physical plant and equipment. We estimated capital costs for physical plant redesign at $50 per square foot (Ref. E45). For establishments with inadequate facilities, we assumed that between 0 and 20 percent of the physical plant would have to be renovated, with 10 percent the most likely. For equipment costs, we assumed that very small establishments would on average spend 0 to $1,000, with $100 the most likely amount. Small establishments would bear costs 3 times that of very small establishments, which is the ratio of the size of the physical plants of small establishments to the size of the physical plants of very small establishments. We assumed that large establishments would bear (if necessary) costs 20 times that of very small establishments, which is the ratio of the size of the physical plants of large establishments to the size of the physical plants of very small establishments. In other words, we assumed capital costs for physical plant and equipment would be proportional to facility size, as measured in square feet.

iii. Testing. Establishments that do not already conduct the required product quality tests of each batch of dietary

ingredients or dietary supplement produced would incur the cost for those tests. Under the option for more restrictive CGMP rules, each lot of components would also be tested. The costs per establishment depend on both the number of tests and the costs per test. We did not estimate the cost of developing new, validated tests methods because we lacked information about the costs for this requirement and the number of such tests that need to be developed. We ask for comments on the costs to develop tests, for the number of tests and the costs for performing each test to comply with this requirement.

- Number of tests: Model

To estimate the costs of testing, we first estimated the number and costs of individual tests, without adjusting for the amount of testing already being done. In this section we show how we estimated the likely number of required tests, unadjusted for current voluntary testing. For a representative manufacturer, the annual number of tests would be the number of new tests per batch multiplied by the number of batches produced in a year.

The proposed rule requires only tests for identity, purity, quality, strength, and composition of the final product. The option for stricter CGMP regulations would also require tests of components. Estimating the number of component tests per batch is complicated, because component tests are made on the shipment

lots, rather than on the parts of the lots that actually go into the final product. For example, if a lot of some ingredient is used in 6 batches of final products, it would probably be tested only once.

The establishment itself may test the shipment lots, and during inprocess stages for identity, purity, quality, strength, and composition, unless final product testing is done.

The number of component tests per batch of final product would equal the number of tests per component, multiplied by the number of components per batch, divided by the batches per shipment lot (to account for the production of multiple batches of dietary supplements from single lots of components).

The option for stricter CGMP regulations options would also require some inprocess tests upon receipt. The number of inprocess tests per batch is the same as the number of potential inprocess product defects. The estimated number of inprocess tests counts only tests for defects that can occur during production, not tests for the defects of dietary ingredients and components supplied to the producer.

We used the following formulas to estimate the number of tests:

Component test per batch = $[\sum_{m_j} (I_j \times R_j) + \sum^{n}_{k} (U_k \times R_k)] \times (S / B)$

Inprocess quality tests per batch = $\sum^{\circ}_{1} (H_1 \times R_1)$

Quality tests per batch of final product = max [m x (1/z), 1]

where:

I_j = jth listed ingredient;

m = number of ingredients per batch;

R_j = required tests for ingredient j;

U_k = kth unlisted component (an inactive substance);

n = number of unlisted components per batch;

R_k = required tests for unlisted component k;

S = number of shipments (or lots) of ingredients and unlisted components;

B = number of batches produced;

H_l = lth inprocess potential defects;

R_l = required inprocess tests per batch for potential defect H_l;

o = number of potential inprocess defects per batch;

z = number of ingredients identified per quality test.

- Number of tests: Evidence and distributions

The quantity and quality of evidence on the variables used to estimate the number of required tests varies greatly. In this section, we explain the evidence and assumptions we used to construct the formulas for the number of tests.

- Number of ingredients

We based our measure of the number of dietary ingredients per product on a sample of almost 3,000 dietary supplement labels (Ref. E46). Although some dietary ingredients may be missing from the labels and some listed dietary ingredients may be missing from the products, the ingredient list represents the best evidence we are likely to have on what dietary ingredients are used in dietary supplements.

- Number of ingredients per batch

According to the sample of listed ingredients (Ref. E46). Vitamin and mineral products contain about 13 listed ingredients. Other dietary supplements, mainly herbals, contain about four.

- Number of tests per ingredient lot

The option for more restrictive CGMP regulations would require that virtually all dietary ingredients be tested for identity and defects at some stage between harvesting the raw product and the beginning of the production of the final product. We assumed one identity test per ingredient lot. The number of tests for defects depends on the number of possible defects, which can include:

Filth;

Microbial pathogens;

Chemical hazards, including pesticides;

Insects;

Physical hazards, such as metals;

Natural toxins, such as aflatoxin; and

Inadequate purity, quality, strength, or composition.

The number of potential defects is potentially unlimited. As a practical maximum, however, few products would have more than five potential defects. In the calculation of ingredient testing costs (part of the option for more restrictive CGMP regulations), we assumed that the average number of tests per listed dietary ingredient would be between one and six: One identity test for identity, purity, strength, quality, and composition and zero to five tests for defects.

- Number of unlisted components

Dietary supplements are manufactured using solvents, binders, and lubricants that may not show up in the final product. An industry source (Ref. E47) says that four to six unlisted components are typical per product, although fewer are certainly possible. The minimum number is zero. We assumed that the number of unlisted components would be zero to six, with four the most likely.

- Number of tests per unlisted components

The unlisted components tend to be manufactured products, such as solvents. Therefore, one identity test would likely be sufficient.

- Number of shipments (or lots) of ingredients and unlisted components

We have no direct evidence on the number of shipment lots of dietary ingredients and components. We also have no evidence on the number of shipments per lot or on the number of shipments per batch. The increasing use of just-in-time inventory practices indicates that one shipment lot of components per batch may be the rule for some products and some producers. It is costly and difficult to store ingredients for an extended time, so establishments tend to buy more and smaller lots of components rather than a few large lots and storing them in bulk over an extended period (Ref. E48). Crude botanical and other ingredients are inherently unstable and may lose their quality in even a short time unless costly temperature, humidity, and light controls are in place (Ref. E49). We also know, however, that some dietary ingredient suppliers produce large amounts and then ship out smaller packages. For dietary supplements produced using part of a large production run of a dietary ingredient, the number of batches per lot could be large. Also, some producers buy a single shipment lot of a raw material and use it in many batches. We assume that as many as 12 batches per shipment lot of dietary ingredient is a plausible maximum. In the cost calculation, we assumed that 1 was minimum and 12 the maximum number of batches produced per lot, with 6.5 the average.

- Number of batches produced

We have survey results (Ref. E2) on the number of batches produced per establishment. According to the survey, very small establishments produce an average of 223 batches per year, small establishments produce an average of 554 batches per year, and large establishments produce an average of 309 batches per year.

- Inprocess potential defects

Inprocess defects involve many of the same potential defects that can occur in components. The more restrictive CGMP option requires inprocess tests at all points where contamination or other defects can occur. Filth, chemicals, microbial pathogens, physical objects, and insects can be introduced into the product during manufacturing. In addition, purity, quality, strength, and composition can be compromised.

- Number of potential inprocess defects

Some processes may have no control points, steps, or stages that involve the potential for defects. If certain manufacturing processes in the production of a dietary supplement can be carried out without being subject to potential defects, no inprocess tests would be required for those processes. We therefore assumed that zero inprocess tests would be the lower bound requirement. For the upper bound, we assumed that no products would have more than five potential control points or steps that could lead to defects. We believe that most production processes will have fewer than 5 control points, so we

assumed an average of 2.5 control points requiring in-process tests for defects.

- Number of required inprocess tests per control point

  We assumed one test per defect per control point.

- Number of ingredients identified per quality test

We had no direct evidence on the number of identity tests per final dietary supplement. For the maximum, we assumed that the number of tests would equal the number of ingredients. The number of ingredients identified per test varies from less than one to a very large number. We assumed that for vitamins and minerals, the minimum number of identity tests would be one and the maximum would be 30, with 2 the most likely. Botanical and herbals are less easily characterized than vitamins; so identifying large numbers of ingredients with a single test would be highly unlikely. We assumed that one to two ingredients would be identified per test for herbal products.

- Number of final product tests per batch

We had no direct evidence on the number of quality tests per final dietary supplement. After adjusting for the possibility of multiple results from a single test, multiple ingredients in single products, and the differing number of ingredients in herbal and vitamin products, we estimated that the proposed rule would require about three tests for identity, purity, quality, strength, and composition for each batch of final product. These

are the only required tests in the proposed rule, but establishments may choose to perform inprocess tests and tests on ingredients in order to prevent waiting until final product testing to discover defects.

iv. Costs per test. We estimated the costs per test partly with published prices of independent laboratories as posted on the Internet (Refs. E50 and E51), and partly from our conversations with FDA and industry experts on testing. We found that testing costs vary according to frequency and complexity. The more frequently technicians perform tests, the lower are the costs per test. Many tests require sophisticated equipment, such as gas chromatography, high pressure liquid chromatography, distillation, extraction, various spectrophotometers, and other types of equipment. Using sophisticated equipment requires trained personnel. Even simple physical or organoleptic testing requires training or experienced personnel. The type of ingredient, compound, or product can also affect the cost because some are easily identified using routine or single step techniques and others require multiple steps or complex techniques, especially if there are similar products that can be mistaken for the products being identified. The type of defect tested for affects the cost; some defects can be found visually if they are found on the surface, but others are latent. Some tests require multiple samples or multiple steps. In addition,

tests require the taking and preparing preparation of samples, whose cost can vary.

We assumed that $20 per test represented a plausible lower bound. This cost represents the full cost of carrying out a test, including collecting and storing the sample, the time for training the personnel who carry out the test, and any associated records. Although some Internet testing prices for tests were as high as $300, we assumed that with frequent testing $150 would be a more plausible upper bound average cost. The majority of listed prices fell into the $20 to $80 range, so we selected $50 (the midpoint) as most likely. The average cost per test was about $60.[8]

Changing our assumption about the midpoint of testing costs would change our estimate of the cost of the rule. If the cost of testing each batch is actually significantly higher, then the

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[8] The average cost is higher than the most likely cost because we modeled costs with a Beta-Pert distribution that was skewed rightward (toward higher costs). The Beta distribution is part of the Bernoulli family of distributions and is closely related to the Binomial. The Binomial gives the distribution of the number of successes (s) in n trials if the probability of the success in each trial is p. The Beta shows the distribution of the value of p when s successes occur in n trials. The Beta-Pert distribution is a Beta distribution that has been rescaled to run between values other than 0 and 1. The Beta-Pert uses a minimum, maximum, and most likely value to generate a distribution running from the minimum to the maximum, with a mean equal to (minimum + (4 x most likely) + maximum)/6. We used the Beta-Pert distribution because we did not have a representative sample to derive the distribution, but we did have enough information to identify a plausible maximum, minimum, and most likely value. The use of the Beta-Pert, then, indicates that we do not know the shape of the probability distribution of possible testing costs, but we do have limited data.

impact to those firms that incur the cost and to society will have been understated.

v. The number and cost of tests: summary. We estimated the number of tests required of the representative manufacturer as a weighted average of the number of tests required for vitamins and minerals and the number of tests required for all other supplements (which were mainly herbal products). We used survey responses to a question about the establishment's primary line of business for the weights used to compute the average number of tests. We dealt with multiple responses by treating all nonvitamin and nonmineral responses as other dietary supplements. The following weights, as shown below, differed by size of manufacturer:

- 24 percent of very small manufacturers produce vitamins and minerals; 76 percent produce other dietary supplements.
- 42 percent of small manufacturers produce vitamins and minerals; 58 percent produce other dietary supplements.
- 69 percent of large manufacturers produce vitamins and minerals; 31 percent produce other dietary supplements.

The annual cost of testing differed by the size of the firm, because the average number of batches produced differed. For the option calling for more strict regulation, the total costs of testing would be much higher than in the proposed rule. The

unadjusted total cost of testing under the more restrictive CGMP option would be:

$148,000 for very small establishments;

$415,000 for small establishments;

$263,000 for large establishments.

We estimate that the adjusted total cost for testing for the proposed regulation will be:

$11,230 for very small establishments;

$19,907 for small establishments;

$7,626 for large establishments.

We found some corroboration for these estimates in a comment on the Advance Notice of Proposed Rulemaking entitled "Current Good Manufacturing Practice in Manufacturing, Packing, or Holding Dietary Supplements" published in the FEDERAL REGISTER of February 6, 1997 (62 FR 5699 to 5709). According to the comment, the cost of testing components and final products inhouse would be at least $650 per batch plus microbiological tests. Testing costs could be more if establishments sent samples to independent laboratories for testing or if they conducted extensive identity tests of herbal and botanical products. If we apply the $650 to the annual number of batches per establishment, the comment implies that very small establishments would perform $145,000 (223 x $650) worth of tests, small establishments would perform $360,000 (554 x $650) worth of tests, and large establishments

would perform $200,000 (309 x $650) worth of tests. These estimates are reasonably close to our simulation estimate.

The unadjusted testing costs represent the total requirements and recommendations, not the additional costs that would be incurred in response to the proposed rule. Tests on incoming components and inprocess tests would not be required by the proposed rule. Most establishments already conduct some tests, or send samples out for testing. We, therefore, adjusted the estimated testing costs of the proposed rule to include only required tests and to account for the testing costs currently borne voluntarily by manufacturers. The survey results showed how many respondents were conducting various types of tests.

Table 14.--Values Used in Testing Cost Calculations

Name	Value or Distribution Used	Source
Number of dietary ingredients per product batch	Vitamins and minerals--13 All other categories--4	Sample from 3,000 dietary supplement labels (Ref. E46)
Number of identity tests per ingredient lot	1 Identity test per ingredient lot	Assumption based on discussions with industry--FDA requests comments
Number of tests for defects per ingredient lot	0 to 5 tests for defects	Assumption based on discussions with industry--FDA requests comments
Number of unlisted components	0 to 6 components; 4 most likely	Ref. E47
Number of tests per unlisted components	1 identity test per component	Assumption based on discussions with industry--FDA requests comments
Number of shipments (Lots) of ingredients and unlisted components	1 to 12 batches per shipment lot of dietary ingredients	Assumption based on discussions with industry--FDA requests comments (Ref. E48)
Number of batches produced	Very small establishments--223 Small establishments--554 Large--309	Ref. E2
Number of inprocess potential defects	0 to 5 potential control points; 2.5 average	Assumption based on discussions with industry--FDA requests comments
Number of inprocess tests per control point	1 test per defect per control point	Assumption based on discussions with industry--FDA requests comments
Number of ingredients identified per identity test	Vitamins and minerals--1 to 30; 2 most likely All other categories--1 to 2	Assumption based on discussions with industry--FDA requests comments
Number of final product tests per batch	3 tests per batch	Assumption based on discussions with industry--FDA requests comments
Costs per test	Beta pert distribution skewed rightward between $20 to $150; $50 most likely; $60 average	Refs. E50 and E51

vi. Labor costs. We used the average manufacturing wage of $15.65 per hour to estimate the cost of labor. We assumed that various tasks required by the proposed rule would take some number of hours per year, per batch of product, or per square foot of physical plant. For example, we assumed that time spent on the sanitation of physical plants is a function of the square footage. We assumed 1 hour per week for very small establishments, 3 hours per week for small establishments, and 20 hours per week for large establishments. We request comment or

data about costs, hours, and the other requirements for these proposed required procedures.

vii. Other costs. The main costs in this category are for pest and rodent control. We consulted a commercial supplier of these services for the estimated monthly costs, which were $400 to $600 a month for very small establishments, $480 to $720 for small establishments, and $700 to $1,000 for large establishments (Ref. E52). For each size of establishment, we selected the midpoint of the range as the most likely value.

d. Estimating costs. We initially gathered information and made assumptions about the full cost of a provision. We then adjusted these estimates to account for the many activities already being carried out, as well other activities that would not have to be carried out by all establishments. We used the survey to estimate the likelihood that an establishment would incur a cost. To get an estimate of the average cost of provision (adjusted for baseline activities) for each category, we multiplied the average cost per establishment by the probability that the establishment would need to undertake the expense (one minus the probability that the establishment was already doing it). For each provision of the proposed rule, the simulation carried out the following calculation:

Cost per unit of analysis for each provision =

number of units of analysis per establishment x

probability that establishment incurs cost x

adjustment for requirement (yes or no) =

cost per provision per establishment

We estimated both a setup cost (a one-time fixed cost) of the provision and an annual recurring cost. The first-year costs would be the setup costs plus the annual costs. To get the total costs of the rule, we multiplied the number of establishments in each size category (from the survey) by the average costs per establishment in that category. We then adjusted for the establishments that did not respond to the survey but are believed to be in the industry. Two hundred thirty eight establishments responded to the survey; we estimated that 1,566 firms are in the industry. We estimated costs with the following calculation:

[Number of very small establishments x costs per very small establishment) +

(number of small establishments x costs per small establishment) +

(number of large establishments x costs per large establishment)] x

adjustment for establishments not in survey

The rule is complex and the industry is made up of very different kinds of firms, so cost estimates are averages with, in some cases, large variances. The cost per unit, number of batches and

employees, and probability that the establishment would incur the cost all contain uncertainty. The values in table 15 of this document are used in the cost estimates, and are generated from multiple sources.

Table 15.--Values Used in Cost Calculations

Name	Value or Distribution Used	Source
Average wage per hour	$15.65	Employment Index, Bureau of Labor Statistics

Average size of establishments in square feet	very small = 24,674;
	small = 71,354;
	large = 596,000
		Ref. E2

Average number of employees	very small = 7.6;
	small = 95;
	large = 1,005
		Ref. E2

Average annual number of batches	very small = 223;
	small = 554;
	large = 309
		Ref. E44

Annual time recordkeeping	1/10 of setup time per provision	Ref. E44
Personnel sanitation	1 hour per week per worker	Assumption, based on requirements of proposed rule
Sanitation time for physical plant	1 hour per week for very small establishments; 3 hours per week for small establishments; 20 hours for physical plant per week for large establishments	Assumption, based on difference in average physical plant size
Sanitation supervisor	Very small and small establishments = 1 hour per week; large establishments = 1 hour per week	Assumption, based on number of workers
Pest control setup costs	$1,500 to $2,000 for very small establishments; $1,800 to $2,400 for small establishments; $2,600 to $3,400 for large establishments. Average for each size establishment was midpoint ($1,750, $2,100, $3,000)	Ref. E52
Pest control annual costs	$400 to $600 per month for very small establishments; $480 to $720 for small establishments; $700 to $1,000 for large establishments. Average for each size establishment was the midpoint ($500, $600, $850)	Ref. E52
Renovation cost	$50 per square foot; with 0 to 20 percent of physical plant to be renovated, with 10 percent most likely	Based on construction costs and square feet
Minimum quality control unit	1 person or 1 percent of establishment work force	Assumption based on requirements of proposed rule
Equipment replacement	For very small establishments, 0 to $1,000, with $100 most likely; small, 0 to $10,000, with $1,000 most likely; large, 0 to $100,000 with $1,000 most likely	Assumption, based on size of establishments
Setup costs for automatic equipment	$500 for hardware, 16 hours	Software costs and assumptions about labor hours

Table 15.--Values Used in Cost Calculations (Continued)

Name	Value or Distribution Used	Source
Annual costs for automatic equipment	1 to 2 hours per month for very small and small establishments; 2 to 4 hours per month for large establishments	Assumption based on average size of establishments
Sanitation of equipment and surfaces	5 hours per week for very small establishments, 15 hours per week for small establishments, 100 hours per week for large establishments	Assumption based on average sizes of establishments
Number of dietary ingredients per batch, supplements other than vitamins	12.8; standard deviation = 15.6	Ref. E46
Number of dietary ingredients per batch, supplements other than vitamins	3.6; standard deviation = 4.8	Ref. E46
Cost per test	$20 to $150, with $50 most likely	See text discussion
Holding products and dietary ingredients: capital requirements	Setup cost for very small 0 to $1,000, with $100 most likely. Multiply by 3 for small establishments and by 20 for large establishments	Based on average sizes of establishments
Default probabilities that establishments are not currently acting in accordance with a provision	For very small establishments, 0.2; for small establishments, 0.1, for large establishments, 0.01	Based on results of survey for other practices

We combined the costs per establishment with the number of establishments and probabilities from the survey, and adjusted for establishments not in the survey to estimate the total costs of the proposed rule. Table 16 of this document summarizes the estimated total costs for very small establishments, small establishments, large establishments, and warehouses. Table 17 of this document shows the total costs for the first year and annually after the first year, assuming that the proposed rule is phased in over 3 years. Table 18 of this document shows the total costs of the proposed rule compared to the total costs of other options.

Table 16.--Summary of Costs by Size of Establishment

	Number of Establishments	1st Year Costs per Establishments	Annual Costs per Establishments	Total 1st Year Costs	Total Annual Costs
Very small establishments	740	$62,000	$38,000	$46 million	$28 million
Small establishments	766	$99,000	$61,000	$76 million	$47 million
Large establishments	60	$83,000	$47,000	$5 million	$3 million
Warehouses and other holders	26,617	$436	$342	$12 million	$9 million

Table 17.--Estimated Total Costs

	1st Year	2nd Year	3rd Year	4th Year and After
Very small establishments	0	0	$46 million	$28 million
Small establishments	0	$76 million	$47 million	$47 million
Large establishments	$5 million	$3 million	$3 million	$3 million
Warehouses	$12 million	$9 million	$9 million	$9 million
Total	$17 million	$88 million	$105 million	$87 million

8. Summary of Benefits and Costs

We estimated that, once it is fully implemented, the measured annual benefits from the proposed rule would be $218 million; measured annual costs would be about $86 million. Additional but unmeasured benefits should also be recognized when comparing the total costs and benefits. Table 18 of this document compares the benefits and costs of the proposed rule to the benefits and costs of the leading regulatory options. Because the phase in period, complicates the comparison for the early years, we limit the comparison to annual benefits once all establishments are covered.

Table 18.--Annual Benfits and Costs of Regulatory Options

Regulatory Option	Annual Benefits	Annual Costs
Proposed rule	$218 million	$86 million
Fewer requirements for vitamins and minerals	$109 million	$69 million
Stricter CGMP	$218 million	$178 million
HACCP only	$42 million	$38 million
Testing only	unable to estimate	$32 million
High risk products only	unable to estimate	less than $86 million

Uncertainties in the analysis. In this section, we list all of the significant assumptions in the analysis, which if varied, could significantly change the estimates of costs and benefits. Such changes could have importance for the construction of any potential final rule. Therefore, we ask that comments address these aspects of the analysis and, where possible, provide FDA with better data to reduce the uncertainty. We estimated the benefits using indirect methods, which required several key assumptions that are critical for our estimates. With the exception of the recall benefit, which is based directly on FDA recall records, each component of the estimated benefits involves assumptions that reflect our uncertainty.

Our basic assumption is that manufacturers lack market-based incentives to prevent hidden product quality defects. Our survey (Ref. E2) indicated that many firms do not have reliable quality control mechanisms in place. The survey was a one-time look at the manufacturing practices during the time of the survey. If the trend in the market is toward the adoption of the controls that we are proposing here in the absence of regulation, then both the cost and benefits of the rule will be less than we estimate. If the market-based trend is toward fewer controls,

then both the cost and benefits of the regulation will be greater. Other key assumptions are listed below:

The assumptions for the health benefits from reducing the number of sporadic illnesses model are:

1. The baseline health of consumers is normal, not perfect. To estimate the change in health status from consuming defective products, we assumed that the baseline health of consumers is normal, which does not mean that we assumed that consumers have perfect health. We recognize that consumers will already have 'background' health problems, by which we mean that many will have health problems unrelated to the consumption of defective products. Our assumption is that only the change in health status is relevant for our analysis. If an immune-compromised consumer is made ill by a defective product, e.g., gets lead poisoning, the consumer might in fact have more difficulty recovering than an otherwise healthy person. However, we assume that the change in productivity, functional state, pain and suffering, and medical costs will be the same, regardless of prior health status. Accounting for confounding factors would have the effect of making health problems worse than we estimate, not better, so our estimate may be understating the true health benefits.

2. The average value of a QALY is $630 per day. That value, $630 per day, is in turn based on: (1) the value of a statistical life of $5 million; (2) the expected remaining life of consumers

of 21.84 years (average), discounted from 36 years; and, (3) the social rate of time preference of 3 percent. The estimate is derived from workers in somewhat risky occupations who demand a wage premium for their additional risk of fatality. If our estimate of the value of a statistical life of workers does not represent the value of a statistical life of consumers of dietary supplements, then our benefits estimate will be different from the true health benefits of the rule. If consumers value their life differently than workers or if consumers place different values for different kinds hazard related deaths than do workers for job-related safety hazards, then we will have incorrect estimates for the true health benefits. If we discount life expectancy by 7 percent instead of 3 percent, the benefits would be much higher.

3. There is one illness for each recall. We assumed that for each class 1 and 2 recalled product there was only one illness that was reported to the public health authority. For instance, if a product was recalled because the defective product contained lead, we assume that a person was made ill from lead poisoning and that was how the recalled product was discovered. If there were more illnesses per recall than one, then our estimates of benefits will be low. If fewer than one illness per recall occurred (or is likely to occur in the future), then our estimate of health benefits will be more than the actual health benefits.

4. The assumed frequency of actual illnesses is 100 times the frequency of reported illnesses. This assumption is based on Ref. E16. We recognize that the factor of 100, although it has empirical support, might be wrong and that there is likely to be considerable uncertainty about this point estimate. It is widely believed in the public health community that most illnesses are underreported to public health authorities, particularly in passive reporting systems, such as the case with dietary supplements. Mild cases are the most underreported. For instance, victims rarely notify public health authorities when they have minor gastrointestinal tract related illnesses. It is even more rare to report the likely source of a mild illness. It is also widely believed that severe illnesses and death are reported much more frequently than milder illnesses, even when the cause of illness or death is not included in the report. Although the number of deaths that are reported probably approach 100 percent, the cause of death from a contaminated dietary supplement product might not be reported. We believe that using a single composite factor--100--to represent the total number of all unreported cases, including mild, severe, and death, does not invalidate our assumption. The factor of 100 represents an estimate of the composite probability of the full range of probabilities for each severity level of an illness being reported. Increasing the factor multiplier from 100 to some

number higher would increase the health benefits, while lowering the multiplier would decrease the health benefits. If we assume that all illnesses are reported - there are no unreported illnesses and no factor of 100, then the health benefits from fewer sporadic illnesses will be less than $1 million.

5. Introducing CGMP's will reduce the probability of a recall to zero. We believe that the proposed CGMP's creates the most reliable means for discovering product adulteration. Indeed, we believe that it will, if strictly used, cause the discovery of all adulteration. Therefore, we assume that once an establishment fully adopts the requirements, there should be no more health risk from adulterated dietary supplements and consequently, no more class 1 and 2 recalls. This conclusion rests on the assumption that there will be 100 percent compliance with this regulation. We recognize that human error is inescapable. If recalls--or a health risk from adulteration--would still exist, then we overstated the true health benefits of the regulation.

The assumptions for the health benefits from lowering the likelihood of rare catastrophic event model are:

1. We assume that a rare catastrophic event would occur every 30 years. We recognize that the occurrence of a single event provides little evidence about what will happen in the future. If the event reported in this analysis was in fact a one-time occurrence, then our estimate of the benefits from the prevention

of the catastrophic health event would overstate the true benefits, which in fact should be zero. There would have been no future event, and there would be no benefit from adopting a rule to avoid it. If a rare event would have happened more frequently than our estimate of once every 30 years, then our estimate of the benefits would underestimate the true health benefits.

2. Number of illnesses per rare event. We based our estimate of the health impact from contaminated L-Tryptophan. If the number of illnesses from a future rare event differed--either more or less--then the health benefits would differ from our estimated benefits. If a future event would have had 10,000 cases, not 1,500 cases, then our estimate would understate the true health benefits of avoiding such a large catastrophe.

The assumptions for fewer products recalled are:

1. The reported class 1 and 2 recalls that have occurred over the last 10 years represent the number and type of recalls that would have occurred in the future but for the implementation of this regulation. If the number or types of recalls are not representative, then we over or under estimated the benefit of avoiding recalls. Avoiding one very large recall could result in significantly higher benefits. Conversely, merely avoiding fewer or smaller recalls would result in smaller benefits.

2. A product recall causes sellers to lose both goodwill and the value of the recalled product and lost goodwill equals the value

of the recalled product. These two embedded assumptions have empirical support from Ref. E24. A product recall adversely affects the wealth of sellers--a recall leads to lost goodwill--by signaling to consumers that products are defective. From evaluating the declines in public share prices after product recalls in various industries, the authors in Ref. E24 determined that the loss in share price is twice the value of the loss of the actual value of the product recalled. They attribute the difference to lost firm goodwill.

3. Full compliance with the proposed CGMP's will reduce the probability of a recall to zero. As in our earlier assumption about the probability of recalls after the rule is adopted, consistency requires that if we believe that the rule will reliably cause the discovery of adulterated products before they are commercially available, there should be no more health risk from adulterated dietary supplements. Consequently, there should be no more recalls.

We developed the hypothetical search model to estimate the implicit value to consumers of better product quality although we lacked a model that could enable us to directly estimate consumer preferences for dietary supplement quality. With the adoption of the proposed rule, the standardization of manufacturing practices will reduce product differentiation. In a perfect information market, the change in product differentiation would be reflected

in the change in the price differences between low and high quality products. In the existing market, price differences alone are an inadequate signal because the differences in product quality are typically hidden from the view of both consumers and (though less so) manufacturers. In this hypothetical model, we assumed that if there were actually indicators of product quality in the market now, consumers would spend a certain amount of time attempting to find a reasonably high quality product. Time spent searching is an economic cost. In fact, in markets where quality is discernible prior to purchase, such search does take place and it is from those markets that our estimates were derived. In such a world of easily available product quality signals, this regulation, by standardizing product quality at the high end, would reduce that search time. Our assumption is that this is a reasonable indicator of consumers' value for high quality products. Further, we assume that in fact consumers of dietary supplements do wish to purchase high quality products, as the absence of quality could mean either an ineffective product or worse, illness or death. We used various assumptions at each step in our model, and the benefits change when the assumptions change. The assumptions that we used for the search model are:

1. Consumers will search until the expected benefits of the search equal the expected cost of additional search. The expected cost is the value of their time, which we estimated is

the average wage rate for manufacturing workers--$15.65/hour. If the true wage rate is different, the benefits of the rule will be different.

2. The three models--drug store, use of time and grocery store models--represent consumers of dietary supplements. If not, then we will not have estimated the true preferences of consumers. If consumers value dietary supplements more highly than either drugs, groceries or other uses of time, and they search more for better quality, then we understated the benefits of product standardization. If consumers value dietary supplements less highly than either drugs, they search more for better quality, then we overstated the benefits.

3. The quality controls will reduce consumer search time by approximately 33 percent. If our estimate is not representative of the true average reduction, then our estimate will be wrong.

4. The type and number of consumers represent the true value. If children, the elderly or other consumers search for these products in significantly greater amounts than average workers or the estimated population, then we may have overstated the benefits, because their foregone wages would be less than that of average workers.

In an ideal analysis, the benefits and costs of each provision would be evaluated. We were not able to quantify the benefits for each of the provisions in our analysis although we

do have fairly detailed estimates of the cost. We request comments on marginal costs and benefits of specific provisions in the rule. Comments can be directed either at how well a specific provision might work to make dietary supplements either safer or of higher quality, or be directed at the cost of the provision. An example of this type of provision follows for recordkeeping:

Benefits of Recordkeeping

Mandatory recordkeeping is intended to help the discovery of manufacturing practices that create defective products. Recordkeeping ensures that preventative controls are carried out for each batch of dietary supplements produced. Records serve as a checklist that quality control personnel can consult to monitor that necessary controls are implemented or corrective actions taken. Further, mandatory recordkeeping provides an incentive for manufacturers to comply more fully with the provisions of the rule where recordkeeping is required. Knowing that FDA inspectors will examine records and that falsifying them is a criminal offense provides strong incentives to keep thorough and accurate records that the required safety functions have been performed adequately and in a timely manner. Thus, the benefits of recordkeeping are to permit detection of defective products and increase compliance with the provisions for which recordkeeping is required. If, for example: (1) the total

benefits of the requirements that have recordkeeping attached to them were $50 million (not the real value); (2) only half of the requirements would be met without recordkeeping; and, (3) recordkeeping raised the compliance rate to 100 percent, then the benefits of recordkeeping would be $25 million. We were not able to quantify the marginal benefits of this requirement with numbers like this. Comments are requested for how well records are likely to perform this function. We estimate that the additional cost to society for the proposed new recordkeeping requirement will be approximately 10 percent of the total annual cost of the proposed regulation, or a little less than $9 million per year.

Further, we request comments on all of the provisions that would be of a similar nature to this example.

The costs of the rule depend on our assumptions about the amount and cost of testing. The amount of testing is highly uncertain; we have tried to model the number of tests based on number of ingredients and types of tests.

We first characterized the uncertainty as a probability distribution. We ran 1,000 computer simulations to estimate both benefits and costs. The simulations used distributions and assumptions from tables 8 through 13 of this document in place of single estimates.

Table 19.--Distribution of Simulation Results for Annual Benefits and Costs

	5th Percentile	Median	Mean	95th Percentile
Annual benefits	$89 million	$198 million	$218 million	$405 million
Annual costs	$62 million	$80 million	$86 million	$128 million

The computer simulation gives the distribution of estimated benefits and costs. If the underlying distributions capture the uncertainty of the estimates, then the results in table 19 of this document give a clear picture of the uncertainty. Another way to show the uncertainty is to see how sensitive the results are to plausible changes in individual variables. We start with benefits.

Table 20.--Sensitivity of Benefits

Description	Estimated Annual Benefits
The proposed rule	$218 million
If reporting rate of illness is 0.1 (baseline is 0.01)	$182 million
If reporting rate of illness is 0.005 (baseline is 0.01)	$257 million
If the value of a statistical life is $3 million (baseline is $5 million)	$175 million
If the value of a statistical life is $7 million (baseline is $5 million)	$259 million
If consumer search time per item is 1 minute (baseline is 3.75 minutes)	$137 million
If consumer search time per item is 5 minutes (baseline is 3.75 minutes)	$250 million
If consumer search time equals 40 percent of shopping time (baseline is 70 percent)	$166 million
If consumer search time is equal to shopping time (baseline is 70 percent)	$254 million
If consumer search for quality accounts for 30 percent of search time (baseline is 20 percent)	$278 million
If consumer search time for quality accounts for 10 percent of search time (baseline is 20 percent)	$158 million
If catastrophic events are not prevented (baseline is $66 million annual benefit from prevention)	$152 million

We mainly looked at the cost effects of changing assumptions about testing and consumer complaints. As table 21 of this document shows, annual costs are quite sensitive to the assumptions about the average cost and number of tests.

Table 21.--Sensitivity of Costs

Description	Estimated Annual Costs
The proposed rule	$86 million
6 tests per batch (baseline is 3)	$119 million
1 test per batch (baseline is 3)	$66 million
$100 per test (baseline is $60)	$101 million
1 consumer complaint per 20 batches (baseline is 1 per 10)	$77 million
1 consumer complaint per 5 batches (baseline is 1 per 10)	$104 million

C. Initial Regulatory Flexibility Analysis

1. Introduction

FDA has examined the economic implications of this proposed rule as required by the Regulatory Flexibility Act (5 U.S.C. 601-612). If a rule has a significant economic impact on a substantial number of small entities, the Regulatory Flexibility Act requires agencies to analyze regulatory options that would

lessen the economic effect of the rule on small entities. We find that this proposed rule would have a significant economic impact on a substantial number of small entities.

2. Economic Effects on Small Entities

a. Number of small entities affected. The proposed regulations would affect many small entities. Our classification of establishment size is based on the Small Business Administration's definition for small, as discussed previously in this document. A small business by this definition is any establishment with fewer than 500 employees. For this analysis, we defined very small establishments as establishments with fewer than 20 employees. Some small and very small establishments produce very large revenues and would probably not incur a large decline in profitability from the proposed CGMP regulations. We lack precise information about those establishments. Based on the survey, we estimated that 830 establishments, 53 percent of the total establishments, could be classified as very small (under 20 employees) and 564 as small (20 to 499 employees), which is 36 percent of the total establishments.

We estimated that 95 percent of all holders (warehouses and wholesalers) covered by this regulation are small using the Small Business Administration definition. The total number of holders likely to be affected by this regulation is 26,617 (see table 4 of this document), so the total number of holders that are small

would be 25,286 (= 0.95 x 26,617).

The small establishments that would be affected by the proposed regulations are those establishments that would have to perform the various required activities, and that would not have done so without the regulations. As in the preliminary regulatory impact analysis (section VII.B of this document), we determined our estimate of baseline (pre-CGMP) manufacturing practices with the survey of the industry (Ref. E2). The survey asked representative respondents to answer a series of questions, including how many employees they had and what their existing practices were. From the survey, we determined that small establishments do not now follow all of the provisions of the proposed CGMP regulations now. Those that do not follow the proposed requirements will incur a cost to do so.

b. Costs to small entities. Implementation costs vary across establishments based on current practices and the types of products manufactured, packaged, or held. We estimated the range of current practices using the survey of the industry. The cost model divided establishments by size, which allowed us to estimate the distribution of costs per establishment for each size and product class. Table 22 of this document shows the cost per establishment for very small and small establishments. For comparison, we include the estimated average cost per large establishment and the median revenues for each size category. As

the table shows, costs per establishment are proportionally higher for very small than for large establishments. The table's most striking result is that costs are highest for small (20 to 499 employees) establishments.

Table 22.--Cost Per Establishment

	1st year	Annual
Very small--fewer than 20 employees; median revenue under $1 million	$62,000	$38,000
Small--20 to 499 employees; median revenue $5 to 10 million	$99,000	$61,000
Large--500 or more employees; median revenue $20 to $50 million	$83,000	$47,000

Small establishments that do not perform a substantial number of the actions required by the proposed CGMP regulations would bear relatively high costs for compliance with the provisions of this proposed rule. As shown in table 22 of this document, we estimated the average annual compliance costs for a very small establishment to be around $38,000. About one-third of those establishments or about 500 firms have annual sales revenues under $500,000. In addition, the average annual compliance cost for a small establishment is around $61,000. As the survey indicated, about 14 percent of establishments with 20 to 499 employees or about 200 firms have annual sales revenues under $500,000. For purposes of our analysis, we regard firms with revenues of $500,000 or less to be low revenue firms. Although the proposed rule would raise product prices, the price increase (which would largely be determined by changes made by large establishments) would be much smaller than the increase in the average costs of very small producers. The average burden to

very small low revenue firms, then, would be at least 8 percent of their annual revenue. The average burden to small low revenue firms would be at least 12 percent of annual revenue. Establishments with above average costs, and even establishments with average costs, would be hard pressed to continue to operate. Therefore, some of these establishments, for example, such as those that produce other products (foods or pharmaceuticals) or are part of firms with more than one establishment, may decide it is too costly and either change product lines or go out of business. If we assume that one half of these firms have sales revenues from other products and locations and remove them from the at-risk group, we are left with approximately 350 very small and small establishments with less than $500,000 in revenue. It is possible that a large number of these 350 very small and small establishments would be unable to absorb the compliance costs and will close.

3. Regulatory Options

a. Exemptions for small entities. The burden on small establishments would be reduced if they were exempt from some provisions of the proposed rule. Most entities affected by this proposed rule, however, are small. Exempting small establishments from some or all of its provisions would be likely to reduce benefits.

b. Longer compliance periods. Lengthening the compliance

period would provide regulatory relief for small entities. A longer compliance period for small entities would allow additional time for setting up recordkeeping, making capital improvements to the physical plant, purchasing new or replacement equipment, and other one-time expenditures. It would also delay the impact of the annual costs of compliance. We have given very small and small firms an additional 2 years for compliance. The proposed rule, then, would be phased-in over 3 years, with large firms complying after 1 year, and both very small and small firms after 3 years. After 3 years, the annual costs would be incurred. The cost savings of delay may well be larger than simply the present value of the delay because very small and small firms may also be able to reduce their compliance costs by taking advantage of increases in industry knowledge and experience in implementing CGMP regulations. A summary of the compliance costs is shown in table 22 of this document.

Although lengthening the compliance period would provide some regulatory relief to small entities, relief for these provisions would also delay the full realization of the benefits of the proposed rule.

4. Description of Recordkeeping and Reporting

The Regulatory Flexibility Act requires a description of the recordkeeping and recording required for compliance with this proposed rule. This proposed rule would require the preparation

of records. As described in the Preliminary Regulatory Impact Analysis, records must be written or electronic documents must be kept that demonstrate that specific action or actions occurred in the manufacturing process in compliance with the proposed regulations. Records that would be required in this proposed rule would demonstrate, that corrective actions were taken, that equipment, instruments, and controls used in laboratory operations and quality control were installed properly, and calibrated; that maintenance programs were followed; and that the results of any testing meet the necessary specifications.

The compliance cost of recordkeeping is the sum of both the initial design and printing of the recordkeeping documents and the recurring costs of maintaining the records. The cost of training personnel to use the new documents is a recurring cost depending on how frequently documents are modified, how often personnel turn over, and how complicated the tasks are that are being recorded. The recurring costs are measured by the workers' wage rate multiplied by the expected labor hours necessary to perform a written or electronic record and the time necessary for management to review the records to see that actions are documented accurately. In addition, electronic records necessitate recurring time spent ensuring that the equipment is serviced and maintained properly.

5. Summary

The proposed CGMP regulations would have a significant economic impact on a substantial number of small entities.

D. Unfunded Mandates

The Unfunded Mandates Reform Act of 1995 (Public Law 104-4) requires cost-benefit and other analyses for rules that would cost more than $100 million in a single year. The current inflation-adjusted statutory threshold is $112 million. The proposed rule qualifies as a significant rule under the statute because there is a significant possibility that the cost of the rule will be above the threshold. Most of the requirements of the Unfunded Mandates are fulfilled in the Executive Order 12866 analysis. The requirements under the Unfunded Mandates Act of 1995 include assessing the rule's effects on future costs; productivity; particular regions, communities, or industrial sectors; economic growth; full employment; job creation; and exports.

Future Costs

The future costs from the rule include the recurring costs, which reach their long-term value in the third year after the proposed rule would become final. These costs would be incurred by the establishments that manufacture, process, pack, transport, distribute, receive, hold, or import dietary ingredients or dietary products. Recurring costs from the regulatory requirements would be incurred in each future year. Table 18, of

this document, summarizes the annual future recurring costs.

Particular regions, communities, or industrial sectors

The costs of the rule will be shared among manufacturers, processors, packagers, transporters, receivers, holders, and importers of dietary ingredients or dietary products as well as domestic consumers. The higher costs incurred by domestic suppliers of dietary supplement products as a result of these regulations will mostly be passed on to consumers in the form of higher prices. Since consumer demand for dietary supplements is price elastic, most of the higher costs incurred by suppliers will be passed on to consumers. Consequently, higher dietary supplement prices will reduce real incomes for many consumers. However, the reduction in real incomes is thought to be more than offset by the benefits from these regulations. These benefits are measured as an improved ability by the FDA to respond to and contain threats of serious adverse health consequences from accidental contamination of dietary supplements.

National productivity, economic growth, job creation, and full employment

Although this proposed regulation is significant, we do not expect it to substantially affect national productivity, growth, jobs, or full employment. The total costs will be small relative to the economy, and will be offset by benefits. The improved ability to respond to, and contain, serious adverse health

consequences means less illness and fewer sick days taken by employees, and lower adjustment costs by firms that would otherwise need to hire replacement employees.

Exports

This proposed rule would require additional controls to be kept throughout the production and distribution chain for the manufacture of dietary ingredients and dietary supplements. The additional control costs would increase the total costs of production and distribution for all of the regulated products, including products sold within the U. S. and across national borders. These increased costs will be largely passed on to consumers in the form of higher prices, which will tend to reduce the quantity demanded of the regulated products. The increased prices of U. S. exports could reduce the quantity of U. S. exports demanded, particularly in comparison with exports from countries that do not implement similar regulations. We expect this effect to be insignificant, because under the proposed rule the increases in the price of United States exports (and resulting decreases in quantity demanded) would be quite small.

VIII. Federalism

FDA has analyzed this proposed rule in accordance with the principles set forth in Executive Order 13132. We consulted with seven State officials to make a tentative determination about whether this proposed rule would have federalism implications.

Based on this consultation, it does not appear that this proposed rule has federalism implications. In addition, we sent a letter on March 7, 2000, to elected State officials and their representative organization to notify them that our unified agenda was published on November 22, 1999, and identified this proposed CGMP rule as a rule that would publish in the year 2000. In that letter, we solicited comments on any federalism implications that this proposed rule may have. To date, no responses have been received to our solicitation. After publishing this proposed rule, FDA will send a letter to elected State officials and their representative organization requesting consultation about any federalism implications. We invite comment on our tentative determination that this proposed rule does not have federalism implications, and therefore, does not contain policies that have substantial direct effects on the States, or on the distribution of power and responsibilities among the various levels of government.

IX. Request for Comments

Interested persons may submit to the Dockets Management Branch (see ADDRESSES) written or electronic comments regarding this document. Submit a single copy of electronic comments to http://www.fda.gov/dockets/ecomments or two hard copies of any written comments, except that individuals may submit one hard copy. Comments are to be identified with the docket number found

in brackets in the heading of this document. Received comments may be seen in the Dockets Management Branch between 9 a.m. and 4 p.m., Monday through Friday.

X. References

We have placed the following references on display in the Dockets Management Branch (see ADDRESSES). You may see them between 9 a.m. and 4 p.m., Monday through Friday.

1. Section 2, "Findings," Dietary Supplement Health and Education Act, Public Law 103-417, pp. 4325-4326, October 25, 1994.

2. "Manufacturing Practices for Nutritional Supplements," United States Pharmacopeia, 12601 Twinbrook Pkwy., Rockville, MD 20852, General Chapter 2750, 2186-2192, and 2834, 1993.

3. "NNFA Good Manufacturing Practice in Manufacturing, Packing, or Holding Dietary Supplements," National Nutritional Foods Association, 3931 MacArthur Blvd., suite 101, Newport Beach, CA 92660, 1999.

4. "Draft Report of the Food Advisory Committee Dietary Supplement Working Group on Ingredient Identity Testing and Records and Retention," FDA Food Advisory Committee Dietary Supplement Working Group, Center for Food Safety and Applied Nutrition, FDA, June 25, 1999.

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3. "NNFA Good Manufacturing Practice in Manufacturing, Packing, or Holding Dietary Supplements," National Nutritional Foods Association, 3931 MacArthur Blvd., suite 101, Newport Beach, CA 92660, 1999.

4. "Draft Report of the Food Advisory Committee Dietary Supplement Working Group on Ingredient Identity Testing and Records and Retention," FDA Food Advisory Committee Dietary Supplement Working Group, Center for Food Safety and Applied Nutrition, FDA, June 25, 1999.

5. "Consumer Use of Dietary Supplements," Rodale Press, 733 Third Ave., New York, NY 10017, 2000.

6. Slifman, N. R., W. R. Obermeyer, B. K. Aloi, S. M. Musser, W. A. Correll, S. M. Cichowicz, J. M. Betz, and L. A. Love, "Contamination of Botanical Dietary Supplements by Digitalis Lanata," New England Journal of Medicine, 339:12, pp. 806-811, 1998.

7. "Cardiac Glycoside Drugs," In: Wagner, H., and S. Bladt, Plant Drug Analysis: A Thin Layer Chromatography Atlas, 2d ed., Berlin, Germany: Springer-Verlag, pp. 99-123, 1996.

8. Bruneton, J., Pharmacognosy, Phytochemistry, Medicinal Plants, Paris, Lavoisier Publishing, pp. 572-598, 1995.

9. Evans, W. C., Trease and Evans' Pharmacognosy. 14th ed., Philadelphia, W. B. Saunders, pp. 309-318, 1996.

10. Moe, G. K. and A. E. Farah, "Digitalis and Allied Cardiac Glycosides," In L. S. Goodman and A. Gilman, eds., The Pharmacological Basis of Therapeutics, 5th ed., New York. Macmillan Publishing, pp. 653-682, 1975.

11. "Survey on Botanical Adulteration," American Herbal Products Association, 8484 Georgia Ave., suite

370, Silver Spring, MD 20910, March 4, 1998.

12. Roy, A. K. and H. K. Chourasia, "Mycotoxin Incidence in Root Drugs," International Journal of Crude Drug Residues, 28:2, pp. 157-160, 1990.

13. Kumar, S. and A. K. Roy, "Occurrence of Aflatoxin in Some Liver Curative Herbal Medicines," Letters in Applied Microbiology, 17, pp. 112-114, 1993.

14. Kumar, S. and G. Prasad, "Efficacy of Medicinal Plant (Andrographis peniculata) Extract on Aflatoxin Production and Growth of Aspergillus flavus," Letters in Microbiology 15, pp. 131-132, 1992.

15. "Adverse Events Associated with Ingestion of Gamma-Butyrolactone: Minnesota, New Mexico, and Texas, 1998-1999," MMWR Weekly, 48:07, pp. 137-140, February 26, 1999.

16. FDA Establishment Inspection Report, Ducoa Co., CFN #1944182, August 31, 1998 and September 1, 1998.

17. FDA Health Hazard Evaluation, Classification, and FDA Enforcement Report for Firm-Initiated Recall--Lead, U.S. FDA Recall #F-006-5 and #F-137/145-5, 1994.

18. FDA Health Hazard Evaluation, Classification, and FDA Enforcement Report for Firm-Initiated Recall Salmonella, U.S. FDA Recall #F-164/171-8, 1988.

19. FDA Health Hazard Evaluation, Classification, and FDA Enforcement Report for Firm-Initiated Recall--Klebsiella Pneumonia, U.S. FDA Recall #F-522-0, 1990.

20. FDA Health Hazard Evaluation, Classification, and FDA Enforcement Report for Firm-Initiated Recall--Botulism, U.S. FDA Recall #F-563/564-9, 1989.

21. FDA Health Hazard Evaluation, Classification, and FDA Enforcement Report for Firm-Initiated Recall--Glass Fragments, U.S. FDA Recall #F-540-3, 1993.

22. FDA Health Hazard Evaluation, Classification, and FDA Enforcement Report for Firm-Initiated Recall Super-Potent Vitamin A, U.S. FDA Recall #F-157/158-5, 1994.

23. FDA Health Hazard Evaluation, Classification, and FDA Enforcement Report for Firm-Initiated Recall--Super-Potent Vitamin D, U.S. FDA Recall #F0610-3, 1993.

24. FDA Health Hazard Evaluation, Classification, and FDA Enforcement Report for Firm-Initiated Recall--Super-Potent Vitamin B-6, U.S. FDA Recall #F-272-3, 1993.

25. FDA Health Hazard Evaluation, Classification, and FDA Enforcement Report for Firm-Initiated Recall Super-Potent Selenium, U.S. FDA Recall #F-007-5, 1994.

26. "Table 1. Tolerable Upper Intake Levels (UL)

for Certain Nutrients and Food Components," Dietary Reference Intakes: A Risk Assessment Model for Establishing Upper Intake Levels, 20, Food and Nutrition Board, Institute of Medicine, National Academy of Sciences, Washington, DC, June 1999.

27. FDA Health Hazard Evaluation, Classification, and FDA Enforcement Report for Firm-Initiated Recall--Sub-Potent Folic Acid, U.S. FDA Recall #F-825-7, 1996.

28. FDA Health Hazard Evaluation, Classification, and FDA Enforcement Report for Firm-Initiated Recall Color Additives, Yellow #6, Red #40, Blue #2, U.S. FDA Recall #F-314-8, 1998.

29. FDA Health Hazard Evaluation, Classification, and FDA Enforcement Report for Firm-Initiated Recall--Color Additives, Yellow #5, U.S. FDA Recall #F-761-4, 1994.

30. FDA Health Hazard Evaluation, Classification, and FDA Enforcement Report for Firm-Initiated Recall--Lactose, U.S. FDA Recall #F-271-6, 1995.

31. FDA Health Hazard Evaluation, Classification, and FDA Enforcement Report for Firm-Initiated Recall--Sulfites, U.S. FDA Recall #F-538/539-9 1999.

32. Weber, R. W., "Food Additives and Allergy," Annals of Allergy, 70, pp. 183-190, 1993.

33. Gurley, B. J., S. F. Gardner, and M. A. Hubbard, "Content Versus Label Claims in Ephedra-containing Dietary Supplements," (Prepublication version) American Journal Health Systems Pharmacy, 57, pp. 963-969, May 15, 2000.

34. Consumer Labs Product Reviews on Ginkgo Biloba, Saw Palmetto, Glucosamine and Chrondroitin, and SAMe, (www.consumerlabs.com).

35. "Methods Validation and Technical Programs," AOAC Official Methods Program, (www.aoac.org), March 17, 2000.

36. Alexander, R. G., D. A. Wilson, and A. G. Davidson, "Medicines Control Agency Investigation of the Microbial Quality of Herbal Products," The Pharmaceutical Journal, pp. 259-261, August 1997.

37. Transcript, FDA and USDA Symposium, "Tissue Distribution, Inactivation, and Transmission of Transmissible Spongiform Encephalopathies of Animals," Riverdale, MD, 1996.

38. "Frontier," "Nature's Herbs," and "Nature's Way," (www.mothernature.com), June 2000.

39. USDA Food Composition Data, National Agricultural Library, Food and Nutrition Information Center, USDA, May 2000.

40. "King-size Gingersnaps, The Good Housekeeping Cookbook, p. 564, New York, NY, 1973.

41. "Food Defect Action Levels: Levels of Natural or Unavoidable Defects in Foods that Present no Health Hazards for Humans," Department of Health and Human Services, Public Health Service, Food and Drug Administration, Center for Food Safety and Applied Nutrition, Washington, DC 20204, May 1998.

42. "Hazard Analysis and Critical Control Point Principles and Application Guidelines," National Advisory Committee on Microbiological Criteria for Foods, August 14, 1997.

43. Presidential Memorandum on Plain Language, The White House, Washington, June 1, 1998.

44. Olsen, A. R., "Regulatory Action Criteria for Filth and Other Extraneous Materials. II. Allergenic Mites: An Emerging Food Safety Issue," Regulatory Toxicology and Pharmacology, 28, pp. 190-198, 1998.

45. U.S. Department of Health and Human Services, Food and Drug Administration, "Food Code," Section 1-201.10(B)(72), p. 15, 1999.

46. "Immunoglobin g (IgG) Dietary Supplement," (www.kingsnutrition.com/immunol.html).

47. Vasarada, P. C. and M. A. Cousin, "Dairy

Microbiology and Safety," In: Dairy Science and Technology Handbook, vol. 2, edited by Y. H. Hui, New York, Chapter 5, pp. 301-426, VCH Publishers, Inc., 1992.

48. Stauffer, J. E., "Quality Assurance and Dairy Processing," In: Dairy Science and Technology Handbook, vol. 3, edited by Y. H. Hui, New York: Chapter 1, pp. 1-76, VCH Publishers, Inc., 1992.

49. Biotics Research Products (http://www.increasedhealth.com/biotics_description.shtml).

50. "Bovine-Derived Materials; Agency Letters to Manufacturers of FDA-Regulated Products," FEDERAL REGISTER, August 29, 1994.

51. "Points to Consider in the Manufacture and Testing of Therapeutic Products for Human Use Derived from Transgenic Animals," FDA, Center for Biologics Evaluation and Research, 1995.

52. "Guidance for Industry, The Sourcing and Processing of Gelatin to Reduce the Potential Risk Posed by Bovine Spongiform Encephalopathy (BSE) in FDA-Regulated Products for Human Use," U.S. Department of Health and Human Services, Food and Drug Administration, September 1997.

53. "Guidance for Industry, Guide to Minimize Microbial Food Safety Hazards for Fresh Fruits and Vegetables," U.S. Department of Health and Human Services, Food and Drug Administration, Center for Food Safety and Applied Nutrition (CFSAN), October 1998.

54. Webster's II New Riverside University Dictionary, Houghton Mifflin Co., 222 Berkeley St., Boston, MA 02116, p. 961, 1994.

55. "FDA Fact Sheet: Shigella in Food," Food and Drug Administration, U.S. Department of Health, Education, and Welfare, Public Health Service, December 1969.

56. Bryan, F. L., "Emerging Foodborne Diseases: I. Their Surveillance and Epidemiology," Journal of Milk and Food Technology, 35:10, pp. 618-625, October 1972.

57. Cross Connection Control Committee, Pacific Northwest Section, American Water Works Association, with the Assistance of EPA, "Cross Connection Control Manual Accepted Procedures and Practice," Section 1 "Introduction to Cross Connection Control and Backflow Prevention," 5th ed., pp. xiv, 1-2, 3-4, 3-5, 3-6, 3-7, May 1990.

58. "Factors Affecting the Growth of

Microorganisms in Foods," The Bad Bug Book, U.S. Food and Drug Administration, Center for Food Safety and Applied Nutrition, Foodborne Pathogenic Microorganisms and Natural Toxins Handbook, 1997.

59. FDA "Guide to Inspections of Computerized Systems in the Food Processing Industry," Division of Emergency and Investigational Operations, Office of Regional Operations, Office of Regulatory Affairs, U.S. Food and Drug Administration, March 1998.

60. Moody, M. W., "How Cleaning Compounds Do the Job," Seafood Technology Cooperative Extension Service, Louisiana State University, pp. 33-41, undated.

61. Lentsch, S., "Sanitizers for an Effective Cleaning Program," Klenzade Division, Economics Laboratories, St. Paul, MN, undated.

62. FDA "Guide to Inspections of Computerized Systems in Drug Processing," February 1983.

63. Hitokoto H., S. Morozumi, T. Wauke, S. Sakai, and H. Kurata, "Fungal Contamination and Mycotoxin Detection of Powdered Herbal Drugs," Applied and Environmental Microbiology, 36:2, pp. 252-256, 1978.

64. Stewart, M. J., V. Steenkamp, and M. Zuckerman, "The Toxicology of African Herbal Remedies," Therapeutic Drug Monitoring, 20, pp. 510-516, 1998.

65. Halt, M., "Moulds and Mycotoxins in Herb Tea

and Medicinal Plants," European Journal of Epidemiology, 14, pp. 269-274, 1998.

66. Pharmacopeial Previews: Nutritional Supplements--Section 2022: Microbial Procedures for Absence of Objectionable Microorganisms in Nutritional and Dietary Articles, Pharmacopeial Forum, vol. 25:5, pp. 8761-8769, September-October 1999.

67. Pharmacopeial Previews: Nutritional Supplements--Section 2023: Microbiological Attributes of Nonsterile Nutritional and Dietary Articles, Pharmacopeial Forum, vol. 25:5, pp. 8770-8773, September-October 1999.

68. AOAC Official Method 967.22, Vitamin C (Total) in Vitamin Preparations, AOAC Official Method 984.26, Vitamin C (Total) in Food, Official Methods of Analysis of AOAC International, 16 ed., Gaithersburg, MD, 1995.

69. Madis, V. H. and V. Madis, "The Sampling of Crude Botanicals," D&CI, (1986), pp. 38-43 and 79.

70. Centers for Disease Control, "Anticholinergic Poisoning Associated With an Herbal Tea--New York City, 1994," Morbidity and Mortality Weekly Report, 44:11, pp. 193-195; March 25, 1995.

71. Ernst, E., "Harmless Herbs? A Review of the Recent Literature," American Journal of Medicine, p.

104, pp. 170-178, 1998.

72. Huxtable, R. J., "The Harmful Potential of Herbal and Other Plant Products," Drug Safety, 5 (Suppl. 1), pp. 126-136, 1990.

73. Betz, J. M., "Plant Toxins," General Referee Reports: Journal of AOAC International, 78:1, pp. 141-144, 1995.

74. Chan, T. Y. K., J. C. N. Chan, B. Tomlinson, and J. A. J. H. Critchley, "Chinese Herbal Medicines Revisited: A Hong Kong Perspective," The Lancet, 342, pp. 1532-1534, 1993.

75. Wong, M. K., P. Tan, and Y. C. Wee, "Heavy Metals in Some Chinese Herbal Plants," Biological Trace Element Research, 36, pp. 135-142, 1993.

76. "Reviewer Guidance, Validation of Chromatographic Methods Center for Drug Evaluation and Research, FDA, November 1994.

77. FDA Health Hazard Evaluation, Classification, and FDA Enforcement Report for Firm-Initiated Recall #F-321-0, 1989.

78. FDA Health Hazard Evaluation, Classification, and FDA Enforcement Report for Firm-Initiated Recall Vitamin C, U.S. FDA Recall #F-657-8, 1998.

79. FDA Health Hazard Evaluation, Classification,

and FDA Enforcement Report for Firm-Initiated Recall Vitamin Mineral Supplement, U.S. FDA Recall #F-717-0, 1990.

80. Report of the Commission on Dietary Supplement Labels, Office of Disease Prevention and Health Promotion, Department of Health and Human Services, Washington, DC 20201, pp. 21 and 45, November 1997.

81. Webster's II New Riverside University Dictionary, Houghton Mifflin Co., 222 Berkeley St., Boston, MA 02116, p. 761, 1994.

82. "Manufacturing Practices for Dietary Supplements, Pharmacopeial Forum, 28:2, pp. 534-552, March/April 2002.

83. Draft Standard NSF 173-2001, Dietary Supplements, NSF International Draft Standard, NSF International, 789 North Dixboro Road, P.O. Box 130140, Ann Arbor, Michigan 48113.

References--Economics

E1. Research Triangle Institute (RTI), 1999a, "Economic Characterization of the Dietary Supplement Industry," Contract No. 223-96-2290: Task Order 3, March 1999.

E2. RTI, "Survey of Manufacturing Practices in the Dietary Supplement Industry," Contract No. 223-96-2290: Task Order 6, May 2000.

E3. NPR/Kaiser Family Foundation/Kennedy School of Government, Survey of Americans and Dietary Supplements, 1999.

E4. Guthrie, J. F., K. M. Koehler, and R. A. Scharff, "Trends in the Consumption of Dietary Supplements Since 1994," Unpublished, 2000.

E5. "US Dietary Supplements Market Size Expressed as Dollar Sales by Top Six Product Categories for 1994 to 1998 and Forecast for 1999 and 2000," Nutrition Business Journal, Dialog File Number 93, San Francisco, The Dialog Corp., 2000.

E6. Supplementary Data Tables, USDA's 1994-96 Continuing Survey of Food Intakes by Individuals; Food Surveys Research Group, Beltsville Human Nutrition Research Center, Agricultural Research Service, U.S. Department of Agriculture, Riverdale, MD; February 1999; accessed at http://www.barc.usda.gov/bhnrc/foodsurvey/home.htm.

E7. Prevention Research Associates, Special Nutritionals Survey, Report for Prevention Magazine, June 8, 1999.

E8. Roe, B. E., B. M. Derby, A. L. Levy, "Demographic, Lifestyle and Information Use Characteristics of Dietary Supplement User Segments,"

A report prepared for the Commission on Dietary Supplement Labeling, Food and Drug Administration, Center for Food Safety and Applied Nutrition, Division of Market Studies, March 12, 1997.

E9. Eisenberg, D. M., R. B. Davis, S. L. Ettner, S. Appel, S. Wildey, M. Van Rompay, R. C. Kessler, "Trends in Alternative Medicine Use in the United States, 1990-1997: Results of a Follow-up National Survey," Journal of the American Medical Association, 280(18):1569-1575, 1998.

E10. Food Marketing Institute, Research Department, and Prevention Magazine, Research Department, A Look at the Self Care Movement, Food Marketing Institute and Prevention Magazine, 1998.

E11. Wilde, L. L., "Information Costs, Duration of Search, and Turnover: Theory and Applications," Journal of Political Economy, 89, December, 1122-1141, 1981.

E12. McCarthy, P. and B. Timbo, Memorandum: Report of Adverse Health Outcomes Associated With the Consumption of Dietary Supplements Which Were Prepared Using Poor Manufacturing Practices, November 17, 1999.

E13. Prevention Magazine and Food Marketing Institute (FMI), "The Growing Self-Care Movement,"

Prevention/FMI Survey, 2000.

E14. Gugliotta, G., "Health Concerns Grow Over Herbal Aids," Washington Post, March 19, 2000.

E15. Koehler, K. M., Memorandum: Tally of AERs Regarding Dietary Supplements, May 30, 2000.

E16. Walker, A. M., "The Relation Between Voluntary Notification and Material Risk in Dietary Supplement Safety," Harvard School of Public Health, March 9, 2000.

E17. Alsop, R. J., 1999, Wall Street Journal Almanac, New York, Ballantine Books, pp. 554-563, 1998.

E18. Viscusi, W. K., "The Value of Risks to Life and Health," Journal of Economic Literature, 31: 1912-1946, 1993.

E19. Economic Report of the President, Washington, DC, United States Government Printing Office, 2000.

E20. Kaplan, M., J. A. Anderson, and T. G. Ganiats, "The Quality of Well-being Scale: Rationale for a Single Quality of Life Index," edited by S. R. Walker and R. M. Rosser, In Quality of Life Assessment: Key Issues in the 1990's, The Netherlands: Kluwer Academic Publishers, 65-94, 1993.

E21. Kaufman, L. D. "Chronicity of the

Eosinophilia-Myalgia Syndrome. A Reassessment After Three Years," Arthritis and Rheumatism, 37:884-887, 1994 Abstract.

E22. Hedberg, C., et al., "Eosinophilia-Myalgia Syndrome, Natural History in a Population Based Cohort," Archives of Internal Medicine, 152:1189-1892, 1992 Abstract.

E23. Vanherweghem, J. L., "Misuse of Herbal Remedies: The Case of an Outbreak of Terminal Renal Failure in Belgium (Chinese Herbs Nephropathy)," Journal of Alternative Complementary Medicine, 4:9-13, 1998.

E24. Jarrell, G. and S. Peltzman, "Impact of Product Recalls on the Wealth of Sellers," Journal of Political Economy, 93:512-536, 1985.

E25. "Herbal Rx: The Promises and Pitfalls," Consumer Reports, March, 44-48, 1999.

E26. ConsumerLab, Independent tests of herbal, vitamin, and mineral supplements, accessed at http://www.consumerlab.com/results on March 16, 2000.

E27. Rothman, G., "Herbal Remedy Ripoffs," D Magazine, April, 39-44, 2000.

E28. Foster, W. and R. E. Just, "Measuring Welfare Effects of Product Contamination with Consumer

Uncertainty," Journal of Environmental Economics and Management, 17, pp. 266-283, 1989.

E29. Jones, P. and J. Hudson, "Standardization and the Costs of Assessing Quality," European Journal of Political Economy, 12:355-361, 1996.

E30. Newman, J. W. and B. D. Lockeman, "Measuring Prepurchase Information Seeking," Journal of Consumer Research, 2:216-222, 1975.

E31. Punj, G. N. and R. Staelin, "A Model of Consumer Information Search Behavior for New Automobiles," Journal of Consumer Research, 9:366-380, 1983.

E32. Duncan C. and R. Olshavsky, "External Search: The Role of Consumer Beliefs," Journal of Marketing Research, 19:32-43, 1982.

E33. Andrews, R. L., "Economics of Information and Heterogeneous Products," Journal of Economic Psychology, 13:399-420, 1992.

E34. Avery, R. J., "Determinants of Search for Nondurable Goods: An Empirical Assessment of the Economics of Consumer Theory," The Journal of Consumer Affairs, 30(2):390-420, 1996.

E35. Hawkins, D. I., R. J. Best, and K. A. Coney, Consumer Behavior: Implications for Marketing Strategy,

6th ed., Chicago: Irwin, 1995.

E36. "The Power of Persuasion at the Moment of Truth," Drug Store News, 19(20):3-8, 22, 24, 1997.

E37. Robinson, J. P. and G. Godbey, Time for Life: The Surprising Ways Americans Use Their Time, University Park, PA: The Pennsylvania State University Press, 1997.

E38. "How Consumers Shop," Progressive Grocer, December, 62-64, 1992.

E39. United States Department of Labor, Bureau of Labor Statistics (BLS), <http://stats.bls.gov/csx/1998/Standard/cucomp.pdf, as obtained on December 8, 1999.

E40. Lippmann S. and J. McCall, "The Economics of Job Search," Journal of Economic Theory, 14:155-189, 1976.

E41. Little, W. R., "Herbal Products: A Retail Pharmacists Perspective," Nutraceuticals World 3 (May/June): 58-66, 2000.

E42. Bureau of Labor Statistics (BLS), "Consumer Price Index-All Urban Consumers," Accessed at http://146.142.4.24/cgi-bin/surveymost?cu on July 13, 1999.

E43. Gurley, B. J. , S. F. Gardner, and M. A.

Hubbard, "Content Versus Label Claims in Ephedra-Containing Dietary Supplements," American Journal Health Systems Pharmacy, 57:963-969, May 15, 2000.

E44. Eastern Research Group (ERG), "Economic Analysis of Proposed Revisions to the Good Manufacturing Practices Regulation for Medical Devices," Contract No. 223-91-8100: Task Order 1, pp. 4-23 to 4-25, November, 1993.

E45. R. S. Means, Building Construction Cost Data, 2000.

E46. RTI, 1999b, "Dietary Supplement Sales Information," Contract No. 223-96-2290: Task Order 4, October, 1999.

E47. Vardon, P., Memorandum: Conversation with industry expert regarding inventory practices, April 4, 2000.

E48. Ramey, V. A. and K. West, "Inventories," National Bureau of Economic Research, working paper 6315, Abstract, 1997.

E49. Madis, V. H. and V. Madis, "The Sampling of Crude Botanicals," Drug and Cosmetic Industry, pp. 38-79, 1986.

E50. Plant Bioactives Research Institute, "Costs for Analysis," accessed at http://www.plant-

bioactives.com on April 10, 2000.

E51. "Fees, Methods, and Analytical Capabilities of Laboratories-Summary," unpublished summary of prices listed on the Internet, 1999.

E52. McLaughlin, C., Memorandum: Costs of pest control, 2000.

List of Subjects

21 CFR Part 111

Dietary foods, Drugs, Foods, Packaging and containers.

21 CFR Part 112

Drugs, Packaging and containers, Labeling.

Therefore, under the Federal Food, Drug, and Cosmetic Act and under authority delegated to the Commissioner of Food and Drugs, FDA proposes to amend 21 CFR chapter I, parts 111 and 112 as set forth below:

PART 111--CURRENT GOOD MANUFACTURING PRACTICE IN MANUFACTURING, PACKING, OR HOLDING DIETARY INGREDIENTS AND DIETARY SUPPLEMENTS

1. The authority citation for part 111 is revised to read as follows:

AUTHORITY: 21 U.S.C. 321, 342, 343, 348, 371, 374, 381, 393; 42 U.S.C. 264.

2. The part heading for part 111 is revised as set forth above.

3. Add new subpart A to part 111 to read as follows: