Proposed § 111.83(a) would require that you hold any reserve samples of components or dietary ingredients collected in a manner that protects against contamination and deterioration.

Proposed § 111.83(b) would require that you hold such reserve samples of dietary supplements in a manner that protects against contamination and deterioration. Further, this provision would require that you hold the reserve samples under conditions of use recommended or suggested in the label of the dietary supplement and, if no conditions of use are recommended or suggested in the label, then under ordinary conditions of use. This proposed requirement also would require that you use the same container-closure system in which the dietary supplement is marketed or one that provides the same level of protection against contamination or deterioration as the marketed container-closure system. It is necessary to hold the reserve sample of a dietary supplement under the same conditions and in the same packaging as you would expect a consumer to hold that dietary supplement so that, if you need to later test that reserve sample, the testing would reflect current conditions under which the dietary supplement is held by the consumer prior to being consumed.

4. What Requirements Apply to Returned Dietary Ingredients or Dietary Supplements? (Proposed § 111.85)

Proposed § 111.85 would establish requirements for returned dietary ingredients or dietary supplements. "Returned" dietary ingredients or dietary supplements are those products that a

distributor, wholesaler, or retailer returns to a manufacturer. Proposed § 111.85(a) would require that you identify returned dietary ingredients or dietary supplements and to quarantine them until your quality control unit conducts a material review and makes a disposition decision. (Your quality control unit would do this under proposed § 111.37.) For example, you could attach a tag or other identifier on the returned dietary ingredient or dietary supplement to show that it is "returned." We would require that you identify and quarantine (not just identify and segregate) returned dietary ingredients or dietary supplements so that they cannot be used. We propose to require that you quarantine returned products because you must assume that the returned product is adulterated until tests show otherwise. Thus, the product should not have physical closeness or contact with nonreturned product to ensure that it will not be mixed up mistakenly with nonreturned product, redistributed or reused in manufacturing.

Proposed § 111.85(b)(1) states that you may salvage returned dietary ingredients and dietary supplements only if:

- Evidence from their packaging (or, if possible, an inspection of the premises where the dietary ingredients and dietary supplements were held) indicates that the dietary ingredients and dietary supplements were not subjected to improper storage conditions. This would require that you have personal knowledge of the exact conditions under which the

returned dietary ingredients or dietary supplements were held. Normally, for most types of packaging, simply examining the packaging will not tell you about the storage conditions that existed. However, we are aware of some technologies that are being used, such as temperature-sensitive materials that change colors, that could provide some information about storage conditions; and

- Tests demonstrate that the dietary ingredients or dietary supplements meet all specifications for identity, purity, quality, strength, and composition. This requirement will ensure that you do not return to distribution a dietary ingredient or dietary supplement that does not meet specifications. Salvage is available for only those products for which testing can be performed on finished product.

For purposes of this discussion, "salvage" means to return to distribution without reprocessing the dietary ingredient or dietary supplement.

Proposed § 111.85(c) would require that you destroy or suitably dispose of the returned dietary ingredients or dietary supplements if they do not meet specifications for identity, purity, quality, strength, and composition, unless the quality control unit conducts a material review and makes a disposition decision to allow reprocessing.

Proposed § 111.85(d) would require that you conduct an investigation of your manufacturing processes and those other batches if the reason for a dietary ingredient or a dietary supplement being returned implicates other batches. The point of the investigation would be to determine whether, for example, the other implicated batches may have the same problem or have been subject to the same problematic manufacturing process for which the dietary ingredient or dietary supplement was returned. Other batches may be implicated if the component or dietary ingredient used in the returned product also was used in additional batches or if your investigation indicates that there was a problem with a step in the manufacturing process that affected additional batches. The proposal also would require that you document the investigation and include your conclusions and followup.

Proposed § 111.85(e) would require you to establish and keep records for any material review and disposition decision and any required testing to determine compliance with specifications done for any returned dietary ingredient or dietary supplement. You should include the following information in your records:

- The name of the person or company or both the name of the person and company who returned the dietary ingredients or dietary supplements;
- A description of the returned dietary ingredient or dietary supplement;
- The batch or lot number of the returned dietary ingredient or dietary supplement and any reprocessed

batch or batch manufactured using the returned dietary ingredient or dietary supplement;

- The reason for the return;
- The quantity returned;
- The disposition of the dietary ingredient or dietary supplement; and
- The date of disposition.

Proposed § 111.85(f) would require that you make and keep records for returned dietary ingredients and dietary supplements in accordance with § 111.125. These records are necessary to ensure that returned products that could be adulterated are not inadvertently redistributed or inadvertently used in manufacturing. Further, records of any reprocessed batch or batch manufactured using the returned product will be useful in the event that a problem arises with a particular batch that is manufactured with returned product. These records also are necessary to demonstrate compliance with the CGMP and quality control procedures. We invite comment on whether we should require, in a final rule, that you establish and follow written procedures for identifying, quarantining, and salvaging returned dietary ingredients and dietary supplements. In addition, we invite comment on whether there are other procedures that we should include in a final rule.

5. What Requirements Apply to Distributing Dietary Ingredients or Dietary Supplements? (Proposed § 111.90)

Proposed § 111.90 would establish requirements concerning the distribution of dietary ingredients and dietary supplements. Proposed § 111.90(a) would require any distribution of dietary ingredients or dietary supplements to be under conditions that will protect them from contamination and deterioration. This is to protect dietary ingredients and dietary supplements from distribution practices that may adulterate them.

As discussed previously, proposed part 111 also would apply to foreign firms that manufacture, package, or hold dietary ingredients and dietary supplements that are imported or offered for import into the United States, unless imported for further processing and export under section 801(d)(3) of the act. It also would apply to persons who distribute imported dietary ingredients and dietary supplements, and to persons who export dietary ingredients and dietary supplements from the United States unless exported in compliance with section 801(e) of the act.

We recognize that the safety of dietary supplements cannot be adequately ensured if the imports are not subject to the same controls as domestic products. In addition, we believe that the importer who distributes a foreign product should share responsibility with the foreign manufacturer for safety. More often than not, it is a U.S. importer, rather than the foreign manufacturer, who actually distributes imported dietary supplements for sale in the United States. Thus, we believe that importers of dietary ingredients or dietary supplements should

take steps to ensure that their shipments are obtained from manufacturers that follow these proposed CGMP requirements.

In addition, these proposed CGMPs would apply to manufacturers who export their dietary ingredient or dietary supplement, unless exported in compliance with section 801(e) of the act. Section 801(e)(1) of the act states that a food intended for export must not be deemed to be adulterated or misbranded under the act if it:

- Accords to the foreign purchaser's specifications;
- Is not in conflict with the laws of the country to which it is intended for export;
- Is labeled on the outside of the shipping package that it is intended for export; and
- Is not sold or offered for sale in domestic commerce.

Dietary ingredients and dietary supplements for export are subject to section 801(e)(1) of the act and would be subject to the notification and recordkeeping requirements of § 1.101 (21 CFR 1.101) and you would be required to comply with the export requirements of § 1.101.

We invite comment on whether we should require, in a final rule, that you make and keep records on the distribution of dietary ingredients and dietary supplements that you manufacture, package, or hold. We believe that such records may be of benefit to you to facilitate recall actions if you choose to recall a product.

G. Consumer Complaints--What Requirements Apply to Consumer Complaints? (Proposed Subpart G, § 111.95)

Proposed § 111.95 would establish requirements for receiving and handling consumer complaints. Consumer complaints can be helpful in alerting you to possible manufacturing and safety problems associated with your dietary ingredients or dietary supplements.

Proposed § 111.95(a) would require that you keep a written record of each consumer complaint. As stated in § 111.3, consumer complaint refers to a possible failure of a dietary ingredient or dietary supplement to meet any of the requirements of this part, including those that, if not met, may result in a possible risk of illness or injury. Thus, whether the complaint was sent by regular mail, electronic mail, or any other form of written communication, or whether received orally, you would be required to keep a written record of each consumer complaint. You should include all information that would allow your quality control unit to determine whether an investigation of the complaint is necessary.

Proposed § 111.95(b) would require that you have a qualified person review all consumer complaints to determine whether the consumer complaint involves a possible failure of a dietary ingredient or dietary supplement to meet any of its specifications, or any other requirements of this part, including those specifications and other requirements that, if not met, may result in a possible risk of illness or injury. A "qualified

person" would be a person who has the training and experience to determine whether a complaint represents a possible failure of a dietary ingredient or dietary supplement to meet any of the requirements in this part, or represents a possible risk of illness or injury that is unrelated to such failure. The qualified person's review is important for distinguishing between those consumer complaints that your quality control unit must review and those consumer complaints that represent a consumer's dissatisfaction with a dietary ingredient or dietary supplement that is unrelated to a possible failure to meet specifications that would be required by this proposal, or any other requirement in this part. For example, some consumer complaints about quality may simply express a personal dislike of the taste, color, odor, or size of tablet, which would probably not require your quality control unit to review them. As stated earlier, consumer complaints related to an illness or injury related to a pharmacologically active substance of a particular dietary ingredient, such as aristolochic acid, would not be a consumer complaint within the meaning of that term in this proposal and thus would not be of the type that the quality control unit must review under this proposed rule.

Proposed § 111.95(c) would require that your quality control unit review all consumer complaints involving the possible failure of a dietary ingredient or dietary supplement to meet any of its specifications, or any of the other requirements in this part, including those specifications and other requirements that

if not met, may results in a possible risk of illness or injury, to determine whether there is a need to investigate the consumer complaint. If the quality control unit determines that an investigation is unnecessary, it would be helpful to you if your quality control unit documents why an investigation was not necessary. This information would be useful to you because it could save time if you receive additional similar consumer complaints about a particular product.

Proposed § 111.95(d) would require that your quality control unit investigate a consumer complaint when there is a reasonable possibility of a relationship between the quality of a dietary supplement and an adverse event. For example, if a manufacturer uses too much of a dietary ingredient in a dietary supplement (e.g., 400 to 4,699 μg of selenium instead of 200 μg of selenium), it is a manufacturing error that may result in an adverse event. Further, if a communication alleges consumer dizziness, vomiting, or lightheadedness after consuming several dietary supplements, it is a adverse event report that is worthy of quality control unit investigation.

Proposed § 111.95(e) would describe what the quality control unit's investigation must include. In brief, the quality control unit's investigation of a consumer complaint must include the batch records associated with the dietary ingredient or dietary supplement involved in the consumer complaint. The quality control unit must extend the investigation to other batches of dietary ingredients or dietary supplements that may have been

associated with a failure to meet a specification or any other requirements of this part. When there is a possible product defect or failure, we recommend that the investigation include laboratory testing of the dietary ingredient or dietary supplement because you will need the test results to determine if specifications or requirements for the dietary ingredient or dietary supplement were not met. Complaints such as those that involve serious adverse events should include followup by a health care provider. For other types of complaints, neither laboratory nor medical investigation may be necessary because the product defect or failure may be identified by reviewing batch documents or the consumer complaint may not involve a serious adverse event.

Proposed § 111.95(f) would require that you make and keep a written record of every consumer complaint that is related to good manufacturing practices. For the purposes of this regulation, a consumer complaint about product quality may or may not include concerns about a possible hazard to health. However, a consumer complaint does not include an adverse event, illness, or injury related to the safety of a particular dietary ingredient independent of whether the product is produced under good manufacturing practices. The consumer complaint written record must include, but is not limited to, the following:

- The name and description of the dietary ingredient or dietary supplement;
- The batch or lot number of the dietary supplement, if

available;

- The complainant's name, if available;
- The nature of the complaint, including how the consumer used the product;
- The reply to the complainant, if any; and
- Findings of the investigation and followup action taken when an investigation is performed.

We suggest that you report the consumer complaint and the investigation results to us when there is a possibility of a relationship between the consumption of a dietary supplement and a serious adverse event. While the proposal would not require that you submit these reports, we strongly suggest that you do so because we may have additional expertise or data that may be helpful in investigating the complaint or determining whether the problem applies to more than one product. We suggest that you submit these reports within 15 days after you receive such information to the FDA MedWatch program by calling our "MedWatch" program (our database for reporting possible adverse events) at 1-800-FDA-1088 (1-800-332-1088) to request that a reporting form (one-page, return postage paid) and instructions on how to complete the form be mailed to you, downloading a form and instructions from the MedWatch internet site at www.fda.gov, or using the interactive form available on the MedWatch internet site at www.fda.gov.

Further, we suggest that you report a consumer complaint even if you are not the manufacturer of a dietary ingredient or

dietary supplement and only package or distribute a dietary ingredient or dietary supplement if you receive a consumer complaint that may be related to the manufacture of the dietary ingredient or dietary supplement. Sometimes consumers submit complaints to the person who distributes a product or the person who is listed on the package label. If this happens, you should notify the manufacturer of the dietary ingredient or dietary supplement of the consumer complaint because the manufacturer may not be aware of possible problems associated with its products.

Proposed § 111.95(g) addresses documentation and recordkeeping. Consumer complaints can alert you (and us) to potential quality problems with a product that is related to good manufacturing practices, such as cases where the manufacturer used the wrong ingredient or put the wrong label on a product. A prudent manufacturer, therefore, must investigate any complaints regarding its products because the results of its investigations might lead to solutions or improvements that will make the product or manufacturing process better and benefit the manufacturer and consumers.

Proposed § 111.95(g)(1) would require the person who performs the requirement established in accordance with this section to document, at the time of performance, that he or she performed the requirement.

Finally, proposed § 111.95(g)(2) would require that you keep consumer complaint records established in accordance with proposed § 111.125. These records are necessary for handling

consumer complaints in a manner that ensures that an unanticipated problem with a dietary ingredient or dietary supplement is reviewed and investigated. These records also are necessary to demonstrate compliance with the CGMP.

We invite comment on whether we should require, in a final rule, that you establish and follow a written procedure for receiving, reviewing, and investigating consumer complaints. We believe that it may be helpful to have such a procedure in place before you get consumer complaints so that you know how to handle such complaints when they arrive. In addition, we invite comment on whether there are other procedures that we should include in a final rule.

H. Records and Recordkeeping--What Requirements Apply to Recordkeeping? (Proposed Subpart H, § 111.125)

Throughout this discussion of the proposed rule, some provisions have included a paragraph that would require that you keep records established in accordance with proposed § 111.125. Proposed § 111.125 would establish general recordkeeping requirements and tell you how long you must keep certain records. As we have stated several times in this document, we determine CGMP compliance by conducting inspections. Records, therefore, enable you to show, and for us to determine, how you complied with the CGMP requirements.

Proposed § 111.125(a) would apply to all records covered by the proposed rule and would require that you keep those records for 3 years beyond the date of manufacture of the last batch of

dietary ingredients or dietary supplements associated with those records.

Proposed § 111.125(b) would deal with the form in which you keep records. The proposal would allow you to keep records required under this part as original records, as true copies (such as photocopies, microfilm, microfiche, or other accurate reproductions of the original records), or as electronic records. If you use reduction techniques, such as microfilming, the proposal would require that you make suitable reader and photocopying equipment readily available to us. If you use electronic records, the proposal would require that you comply with part 11 (our requirements for electronic records).

Proposed § 111.125(c) would require that you make your records available for inspection and copying by us when requested. We sometimes need to copy records when our field inspectors need guidance or additional expertise from our headquarters staff; if we were unable to copy records, our inspections would become more complicated and longer in duration, particularly if the inspection involved a complex scientific or technical issue that normally would be handled at FDA headquarters.

IV. Statement Concerning the Use of Plain Language

In response to the June 1, 1998, White House Presidential Memorandum on Plain Language, we drafted this proposed rule in plain language. Plain language is intended to help readers find requirements quickly and understand them easily. To do that, we

have reorganized sections modeled after existing regulations and reworded the paragraphs using:

- Short sections, paragraphs, sentences, and words to speed up reading and enhance understanding;
- Sections as questions and answers to focus sections better; and
- Personal pronouns to reduce passive voice and draw readers into the text.

In some cases, we modeled a proposed provision after an existing regulation, but wrote the proposed rule using plain language techniques. We invite the public to comment on the plain language techniques used in this proposed rule. In developing your comments, please consider addressing the following points:

- Do you like the proposed rule's appearance?
- Do plain language techniques make the document easier to read and understand? and
- Do you have other suggestions to improve the format?

V. Paperwork Reduction Act of 1995

This proposed rule contains information collection requirements that are subject to review by the Office of Management and Budget (OMB) under the Paperwork Reduction Act of 1995 (44 U.S.C. 3501-3520). A description of these requirements is given below with an estimate of the annual recordkeeping burden. Included in the estimate is the time for reviewing instructions, searching existing data sources, gathering and maintaining the data needed, and completing and reviewing each

collection of information.

We invite comments on: (1) Whether the proposed collection of information is necessary for the proper performance of our functions, including whether the information will have practical utility; (2) the accuracy of our estimate of the burden of the proposed collection of information, including the validity of the methodology and assumptions used; (3) ways to enhance the quality, utility, and clarity of the information to be collected; and (4) ways to minimize the burden of the collection of information on respondents, including the use of automated collection techniques, when appropriate, and other forms of information technology.

Title: Current Good Manufacturing Practice in Recordkeeping and Reporting for Dietary Ingredients and Dietary Supplements

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

For this proposed CGMP rule for dietary ingredients and dietary supplements, recordkeeping is necessary to provide the

type of documentation that would demonstrate that dietary ingredients and dietary supplements are manufactured, packaged, and held under the conditions that would be required under the proposed CGMP regulations. Under section 701(a) of the act, we may issue regulations necessary for the efficient enforcement of the act. If you did not keep records, for example, documenting practices performed during previous production runs, it would be difficult for us to determine whether, as stated under section 402(g)(1) of the act, the dietary supplement had been manufactured, packaged, and held under CGMPs. By requiring records, we will be able to ensure that you follow CGMPs and that your dietary supplements are not adulterated and misbranded during manufacturing, packaging, or holding operations.

The proposed rule would establish the minimum manufacturing practices necessary to ensure that dietary supplements are manufactured, packaged, or held in a manner that will not adulterate and misbrand the dietary ingredients or dietary supplements.

The proposed regulations would impose requirements for: (1) Personnel, (2) physical plants, (3) equipment and utensils, (4) production and process controls, (5) holding and distributing, (6) consumer complaints, and (7) records and recordkeeping.

We are proposing recordkeeping requirements that include records pertaining to: (1) Calibration of instruments and

controls; (2) automatic, mechanical, or electronic equipment calibration, inspection, or checks; (3) production and process controls; (4) quality control; (5) receiving components, dietary supplements, packaging, and labels; (6) master manufacturing and batch production; (7) packaging and label operations; (8) returned dietary ingredients or dietary supplements; and (9) consumer complaints.

Description of Respondents: Dietary ingredient manufacturers, dietary supplement manufacturers, packagers and repackagers, distributors, warehousers, exporters, importers, large businesses, and small businesses.

We estimate the burden of this collection of information as follows:

Table 1.--Estimated Annual Recordkeeping Burden[1]

21 CFR Section	No. of Recordkeepers	Annual Frequency of Recordkeeping	Total Annual Records	Hours per Record	Total Hours
111.15(b)(3)	231	12	2,772	0.1	277
111.15(d)(3)	231	260	60,060	0.25	15,015
111.25(c)	213	365	77,745	0.5	38,873
111.30(b)(2) and (b)(5)	707	260	183,820	0.5	91,910
111.35(d)	10	1	10	10	100
111.35(e)	367	260	95,420	0.25	23,855
111.35(f)	367	260	95,420	0.1	9,542
111.35(i)(1)	367	10	3,670	0.25	918
111.35(j)	367	260	95,420	.25	23,855
111.35(m)	367	365	133,955	0.1	13,396
111.37(b)(1), (b)(3) through (b)(5), (b)(7) through (b)(10), and (b)(12)(i)	286	260	74,360	0.5	37,180
111.37(c)	286	365	104,390	0.5	52,195
111.40(a)(3), (a)(4), (b)(2), and (b)(3)	449	365	163,885	0.1	16,389
111.40(c)(1)	218	365	79,570	0.5	39,785
111.45(a)[2] and (b)[2]	200	1	200	30	6,000
111.50(a) through (c), (d)(1), and (e)	68	260	17,680	1	17,680
111.50(g)	68	260	17,680	0.5	8,840
111.60(b)(2)	133	365	48,545	1	48,545
111.60(d)[2]	133	1	133	3	399
111.65(c)(7), (c)(10), and (c)(11)	133	365	48,545	0.1	4,855
111.65(e)(1) and (e)(2)	53	260	13,780	0.25	3,445
111.70(b)(5) through (b)(6), (d), and (e)	245	260	63,700	0.1	6,370
111.70(g)	245	260	63,700	0.50	31,850

Table 1.--Estimated Annual Recordkeeping Burden[1] (Continued)					
21 CFR Section	No. of Recordkeepers	Annual Frequency of Recordkeeping	Total Annual Records	Hours per Record	Total Hours
111.74(a)	200	12	2,400	0.1	240
111.82(a)	53	52	2,756	0.1	276
111.85(a)	53	260	13,780	0.1	1,378
111.85(d) and (e)	53	260	13,780	0.5	6,890
111.95(a) and (f)	53	75	3,975	0.1	398
111.95(g)(1)	93	75	6,975	0.5	3,488
111.125	220	4	880	0.1	88
Total					504,032

[1]There are no capital costs or operating and maintenance costs associated with this collection of information.

[2]One time burden.

The burden estimates above are based on our institutional experience with CGMP requirements for drugs and on data provided by Research Triangle Institute (RTI) in the "Survey of Manufacturing Practices in the Dietary Supplement Industry" (Refs. E1 and E2). We tentatively conclude that there are no capital costs or operating costs associated with this proposed rule. However, we invite comments on information provided in table 1 of this document or on any anticipated costs.

The estimates for number of firms affected by each provision of the rule are based on the percentage of manufacturers, ingredient suppliers, repacker/relabelers, distributors, and warehousers that reported to RTI that they have not established or do not maintain records that would be required or recommended

under the proposed rule. The RTI survey estimated that 1,566 firms would be covered by this rule including manufacturers, dietary ingredient suppliers, repacker/relabelers, distributors, and warehousers. The time estimates include the burden involved in documenting that certain requirements are performed and in recordkeeping. We used an estimated annual batch production of 260 batches per year to estimate the burden of requirements that are related to the number of batches produced annually, e.g., proposed § 111.50, "What requirements apply to establishing a batch production record?" The estimate of 260 batches per year is near the midpoint of the number of annual batches reported by RTI survey firms.

Proposed § 111.125 prescribes the length of time for which CGMP records must be maintained. The burden chart reflects the estimated annual burden for record maintenance, for periodically reviewing records to determine if they may be discarded, and for any associated documentation for that activity for records that would be required under part 111. To avoid double-counting, we have not included a separate estimate of burden for those sections that would require maintaining records in accordance with proposed § 111.125, but have included a single burden estimate for all such records maintenance under proposed § 111.125. For example, proposed § 111.50(a) would require that the batch production records be prepared every time a batch is

manufactured and § 111.50(i) would require that batch production records be kept in accordance with proposed § 111.125. The estimated burden for establishing the batch production records is counted in proposed § 111.50(a) and the estimated burden for keeping the batch production records as would be required in accordance with § 111.50(i) is counted in proposed § 111.125.

In compliance with the Paperwork Reduction Act of 1995 (44 U.S.C. 3507(d)), the agency has submitted a copy of this proposed rule to OMB for its review. Interested persons are requested to send comments regarding information collection to the Office of Information and Regulatory Affairs, OMB (see ADDRESSES).

VI. Environmental Impact Considerations

The agency has determined under 21 CFR 25.30(j) that this action is of a type that does not individually or cumulatively have a significant effect on the human environment. Therefore, neither an environmental assessment nor an environmental impact statement is required.

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 Unfunded Mandates Reform Act of 1995 (2 U.S.C. 1501 et seq.), requiring cost-benefit and other analyses, in section 1532(a) defines a significant rule as "a Federal mandate that may result in the expenditure by State, local, and tribal governments in the aggregate, or by the private sector, of $100

million (adjusted annually for inflation) in any one year." The current inflation-adjusted statutory expenditure is a threshold of $112 million. Since the estimated annual expenditure for this proposed rule is below $112 million, FDA has determined that this proposed rule, if it were to become a final rule, would not be a significant rule under the Unfunded Mandates Reform Act of 1995.

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 publically 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.

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.

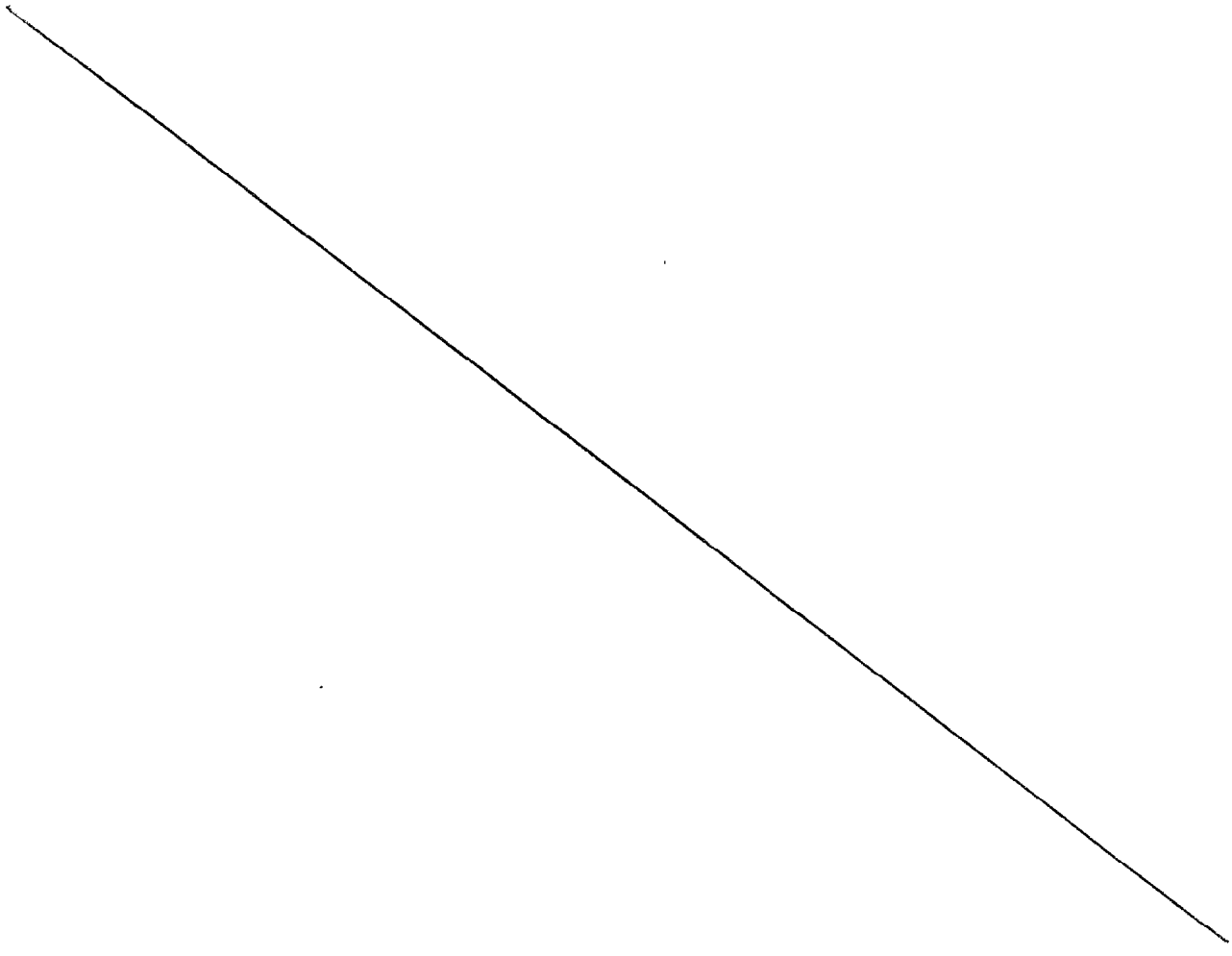

Table 2.--Covered Establishments by Product Type and Size From Dietary Supplement Enhanced Establishment Database (DS-EED)

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.

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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.

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 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.

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, 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

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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.

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 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

[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.

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 the number of illnesses reported is substantially less than the number occurring, we assumed that the proxy for reported illnesses would represent approximately 1 percent of total illnesses (Ref. E16). That assumption has often been used to get a default multiplier of 100 linking known cases of foodborne illness to total incidence. We show the sensitivity of benefits to the choice of multiplier below, in the uncertainty and sensitivity analysis of our results.

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. 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

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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.

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.

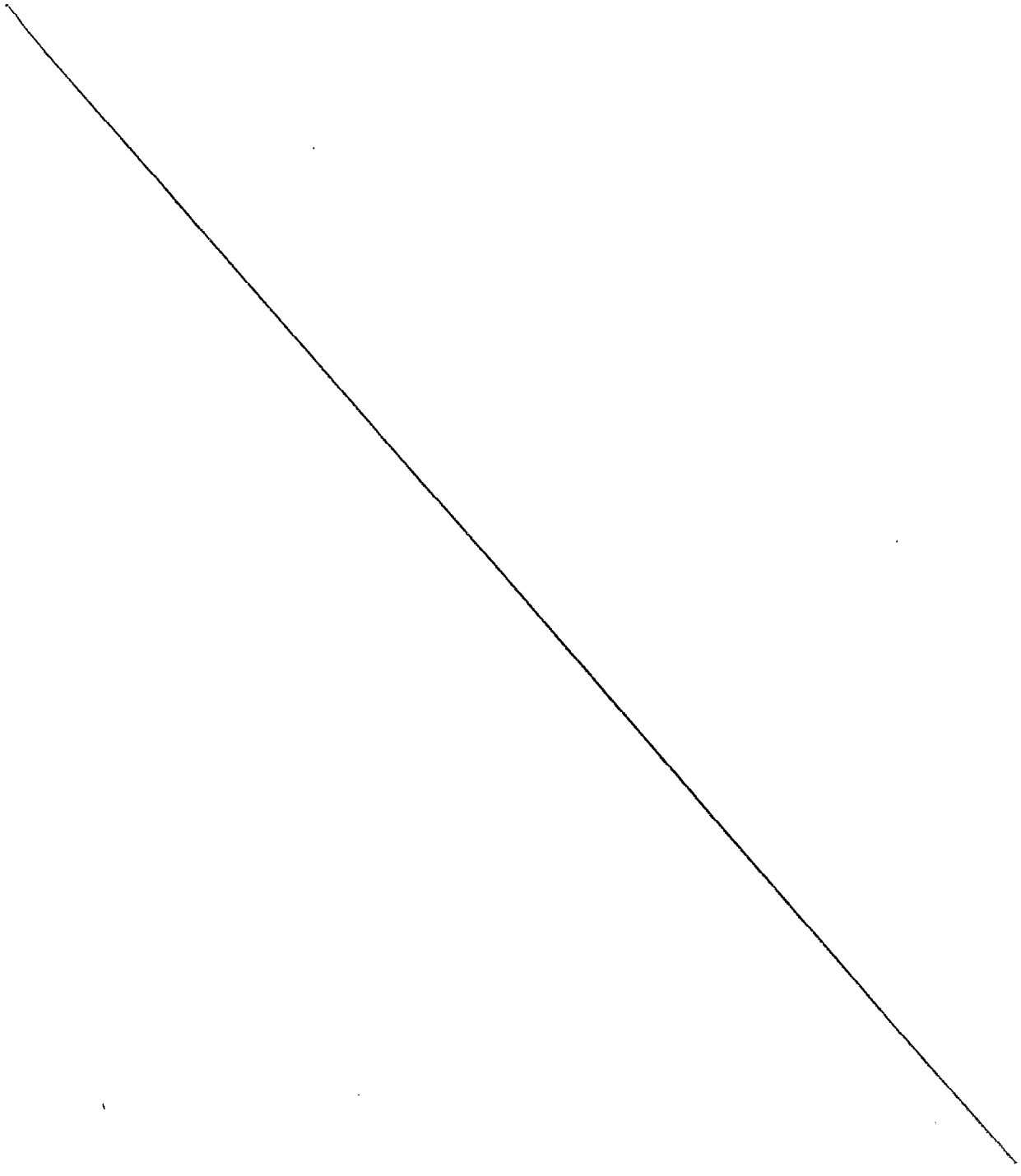

Table 10.--Health Benefits From Preventing Rare Catastrophic Event

	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 categories. In the final cost estimates, we used 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;