61

practices in the absence of this rule. The universe for the survey includes the establishments discussed in section VII.B.3 of this document. Insert #33

1. 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.

Page 353 Econ Insert #33
If firms start good manufacturing practices in the absence of this rule, both the costs and benefits of the rule would be less than we estimate. If firms were to stop in the absence of the rule, both the costs and benefits would be more than we estimate. We lack information about the trend in the industry, so we assumed that the survey reflects both the current and future practices in the industry. We request comment or information about the industry trend in adopting good manufacturing practices.

62

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.

Insert #34 → ~~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.~~

Insert #34a → 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

Page 362 Econ Insert #34:
Because there are no well established systems for the notification of adverse health events related to dietary supplements, and some significant barriers to reporting, we assume that unreported illnesses caused by poor manufacturing practices are substantially greater than reported illnesses. We relied on Ref. E16 to estimate a more precise relationship between reported and unreported rates. Based on empirical data for drug and vaccine reporting rates among other studies, the author of Ref. E16 determined that for dietary supplements, reported illnesses represent at best approximately 1 percent of total illnesses (Ref. E16). A similar multiplier of 100 linking known cases of foodborne illness to total incidence is often used. We assume that reporting adverse health events due to poorly manufactured dietary supplements would occur at the same proportion as adverse health events caused for other reasons by dietary supplements. We show the sensitivity of benefits to the choice of multiplier below, in the uncertainty and sensitivity analysis of our results.

Page 362 , ~~Insert~~ #34a:
The outbreak of EMS resulting from contaminated L-Tryptophan resulted in the recall of the contaminated products. In part based on this example, we assume that product recalls can indicate when there are adverse health events. We also assume that the reported class 1 and class 2 recalls that have occurred over the last 10 years represent the number and type of recalls that will occur in the future but for the implementation of this regulation.

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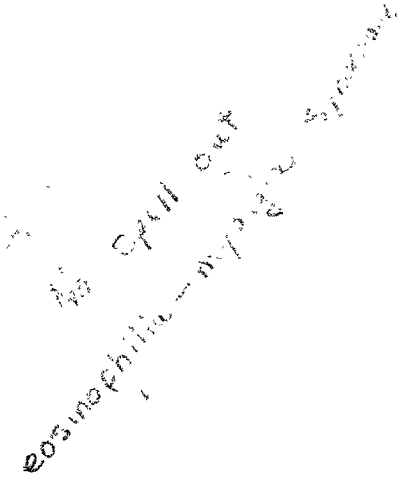

63

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

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

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

$148,000 for very small establishments;

$415,000 for small establishments;

$263,000 for large establishments.

✓ Insert # 36

We found some corroboration for these estimates in a comment on the Advance Notice of Proposed Rulemaking entitled "Current Good Manufacturing Practice in Manufacturing, Packing, or Holding Dietary Supplements" published in the FEDERAL REGISTER of February 6, 1997 (62 FR 5699 to 5709). According to the comment, the cost of testing components and final products inhouse would be at least $650 per batch plus microbiological tests. Testing costs could be more if establishments sent samples to independent laboratories for testing or if they conducted extensive identity tests of herbal and botanical products. If we apply the $650 to the annual number of batches per establishment, the comment implies that very small establishments would perform $145,000 (223 x $650) worth of tests, small establishments would perform $360,000 (554 x $650) worth of tests, and large establishments would perform $200,000 (309 x $650) worth of tests. These estimates are reasonably close to our simulation estimate.

The unadjusted testing costs represent the total requirements and recommendations, not the additional costs that would be incurred in response to the proposed rule. Tests on

Page 417 Insert # 36

Insert directly under the line that reads "$263,000 for large establishments"

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

$ 11,230	for very small establishments ;
$ 19,907	for small establishments ; and
$ 7,626	for large establishments.

64

Table 14 --Values Used in Testing Cost Calculations

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

vi. Labor costs. We used the average manufacturing wage of $15.65 per hour to estimate the cost of labor. We assumed that various tasks required by the proposed rule would take some number of hours per year, per batch of product, or per square foot of physical plant. For example, we assumed that time spent on the sanitation of physical plants is a function of the square footage. We assumed 1 hour per week for very small establishments, 3 hours per week for small establishments, and 20 hours per week for large establishments. Insert # 35

V.

Page 419 Econ Insert #35:
We request comment or data about costs, hours, and the other requirements for these proposed required procedures.

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delete

Uncertainties in the analysis. In this section, we list many of the assumptions that we made and, if varied, could change the estimates of costs and benefits significantly. Such changes could have significance for the construction of any potential final rule. Therefore, we ask that comments address these aspects of the analysis and, where possible, provide FDA with better data to reduce the uncertainty. We estimated the benefits using indirect measures of the frequency of illness associated with poor manufacturing practices. These indirect measures required several assumptions that, when combined, produced our estimates. With the exception of the recall benefit, which is based directly on FDA recall records, each component of estimated benefits involves assumptions that reflect our uncertainty. For the health benefits, the assumption that the number or illnesses was 100 times the number of recalls is important, because varying the multiplier greatly varies the health benefits. For the rare catastrophic event model, the assumption that an event would occur every 30 years mattered to the estimated benefits. Indeed, if the event was a one-time occurrence, the benefits from the prevention of the catastrophic health event would be zero. Our hypothetical search model used assumptions at each step, and those benefits change when the assumptions change, as we show below.

Page 426, Insert #21:

Insert the following seven page addition at page 426 to replace everything on page 426. All of the preceding pages to page 426, and all of the following pages should remain the same. Only page 426 changes by this addition.

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

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

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

   a. The baseline health of consumers is normal, not perfect.

   To estimate the change in health status from consuming defective products, we assumed that the baseline health of consumers is normal, which does not mean that we assumed that consumers have perfect health. We recognize that consumers will already have 'background' health problems, by which we mean that many will have health problems unrelated to the consumption of defective products. Our assumption is that only the change in health status is relevant for our analysis. If an immune-compromised consumer is made ill by a defective

product, e.g., gets lead poisoning, the consumer might in fact have more difficulty recovering than an otherwise healthy person. However, we assume that the change in productivity, functional state, pain and suffering, and medical costs will be the same, regardless of prior health status. Accounting for confounding factors would have the effect of making health problems worse than we estimate, not better, so our estimate may be understating the true health benefits.

2 b. The average value of a QALY is $630 per day.

That value, $630 per day, is in turn based on: (1) the value of a statistical life of $5 million; (2) the expected remaining life of consumers of 21.84 years (average), discounted from 36 years; and, (3) the social rate of time preference of 3%. The estimate is derived from workers in somewhat risky occupations who demand a wage premium for their additional risk of fatality. If our estimate of the value of a statistical life of workers does not represent the value of a statistical life of consumers of dietary supplements, then our benefits estimate will be different from the true health benefits of the rule. If consumers value their life differently than workers or if consumers place different values for different kinds hazard related deaths than do workers for job-related safety hazards, then we will have incorrect estimates for the true health benefits. If we discount life expectancy by 7 percent instead of 3 percent, the benefits would be much higher.

3 c. There is one illness for each recall.

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

4. The assumed frequency of actual illnesses is 100 times the frequency of reported illnesses.

This assumption is based on Ref. E16. We recognize that the factor of 100, although it has empirical support, might be wrong and that there is likely to be considerable uncertainty about this point estimate. It is widely believed in the public health community that most illnesses are underreported to public health authorities, particularly in passive reporting systems, such as the case with dietary supplements. Mild cases are the most underreported. For instance, victims rarely notify public health authorities when they have minor gastrointestinal tract related illnesses. It is even more rare to report the likely source of a mild illness. It is also widely believed that severe illnesses and death are reported much more frequently than milder illnesses, even when the cause of illness or death is not included in the report. Although the number of deaths that are reported probably approach 100%, the cause of death from a contaminated dietary supplement product might not be reported. We believe that using a single composite factor - 100 - to represent the total number of all unreported cases, including mild, severe, and death, does not invalidate our assumption. The factor of 100 represents an estimate of the composite probability of the full range of probabilities for each severity level of an illness being reported. Increasing the factor multiplier from 100 to some number higher would increase the health benefits, while lowering the multiplier would decrease the health benefits. If we assume that all illnesses are reported - there are no unreported illnesses and no factor of 100, then the health benefits from fewer sporadic illnesses will be less than $1 million.

5. Introducing CGMP's will reduce the probability of a recall to zero.

We believe that the proposed CGMP's creates the most reliable means for discovering product adulteration. Indeed, we believe that it will, if strictly used, cause the discovery of all adulteration. Therefore, we assume that once an establishment fully adopts the requirements, there should be no more health risk from adulterated

dietary supplements and consequently, no more class 1 and 2 recalls. This conclusion rests on the assumption that there will be 100% compliance with this regulation. We recognize that human error is inescapable. If recalls - or a health risk from adulteration - would still exist, then we overstated the true health benefits of the regulation.

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

1 ~~a~~. We assume that a rare catastrophic event would occur every 30 years.

We recognize that the occurrence of a single event provides little evidence about what will happen in the future. If the event reported in this analysis was in fact a one-time occurrence, then our estimate of the benefits from the prevention of the catastrophic health event would overstate the true benefits, which in fact should be zero. There would have been no future event, and there would be no benefit from adopting a rule to avoid it. If a rare event would have happened more frequently than our estimate of once every thirty years, then our estimate of the benefits would underestimate the true health benefits.

2. ~~b~~. Number of illnesses per rare event.

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

~~III.~~ The assumptions for fewer products recalled are:

1. ~~a~~. The reported class 1 and 2 recalls that have occurred over the last 10 years represent the number and type of recalls that ~~will~~ would have occurred in the future but for the implementation of this regulation.

If the number or types of recalls are not representative, then we over or under estimated the benefit of avoiding recalls. Avoiding one very large recall could result in significantly higher benefits. Conversely, merely avoiding fewer or smaller recalls would result in smaller benefits.

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

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

3 c. Full compliance with the proposed CGMP's will reduce the probability of a recall to zero.

As in our earlier assumption about the probability of recalls after the rule is adopted, consistency requires that if we believe that the rule will reliably cause the discovery of adulterated products before they are commercially available, there should be no more health risk from adulterated dietary supplements. Consequently, there should be no more recalls.

~~IV.~~ We developed the hypothetical search model to estimate the implicit value to consumers of better product quality although we lacked a model that could enable us to directly estimate consumer preferences for dietary supplement quality. With the adoption of the proposed rule, the standardization of manufacturing practices will reduce product differentiation. In a perfect information market, the change in product differentiation would be reflected in the change in the price differences between low and high quality products. In the existing market, price differences alone are an inadequate signal because the differences in product quality are typically hidden from the view of both consumers and (though less so) manufacturers. In this hypothetical model, we assumed that if there were actually indicators of product quality in the market now, consumers would spend a certain amount of time attempting to find a reasonably high quality product. Time spent searching is an economic cost. In fact, in markets where quality is discernible prior to purchase, such search does take place and it is from those markets that our estimates were derived. In such a world of easily available product quality signals, this regulation, by standardizing product quality at the high end, would reduce that

search time. Our assumption is that this is a reasonable indicator of consumers' value for high quality products. Further, we assume that in fact consumers of dietary supplements do wish to purchase high quality products, as the absence of quality could mean either an ineffective product or worse, illness or death. We used various assumptions at each step in our model, and the benefits change when the assumptions change. The assumptions that we used for the search model are:

1 a. Consumers will search until the expected benefits of the search equal the expected cost of additional search.

The expected cost is the value of their time, which we estimated is the average wage rate for manufacturing workers - $15.65/hour. If the true wage rate is different, the benefits of the rule will be different.

2. b. The three models - drug store, use of time and grocery store models - represent consumers of dietary supplements.

If not, then we will not have estimated the true preferences of consumers. If consumers value dietary supplements more highly than either drugs, groceries or other uses of time, and they search more for better quality, then we understated the benefits of product standardization. If consumers value dietary supplements less highly than either drugs, they search more for better quality, then we overstated the benefits.

3 c. The quality controls will reduce consumer search time by approximately 33%.

If our estimate is not representative of the true average reduction, then our estimate will be wrong.

4 d. The type and number of consumers represent the true value.

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

V. In an ideal analysis, the benefits and costs of each provision would be evaluated. We were not able to quantify the benefits for each of the provisions in our analysis although we do have fairly detailed estimates of the cost. We request comments on marginal costs and benefits of specific provisions in the rule. Comments can be directed either at how well a specific provision might work to make dietary supplements either safer or of higher quality, or be directed at the cost of the provision. An example of this type of provision follows for recordkeeping:

Benefits of recordkeeping:

Mandatory recordkeeping is intended to help the discovery of manufacturing practices that create defective products. Recordkeeping ensures that preventative controls are carried out for each batch of dietary supplements produced. Records serve as a checklist that quality control personnel can consult to monitor that necessary controls are implemented or corrective actions taken. Further, mandatory recordkeeping provides an incentive for manufacturers to comply more fully with the provisions of the rule where recordkeeping is required. Knowing that FDA inspectors will examine records and that falsifying them is a criminal offense provides strong incentives to keep thorough and accurate records that the required safety functions have been performed adequately and in a timely manner. Thus, the benefits of recordkeeping are to permit detection of defective products and increase compliance with the provisions for which recordkeeping is required. If, for example, 1) the total benefits of the requirements that have recordkeeping attached to them were $50 million (not the real value); 2) only half of the requirements would be met without recordkeeping; and, 3) recordkeeping raised the compliance rate to 100%, then the benefits of recordkeeping would be $25 million. We were not able to quantify the marginal benefits of this requirement with numbers like this. Comments are requested for how well records are likely to perform this function. We estimate that the additional cost to society for the proposed new recordkeeping requirement will be approximately 10% of the total annual cost of the proposed regulation, or a little less than $9 million per year.

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

~~Place in p. 324~~

VII D 1

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Unfunded Mandates

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

delete Comma para and add this para as VII.D.

Future Costs

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

Particular regions, communities, or industrial sectors

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

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

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

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

Exports

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

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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.

Insert 31-7

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

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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

66

have a health condition described in paragraph (a)(1) of this section that could contaminate any components, dietary ingredients, dietary supplements, or any contact surface.

(b) Hygienic practices. If you work in operations during which adulteration of the component, dietary ingredients, dietary supplement, or contact surface may occur, you must use hygienic practices to the extent necessary to protect against contamination of components, dietary ingredients, dietary supplements, or contact surfaces. These hygienic practices include, but are not limited to:

(1) Wearing outer garments in a manner that protects against the contamination of components, dietary ingredients, dietary supplements, or any contact surface;

(2) Maintaining adequate personal cleanliness;

(3) Washing hands thoroughly (and sanitizing if necessary to protect against contamination with microorganisms) in an adequate hand-washing facility:

(i) Before starting work;

~~(ii) After each absence from the work station; and~~

(iii) At any ~~other~~ time when the hands may have become soiled or contaminated;

(4) Removing all unsecured jewelry and other objects that might fall into components, dietary ingredients, dietary supplements, equipment, or packaging, and removing hand jewelry

(5) Have your quality control unit review and approve any material review and disposition decision described in paragraphs (i)(2) and (i)(3) of this section.

(j) The person who conducts the material review and makes the disposition decision must, at the time of performance, document every material review and disposition decision in paragraph (i) of this section. The documentation must be included in the appropriate batch production record and must:

(1) Identify the specific deviation from the specification or the unanticipated occurrence;

(2) Describe your investigation into the cause of the deviation from the specification or the unanticipated occurrence;

(3) Evaluate whether or not the deviation from the specification or unanticipated occurrence has resulted in or could lead to adulteration. (4) For any deviation or unanticipated occurrence which resulted in or could lead to adulteration of the component, dietary ingredient, dietary supplement, packaging, or label, (i) you must reject the component, dietary ingredient, dietary supplement, packaging, or label, unless the quality control unit determines that in-process adjustments are possible to correct the deviation or occurrence. (ii) You must not reprocess a rejected component, dietary ingredient, or dietary supplement unless approved by the quality control unit. (iii) You must not reprocess any component, dietary ingredient or dietary supplement if it is

(4) → 68

111.35 A new (i)(4) with sub (i)(ii)(iii)

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rejected because of contamination with microorganisms or other contaminants, such as heavy metals;

(4) Identify the action(s) taken to correct and prevent a recurrence of the deviation or the unanticipated occurrence; and

(5) Discuss what you did with the component, dietary ingredient, dietary supplement, packaging, or label; and

~~(6) Show that your quality control unit approved the material disposition decision.~~

(k) You must test or examine components, dietary ingredients, and dietary supplements for those types of contamination that may adulterate or may lead to adulteration. You must use an appropriate scientifically valid method for the test or examination. The types of contamination include, but are not limited to, the following:

(1) Filth, insects, or other extraneous material;

(2) Microorganisms; and

(3) Toxic substances.

(l) Tests in accordance with this section must include at least one of the following:

(1) Gross organoleptic analysis;

(2) Microscopic analysis;

(3) Chemical analysis; or

(4) Other appropriate test.

(m) You must record results of all testing and examinations

If a test or examination is performed in a batch production you must record the test or examination result in the batch production record in accordance with § 111.50(c)(10).

10

performed in accordance with this section. Your records must document whether the testing and examination demonstrates that specifications are met.

(n) For any specification that is not met, you must conduct a material review and disposition decision under paragraph (i) of this section.

(o) You must make and retain records, in accordance with § 111.125, to ensure that you follow the requirements of this section. The records must include, but are not limited to:

(1) The specifications established;

(2) The actual results obtained during the monitoring operation;

(3) Any deviation from specifications and any unanticipated occurrences;

(4) Any corrective actions taken;

(5) The disposition decisions and followup; and

(6) The identity of the individual qualified by training and experience who investigated any deviation from specifications or unanticipated occurrence and the identity of the individual from the quality control unit who reviewed the results of that investigation.

§ 111.37 What requirements apply to quality control?

(a) You must use a quality control unit to ensure that your manufacturing, packaging, label, and holding operations in the

(iii) Dietary ingredients and dietary supplements that you manufacture to ensure that they meet specifications; and

(iv) Packaged and labeled dietary ingredients and dietary supplements to ensure that you used the packaging specified in the master manufacturing record and you applied the label specified in the master manufacturing record.

(14) Review and approve all material review and disposition decisions.

(15) Approve the reprocessing or distribution of returned dietary ingredients or dietary supplements.

(c) Your quality control unit must establish and maintain written documentation at the time of performance that it ~~met~~ performed the requirements of this section by recording the following: review, approval, or rejection

(1) Date the ~~requirement~~ review, approval, or rejection was performed; and

(2) Signature of the person performing the requirement; ~~and~~

~~(3) Results of any test and examination performed.~~

(d) You must keep quality control records in accordance with § 111.125.

§ 111.40 What requirements apply to components, dietary ingredients, dietary supplements, packaging, and labels you receive?

(a) For components, dietary ingredients, or dietary supplements you receive, you must:

(1) Visually examine each container or grouping of containers in a shipment for appropriate content label, container damage, or broken seals to determine whether the container

72

(v) Corrective action plans for use when a specification is not met.

(c) You must have the quality control unit review and approve each master manufacturing record and any modifications to a master manufacturing record.

(d) You must keep master manufacturing records in accordance with § 111.125.

§ 111.50 What requirements apply to establishing a batch production record?

(a) You must prepare a batch production record every time you manufacture a batch of a dietary ingredient or dietary supplement and the batch production record must include complete information relating to the production and control of each batch.

(b) Your batch production record must accurately follow the appropriate master manufacturing record and you must perform each step in producing the batch.

(c) The batch production record must include, but is not limited to, the following information:

(1) The batch, lot, or control number;

(2) Documentation at the time of performance, showing the date on which each step of the master manufacturing record was performed, and the initials of the persons performing each step;

(3) The identity of equipment and processing lines used in producing the batch;

including, but not limited to:

(i) the person responsible for weighing or measuring each component used in the batch, and

(ii) the person responsible for adding the components to the batch.

73

(4) The date and time of the maintenance, cleaning, and sanitizing of the equipment and processing lines used in producing the batch;

(5) The shipment lot unique identifier of each component, dietary ingredient, dietary supplement, packaging, and label used;

(6) The identity and weight or measure of each component used;

at the time of performance or at the completion of the batch ✓

(7) The initials of the person responsible for ~~weighing or measuring~~ of each component used in the batch ~~and the initials of the person~~ verifying the weight or measure;

at the time of performance or at the completion of the batch ✓

(8) The initials of the person responsible for ~~adding the~~ of components to the batch ~~and the initials of the person~~ verifying the addition;

(9) A statement of the actual yield and a statement of the percentage of theoretical yield at appropriate phases of processing;

(10) The actual test results for any testing performed during the batch production;

(11) Documentation that the dietary ingredient and dietary supplement meets specifications;

(12) Copies of all container labels used and the results of examinations conducted during the label operation to ensure that the containers have the correct label;

74

(13) Any documented material review and disposition decision; and

(14) Signature of the quality control unit to document batch production record review and any approval for reprocessing or repackaging.

(d) The quality control unit must review the batch production record established in paragraph (c) of this section.

(1) If a batch deviates from the master manufacturing record, including any deviation from specifications, the quality control unit must conduct a material review and make a disposition decision and record any decision in the batch production record.

(2) The quality control unit must not approve and release for distribution any batch of dietary ingredient or dietary supplement that does not meet all specifications.

(e) The quality control unit must document the review performed in accordance with paragraph (d) of this section and it must be documented at the time of performance. The review and documentation must include, but is not limited to, the following:

(1) Review of component, dietary ingredient, and dietary supplement receiving records including review of testing and examination results;

(2) Identification of any deviation from the master manufacturing record that may have caused a batch or any of its

75

used during manufacturing to indicate their contents including the name of the dietary ingredient or dietary supplement and the specific batch or lot number and, when necessary, the phase of manufacturing.

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

~~(e)(1) The person who performs the material review and~~ disposition decision in accordance with this section must ~~document at the time of performance the~~ results of the material review and disposition decision ~~and such documentation must be maintained with~~ the batch production record.

delete

~~(2) The documentation must include, but not be limited to:~~

~~(i)~~ The ~~date and time the requirement was performed;~~ and

~~(ii) The signature~~ of the person who performed the requirement.

~~(3) You must keep manufacturing operation records in accordance with § 111.125.~~

76

must be under conditions that will protect the dietary ingredients and dietary supplements against contamination and deterioration.

10. Add subpart G to part 111 to read as follows:

Subpart G--Consumer Complaints

§ 111.95 What requirements apply to consumer complaints?

~~(a) You must keep a written record of each consumer complaint.~~

(a) A qualified person must 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.

(b) Your quality control unit must review all consumer complaints involving the 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, to determine whether there is a need to investigate the consumer complaint.

(c) Your quality control unit must investigate a consumer

77

complaint when there is a reasonable possibility of a relationship between the quality of a dietary supplement and an adverse event.

(e) Your 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. Your quality control unit must extend the investigation to other batches of dietary ingredients or dietary supplements that may have been associated with an adverse event.

(f) You must 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:

(1) The name and description of the dietary ingredient or dietary supplement;

(2) The batch or lot number of the dietary supplement, if available;

78

(3) The name of the complainant, if available;

(4) The nature of the complaint including how the consumer used the product;

(5) The reply to the complainant, if any; and

(6) Findings of the investigation and followup action taken when an investigation is performed.

(g)(1) The person who performs the requirements in accordance with this section must document at the time of performance that the requirement was performed.

(2) You must keep consumer complaint records in accordance with § 111.125.

11. Add subpart H to part 111 to read as follows:

Subpart H--Records and Recordkeeping

§ 111.125 What requirements apply to recordkeeping?

(a) You must keep written records required by this part for 3 years beyond the date of manufacture of the last batch of dietary ingredients or dietary supplements associated with those records.

(b) Records required under this part must be kept as original records, as true copies (such as photocopies, microfilm, microfiche, or other accurate reproductions of the original

Strong, Joyce A Insert # 17

From: Smith, Kennon M
Sent: Wednesday, January 15, 2003 2:51 PM
To: Strong, Joyce A
Subject: FW: FDA responses to 1-13-03 OMB comments on DS CGMP proposal

p. 417

Unfunded mandates p. 324 & 325


DS GMP insert 36.wpd


UMRA DS CGMP.wpd

PRINT

More stuff

-----Original Message-----
From: Vardon, Peter J
Sent: Tuesday, January 14, 2003 5:28 PM
To: Smith, Kennon M
Cc: Nardinelli, Clark; Strauss, Karen F
Subject: RE: FDA responses to 1-13-03 OMB comments on DS CGMP proposal

Attached is our response for the two unresolved issues

-----Original Message-----
From: Smith, Kennon M
Sent: Tuesday, January 14, 2003 3:57 PM
To: Vardon, Peter J
Subject: FW: FDA responses to 1-13-03 OMB comments on DS CGMP proposal

FYI

-----Original Message-----
From: Stuart_Shapiro@omb.eop.gov
[mailto:Stuart_Shapiro@omb.eop.gov]
Sent: Tuesday, January 14, 2003 2:45 PM
To: Smith, Kennon M
Subject: Re: FDA responses to 1-13-03 OMB comments on DS CGMP proposal

That leaves pages 325 and 417 unresolved. Thanks.

1/21

Proposed § 111.10(b) would apply if you work in operations where adulteration of components, dietary ingredients, dietary supplements, or contact surfaces may occur. The proposal would require that you use hygienic practices to the extent necessary to protect against contamination of those components, dietary ingredients, dietary supplements, or contact surfaces.

These hygienic practices would include, but would not be limited to:

- Wearing outer garments in a manner that protects against contamination of components, dietary ingredients, dietary supplements, or any contact surface. Outer garments may include gowns or aprons;
- Maintaining adequate personal cleanliness;
- Washing hands thoroughly (and sanitizing if necessary to protect against contamination with microorganisms) in an adequate hand-washing facility:
  1. Before starting work;
  ~~After each absence from the work station;~~ and
  2. At any ~~other~~ time when hands may become soiled or contaminated. Hands may become soiled or contaminated after meals or after using the bathroom;
- Removing all unsecured jewelry and other objects that might fall into components, dietary ingredients,

1/21/03

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(d)	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 (e)	53	75	3,975	0.1	398
111.95(g)(1) (f)	93	75	6,975	0.5	3,488
111.125	220	4	880	0.1	88
Total					~~504,032~~ 500,587

[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

Pre-Publication Editorial Revisions made by the Office of the Federal Register and FDA's Regulations Editorial Section

Pre-Publication Editorial Revisions
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and FDA's Regulations Editorial Section

4160-01-P

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Display Date 3-7-03@11:30am.
Publication Date 3-13-03
Certifier D. Hawkins

Food and Drug Administration

21 CFR Parts 111 and 112

[Docket No. 96N-0417]

RIN 0910-AB88

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

AGENCY: Food and Drug Administration, HHS.

ACTION: Proposed rule.

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

DATES: Submit written or electronic comments by [insert date 90 days after date of publication in the FEDERAL REGISTER]. Submit ~~written or electronic~~ comments on the collection of information

JS per Ken Smith

CF97107
Revised 2/4/02

by [insert date 30 days after date of publication in the FEDERAL REGISTER].

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

Submit written comments on the information collection to the Office of Information and Regulatory Affairs, Office of Management and Budget (OMB), New Executive Office Bldg., 725 17th St. NW., rm. 10235, Washington, DC 20503, Attn: Stuart Shapiro, Desk Officer for FDA.

FOR FURTHER INFORMATION CONTACT:

Karen Strauss,

Center for Food Safety and Applied Nutrition (HFS-821),

Food and Drug Administration,

5100 Paint Branch Pkwy.,

College Park, MD 20740,

301-436-2371.

5

KS

SUPPLEMENTARY INFORMATION:

Table of Contents

Revised 3/5/03

by [insert date 30 days after date of publication in the FEDERAL REGISTER].

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

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FOR FURTHER INFORMATION CONTACT:

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

SUPPLEMENTARY INFORMATION:

Table of Contents

CF

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

FOR FURTHER INFORMATION CONTACT:

Karen Strauss,

Center for Food Safety and Applied Nutrition (HFS-821),

Food and Drug Administration,

5100 Paint Branch Pkwy.,

College Park, MD 20740,

301-436-2375.

SUPPLEMENTARY INFORMATION:

Table of Contents

Subpart A--General Provisions

Sec.

Subpart A--General Provisions

§ 111.1 Who is subject to these regulations?

You are subject to these regulations in this part if you manufacture, package, or hold a dietary ingredient or dietary supplement.

§ 111.2 What are these regulations intended to accomplish?

These regulations in this part establish the minimum current good manufacturing practices that you must use to the extent that you manufacture, package, or hold a dietary ingredient or dietary supplement.

§ 111.3 What definitions apply to this part?

The definitions and interpretations of terms in section 201 of the Federal Food, Drug, and Cosmetic Act (the act) apply to such terms when used in these regulations. For the purpose of these regulations, the following definitions also apply:

Actual yield means the quantity that is actually produced at any appropriate step of manufacture or packaging of a particular dietary ingredient or dietary supplement.

gs per text ~~6.1s~~ off Vince Greenwald

tablet size or size variation, under-filled container, foreign material in a dietary supplement container, improper packaging, or mislabeling. For the purposes of these regulations 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.

Contact surface means any surface that contacts a component, dietary ingredient, dietary supplement, and those surfaces from which drainage onto the component, dietary ingredient, dietary supplement, or onto surfaces that contact the component, dietary ingredient, or dietary supplement ordinarily occurs during the normal course of operations. Examples of contact surfaces include, but are not limited to, containers, utensils, tables, contact surfaces of equipment, and packaging.

Ingredient means any substance that is used in the manufacture of a dietary ingredient or dietary supplement that is intended to be present in the finished dietary ingredient or dietary supplement. An ingredient includes, but is not necessarily limited to, a dietary ingredient as described in section 201(ff) of the act.

Inprocess material means any material that is fabricated,

logs, which is equal to 99.999 percent reduction, of representative disease microorganisms of public health significance and substantially reduce the numbers of other undesirable microorganisms, but without adversely affecting the product or its safety for the consumer.

Theoretical yield means the quantity that would be produced at any appropriate step of manufacture or packaging of a particular dietary ingredient or dietary supplement, based upon the quantity of components or packaging to be used, in the absence of any loss or error in actual production.

Water activity (a_w) is a measure of the free moisture in a component, dietary ingredient, or dietary supplement and is the quotient of the water vapor pressure of the substance divided by the vapor pressure of pure water at the same temperature.

We means the United States Food and Drug Administration (FDA).

You means a person who manufactures, packages, or holds dietary ingredients or dietary supplements.

§ 111.5 Do other statutory provisions and regulations apply?

In addition to ~~the~~ ~~these~~ regulations in this part, you must comply with other applicable statutory provisions and regulations under the act related to the manufacturing, packaging, or holding of dietary ingredients or dietary supplements.

gs per Vince Greenwood OFR 3/5/03

§ 111.6 Exclusions.

The ... in this part
~~These~~ regulations do not apply to a person engaged solely in activities related to the harvesting, storage, or distribution of raw agricultural commodities that will be incorporated into a dietary ingredient or dietary supplement by other persons.

OS per Vince Greenwald OFR 3/5/03

4. Add new subpart B to part 111 to read as follows:

Subpart B--Personnel

111.10 What microbial contamination and hygiene requirements apply?

111.12 What personnel qualification requirements apply?

111.13 What supervisor requirements apply?

Subpart B--Personnel

§ 111.10 What microbial contamination and hygiene requirements apply?

(a) Microbial contamination. You must take measures to exclude from any operations any person who might be a source of microbial contamination of any material including components, dietary ingredients, dietary supplements, and contact surfaces used in the manufacture, packaging, or holding of a dietary ingredient or a dietary supplement. Such measures include, but are not limited to, the following:

(1) Excluding any person who, by medical examination or supervisory observation, is shown to have, or appears to have an illness, open lesion, or any other abnormal source of microbial contamination, which may be expected to result in microbial

(iii) Use of sampling plans for obtaining representative samples of:

(A) Components, dietary ingredients, and dietary supplements received to determine whether specifications are met;

(B) In-process materials during the batch manufacturing when testing or examination is required in the master manufacturing record;

(C) Each batch of dietary ingredient or dietary supplement manufactured to determine that the dietary ingredient or dietary supplement meets specifications;

(D) Packaging and labels received to determine that the materials meet specifications; and

(E) Each batch of packaged and labeled dietary ingredients or dietary supplements to ensure that the label specified in the master manufacturing record has been applied.

(iv) Use of criteria for selecting standard reference materials used in performing tests and examinations;

(v) Use of appropriate test method validations; and

(vi) Use of test methods and examinations in accordance with established criteria.

(2) The person who conducts the testing and examination at the time of performance, must document that laboratory methodology established in accordance with this section is followed. The documentation must include the testing and

consumer complaint that is related to good manufacturing practices. For the purposes of this ~~regulation~~ regulations in this part, a consumer complaint about product quality may or may not include concerns about a possible hazard to health. However, a consumer complaint does not include an adverse event, illness, or injury related to the safety of a particular dietary ingredient independent of whether the product is produced under good manufacturing practices. The consumer complaint written record must include, but is not limited to, the following:

As per Vince Greenwald OFR 3/5/03

(1) The name and description of the dietary ingredient or dietary supplement;

(2) The batch or lot number of the dietary supplement, if available;

(3) The name of the complainant, if available;

(4) The nature of the complaint including how the consumer used the product;

(5) The reply to the complainant, if any; and

(6) Findings of the investigation and followup action taken when an investigation is performed.

(f)(1) The person who performs the requirements in accordance with this section must document at the time of performance that the requirement was performed.

Revised 2-3-03

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

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

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

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

add Ref. 83 per Karen Strauss e-mail on 1-30-03

References--Economics

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

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

Reference

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

2. What Requirements Apply to Holding In-Process Material? (Proposed § 111.82)

3. What Requirements Apply to Holding Reserve Samples of Components, Dietary Ingredients, and Dietary Supplements? (Proposed § 111.83)

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

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

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

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

IV. Statement Concerning the Use of Plain Language

V. Paperwork Reduction Act of 1995

VI. Environmental Impact Considerations

VII. Analysis of Impacts

A. Introduction

B. Preliminary Regulatory Impact Analysis

1. The Need for the Proposed CGMP Regulations

2. Regulatory Options

a. No new regulatory action

b. Fewer requirements for vitamins and minerals

Abby, make sure "HACCP" was defined in this doc. (search) then delete the phrase here

c. More restrictive CGMP regulations than the proposed regulations

d. ~~Hazard analysis critical control point~~ (HACCP) without the other elements of CGMP regulations

e. Require final product testing only

f. Regulate only high-risk products p. 340

3. Coverage of the Proposed Rule

4. Baseline Practices

5. Baseline Risk

6. Benefits and Costs

a. Reduced illnesses

b. Fewer products recalled

c. Reduced hypothetical search costs as a measure of the benefit from increased assurance of quality

d. Other benefits

e. Total measured benefits

7. Costs

a. Description of the costs pa p. 399

b. Costs of general activities

c. Major costs by type of activities p. 409

d. Estimating costs

8. Summary of Benefits and Costs

C. Initial Regulatory Flexibility Analysis

1. Introduction

2. Economic Effects on Small Entities

Revising

Revised 1/23/03

considering operational limits in establishing production procedures; determining whether the software matches the assigned operational function; testing simulated production conditions including "worst case" conditions;
repeating tests enough times to assure a reasonable measure of consistent reproducible results;
documenting the verification program; and initiating reverification when significant changes are made to the system or when errors are noted.

Although verification steps would vary according to the nature of the dietary supplement and the complexity of the process, the basic elements of a verification system would be generally applicable to all dietary ingredients and dietary supplements. The primary benefit of a verification system would be to provide a foundation for building a comprehensive approach to ensure that the equipment performs in a predetermined way, but verification could impose additional costs on manufacturers.

We invite comment on whether automatic, mechanical, and electronic equipment verification and reverification elements that we have discussed should be done, should be included in the final rule as requirements, which would include requirements to document the verification steps. We invite comment on whether we should regulate computerized systems separately from other automatic equipment. We seek comment on whether any of the

Revised

recording the date when the review, approval, or rejection and requirement was performed, and the signature of the person performing the requirement. As we explained elsewhere in this document, one of the ways we determine compliance with CGMP's is by conducting inspections, so records enable you to show, and for us to determine, compliance with CGMP's. We invite comment on whether we should require, in a final rule, written procedures for the quality control unit duties required in § 111.37. If comments assert that written procedures are necessary, comments should include an explanation of why the requirement is necessary to prevent adulteration including how such a requirement would ensure the identity, purity, quality, strength, and composition of the dietary ingredient or dietary supplement. Conversely, if comments assert that written procedures are not necessary, comments should include an explanation of why the requirement is not necessary including how, in the absence of the requirement, one can prevent adulteration and ensure the identity, purity, quality, strength, and composition of the dietary ingredient or dietary supplement.

3. What Requirements Apply to Components, Dietary Ingredients, Dietary Supplements, Packaging, and Labels You Receive? (Proposed § 111.40)

Proposed § 111.40 would establish requirements to ensure that the components, dietary ingredients, dietary supplement,

Revised 1/23/02

in packaging; and the control number, if applicable, of the label to be used in packaging the dietary ingredient or dietary supplement. We are not aware of evidence of that dietary supplement manufacturers are using unlawful containers. Section 201(s) of the act defines "food additive" to mean any substance the intended use of which results or may reasonably be expected to result, directly or indirectly, in it's becoming a component or otherwise affecting the characteristics of any food (including any substance intended for use in producing, manufacturing, packing, processing, preparing, treating, packaging, transporting, or holding food; and including any source of radiation intended for any such use). Materials used in packaging that come in contact with food or that react chemically with food, may be considered to be food contact substances or food additives. Foods and dietary ingredients may contain active substances that can react with packaging materials. Thus, FDA is proposing a CGMP requirement that manufacturer's use containers that are lawful under the act and that do not impose a risk such as leakage or the possibility of physical contamination of dietary ingredients or dietary supplements. Information on packaging and labels

Revised 1/23/03

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(b) 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. When there is a reasonable possibility of a relationship between the quality of a dietary supplement and an adverse event, such as a report of an illness or injury that may be due to a wrong ingredient or wrong label, then the manufacturer would be required to do an investigation that includes both batch records associated with the dietary ingredient or dietary supplement involved in the consumer complaint. ~~In order to limit the burden to manufacturers, FDA is not proposing such requirements~~. However, if the quality control unit

Revised 1/23/03

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(e) ~~and (f)~~	53	75	3,975	0.1	398
111.95(f)(1)	93	75	6,975	0.5	3,488
111.125	220	4	880	0.1	88
Total					500,587

[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

Revised 1/23/03

representative disease microorganisms of public health significance and substantially reduce the numbers of other undesirable microorganisms, but without adversely affecting the product or its safety for the consumer.

Theoretical yield means the quantity that would be produced at any appropriate step of manufacture or packaging of a particular dietary ingredient or dietary supplement, based upon the quantity of components or packaging to be used, in the absence of any loss or error in actual production.

You means a person who manufactures, packages, or holds dietary ingredients or dietary supplements.

Water activity (a_w) is a measure of the free moisture in a component, dietary ingredient, or dietary supplement and is the quotient of the water vapor pressure of the substance divided by the vapor pressure of pure water at the same temperature.

We means the United States Food and Drug Administration (FDA).

§ 111.5 Do other statutory provisions and regulations apply?

In addition to these regulations, you must comply with other applicable statutory provisions and regulations under the act related to the manufacturing, packaging, or holding of dietary ingredients or dietary supplements.

§ 111.6 Exclusions.

These regulations do not apply to a person engaged solely in

Revised 1/23/03

supplements, or contact surfaces, from working in any operations until the condition is corrected; and

(2) Instructing your employees to notify their supervisor(s) if they have or if there is a reasonable possibility that they have a health condition described in paragraph (a)(1) of this section that could contaminate any components, dietary ingredients, dietary supplements, or any contact surface.

(b) Hygienic practices. If you work in operations during which adulteration of the component, dietary ingredients, dietary supplement, or contact surface may occur, you must use hygienic practices to the extent necessary to protect against contamination of components, dietary ingredients, dietary supplements, or contact surfaces. These hygienic practices include, but are not limited to:

(1) Wearing outer garments in a manner that protects against the contamination of components, dietary ingredients, dietary supplements, or any contact surface;

(2) Maintaining adequate personal cleanliness;

(3) Washing hands thoroughly (and sanitizing if necessary to protect against contamination with microorganisms) in an adequate hand-washing facility:

(i) Before starting work; and

(ii) At any ~~other~~ time when the hands may have become soiled or contaminated;

Revised 1/23/03

section was performed.

(d) You must identify the following for calibration~~~~ing instruments and controls in any written procedure or at the time of performance:

(1) The instrument or control calibrated;

(2) The date of calibration;

(3) The reference standard used including the certification of accuracy of the known reference standard and a history of recertification of accuracy;

(4) The calibration method used including appropriate limits for accuracy and precision of instruments and controls when calibrating;

(5) The calibration reading or readings found; and

(6) The recalibration method used if accuracy or precision or both accuracy and precision limits for instruments and controls were not met; and

(7) The initials of the person who performed the calibration.

(d) You must repair or replace instruments or controls that cannot be adjusted to agree with the reference standard.

(e)(1) You must maintain, clean, and sanitize as necessary, all equipment, utensils, and any other contact surfaces that are used to manufacture, package, or hold components, dietary ingredients, or dietary supplements. Equipment and utensils must

Revised 1/23/03

(iii) If there is any unanticipated occurrence during the manufacturing operations that adulterates or may lead to adulteration of the component, dietary ingredient, dietary supplement, packaging, or label;

(iv) If calibration of an instrument or control suggests a problem that may have caused batches of a dietary ingredient or dietary supplement to become adulterated; or

(v) If a dietary ingredient or dietary supplement is returned.

(4) For any deviation or unanticipated occurrence which resulted in or could lead to adulteration of the component, dietary ingredient, dietary supplement, packaging, or label:

(*i*) You must reject the component, dietary ingredient, dietary supplement, packaging, or label, unless the quality control unit determines that in-process adjustments are possible to correct the deviation or occurrence;

(*ii*) You must not reprocess a rejected component, dietary ingredient, or dietary supplement unless approved by the quality control unit; and

(*iii*) You must not reprocess any component, dietary ingredient or dietary supplement if it is rejected because of contamination with microorganisms or other contaminants, such as heavy metals;

(5) Have your quality control unit review and approve any

material review and disposition decision described in paragraphs (i)(2) and (i)(3) of this section.

(j) The person who conducts the material review and makes the disposition decision must, at the time of performance, document every material review and disposition decision in paragraph (i) of this section. The documentation must be included in the appropriate batch production record and must:

(1) Identify the specific deviation from the specification or the unanticipated occurrence;

(2) Describe your investigation into the cause of the deviation from the specification or the unanticipated occurrence;

(3) Evaluate whether or not the deviation from the specification or unanticipated occurrence has resulted in or could lead to adulteration;

(4) Identify the action(s) taken to correct and prevent a recurrence of the deviation or the unanticipated occurrence; and

(5) Discuss what you did with the component, dietary ingredient, dietary supplement, packaging, or label.

(k) You must test or examine components, dietary ingredients, and dietary supplements for those types of contamination that may adulterate or may lead to adulteration. You must use an appropriate scientifically valid method for the test or examination. The types of contamination include, but are not limited to, the following:

Revised 1/23/04

(1) Filth, insects, or other extraneous material;

(2) Microorganisms; and

(3) Toxic substances.

(l) Tests in accordance with this section must include at least one of the following:

(1) Gross organoleptic analysis;

(2) Microscopic analysis;

(3) Chemical analysis; or

(4) Other appropriate test.

(m) You must record results of all testing and examinations performed in accordance with this section. If a test or examination is performed in a batch production you must record the test or examination result in the batch production record in accordance with § 111.50(c)(10). Your records must document whether the testing and examination demonstrates that specifications are met.

(n) For any specification that is not met, you must conduct a material review and disposition decision under paragraph (i) of this section.

(o) You must make and retain records, in accordance with § 111.125, to ensure that you follow the requirements of this section. The records must include, but are not limited to:

(1) The specifications established;

(2) The actual results obtained during the monitoring

Revised 1/23/03

specifications for identity, purity, quality, strength, and composition. The reserve samples must:

(i) Be identified with the batch or lot number; and

(ii) Consist of at least twice the quantity necessary for tests.

(13) Perform appropriate tests and examinations of:

(i) Components, dietary ingredients, dietary supplements, packaging, and labels received to ensure that they meet specifications;

(ii) Dietary ingredient and dietary supplement batch production at points, steps, or stages identified in the master manufacturing record where control is necessary to prevent adulteration;

(iii) Dietary ingredients and dietary supplements that you manufacture to ensure that they meet specifications; and

(iv) Packaged and labeled dietary ingredients and dietary supplements to ensure that you used the packaging specified in the master manufacturing record.

(14) Review and approve all material review and disposition decisions; and

(15) Approve the reprocessing or distribution of returned dietary ingredients or dietary supplements.

(c) Your quality control unit must establish and maintain

Revised 1/23/03

(5) The shipment lot unique identifier of each component, dietary ingredient, dietary supplement, packaging, and label used;

(6) The identity and weight or measure of each component used;

(7) The initials at the time of performance or at the completion of the batch of the person responsible for verifying the weight or measure of each component used in the batch;

(8) The initials at the time of performance or at the completion of the batch of the person responsible for verifying the addition of components to the batch;

(9) A statement of the actual yield and a statement of the percentage of theoretical yield at appropriate phases of processing;

(10) The actual test results for any testing performed during the batch production;

(11) Documentation that the dietary ingredient and dietary supplement meets specifications;

(12) Copies of all container labels used and the results of examinations conducted during the label operation to ensure that the containers have the correct label;

(13) Any documented material review and disposition decision in accordance with § 111.35(j); and

(14) Signature of the quality control unit to document

Revised 1/23/03

Revised 1/23/03

c. More restrictive CGMP regulations than the proposed regulations

d. Hazard analysis critical control point (HACCP) without the other elements of CGMP regulations

e. Require final product testing only

f. Regulate only high-risk products

3. Coverage of the Proposed Rule

4. Baseline Practices

5. Baseline Risk

6. Benefits and Costs

a. Reduced illnesses

b. Fewer products recalled

c. Reduced hypothetical search costs as a measure of the benefit from increased assurance of quality

d. Other benefits

e. Total measured benefits

7. Costs

a. Description of the costs

b. Costs of general activities

c. Major costs by type of activities

d. Estimating costs

8. Summary of Benefits and Costs

C. Initial Regulatory Flexibility Analysis

1. Introduction

2. Economic Effects on Small Entities

Revised 1/23/03

ingredients and dietary supplements must be manufactured in compliance with CGMP requirements and that such compliance does not mean that the dietary ingredient or dietary supplement is safe or effective. As usual, the manufacturer would be responsible for ensuring that any such voluntary labeling statements on its dietary ingredient and dietary supplement products are truthful and not misleading. The agency would review the lawfulness of such statements under sections 403(a)(1) and 201(n) of the act.

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

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

Proposed "physical plant" requirements are intended to help prevent contamination from your physical plant environment. You

Revised
1/23/03

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

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

Revised
1/23/03

growth, and that, in turn, can play a part in the contamination of your components, dietary ingredients, and dietary supplements.

Proposed § 111.3 defines "you" as "a person who manufactures, packages, or holds dietary ingredients or dietary supplements." "You" is the recommended "plain language" term designed to make regulations easier to understand. In this proposed rule, "you" refers to any person, within the meaning of section 201(e) of the act, who engages in any activity covered by this proposed rule. You should note that "you" includes, but is not limited to, the owner of the manufacturing firm as well as supervisors responsible for ensuring that these CGMPs are followed. In other words, "you" can be the person who owns the dietary ingredient or dietary supplement company as well as persons who work for the company.

Proposed § 111.3 defines "we" as meaning the U.S. Food and Drug Administration.

4. Do Other Statutory Provisions and Regulations Apply? (Proposed § 111.5)

Proposed § 111.5 would require that you comply with the regulations in proposed part 111, and with other applicable statutory provisions, and regulations under the act, related to manufacturing, packaging, or holding dietary ingredients or dietary supplements. Other statutory provisions or regulations that may apply to the manufacture, packaging, or holding of

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