Docket No. 96N-0417

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BEFORE

THE UNITED STATES OF AMERICA

DEPARTMENT OF HEALTH AND HUMAN SERVICES

FOOD AND DRUG ADMINISTRATION

COMMENTS OF THE

American Herbal Products Association

ON THE PROPOSED RULE FOR

Current Good Manufacturing Practice

in Manufacturing, Packing or Holding

Dietary Ingredients and Dietary Supplements

Addendum:

Comments on the Analysis of Impacts of the Proposed Rule

September 9, 2003

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The American Herbal Products Association ("AHPA") is the national trade association and voice of the herbal products industry, comprised of companies doing business as growers, processors, manufacturers, and marketers of herbs and herbal products. AHPA serves its members by promoting the responsible commerce of products that contain herbs.

Background and Subject of these Comments

FDA issued, in a Federal Register notice published on March 13, 2003, a proposed rule for cGMP in manufacturing, packing, or holding dietary supplements and dietary ingredients (the Proposed Rule).

Most of AHPA's members are companies that grow and/or harvest herbs that are used as ingredients in dietary supplements; that sell bulk herbs or herbal extracts; that manufacture or process herbal dietary ingredients or dietary supplements containing herbs; that market dietary supplements containing herbs; or that are engaged in some combination of the above listed activities. All such AHPA members, with the exception of those whose business is limited to raw agricultural commodities, will be required to comply with whatever subsequent final rule (the Final Rule) that is established by FDA for manufacturing, packing, or holding dietary ingredients and dietary supplements. AHPA members therefore have an interest in the Proposed Rule.

AHPA therefore submitted comments to the Proposed Rule on August 11, 2003 to address most of the issues that were identified as important to AHPA member companies (AHPA's August 11th Comments or the August 11th Comments). AHPA also expressed concern in the August 11th Comments that FDA's discussion of the economic implications of the Proposed Rule may have significantly underestimated the costs that firms will bear to implement any Final Rule that is the same as or closely resembles the Proposed Rule. AHPA forwarded some limited information that had been provided by a number of AHPA member companies that have calculated the costs that they believe are associated with the Proposed Rule.

AHPA also expressed concern about other aspects of the agency's economic analysis, including FDA's use of a dated survey of dietary supplement manufacturers and its apparently inaccurate presentation of certain information in that survey, and certain of the assumptions and calculations that FDA presented in determining benefits, including the agency's discussion of costs saved by a projected reduction in product recalls and money saved by consumers from reduced shopping time.

As stated in the August 11th Comments, AHPA requested and was granted an extension of time for a period of 30 days to allow additional comments related to the economic impact of the Proposed Rule to be submitted to this Docket until September 9, 2003. In addition, AHPA submitted an electronic request on July 22, 2003 under the Freedom of Information Act (FOIA) for information related to this economic analysis, and specifically the spreadsheets that were used to develop the tables that accompanied the economic analysis. Although this FOIA request was fulfilled on August 7, 2003, most if not all of these requested spreadsheets that were provided by FDA were formatted in such a manner that many of the calculations that were included in the spreadsheets were not legible. Nevertheless, AHPA has attempted to utilize the files provided to the best of its abilities to evaluate FDA's economic calculations.

In summary, the comments contained herein represent AHPA's additional comments to the FDA's economic analysis of the Proposed Rule. In addition, comments are provided here on other elements of the agency's analysis of impacts of the Proposed Rule to the degree that such additional comments are necessary to clarify comments on the agency's economic analysis. These comments were prepared in consultation with the Food Policy Institute at Rutgers University. Certain of the specific comments of this advisor are identified as such below.

Overview

The agency provided a preliminary regulatory impact analysis that addressed issues such as the need for the Proposed Rule; baseline practices of both consumers and manufacturers; baseline risks; benefits and costs; and other issues. In addition, the agency provided estimates in its initial regulatory flexibility analysis of the economic implications of the Proposed Rule and the economic effects on firms.

These comments are primarily addressed to the agency's analysis of benefits and costs and of the projected economic effects on small and large firms. However, as the agency's analysis of these factors to some degree relied on its analysis of the need for the Proposed Rule and various baseline factors, those issues are also addressed herein.

Need for the Proposed Rule

As stated in the August 11th Comments, AHPA and its members support the establishment of cGMP that are specific to dietary supplements. AHPA's support for new rules stems from a belief that, although full enforcement of the current cGMP for foods, to which all dietary supplement manufacturers are bound, already protect the public health, new rules can more accurately reflect practices that are more representative of current industry practices and can more fully implement current industry thinking as to what constitutes good manufacturing practice for this diverse and important class of goods.

The agency states, in the very first sentence of its preliminary regulatory impact analysis, that the Proposed Rule is needed because firms "may not have sufficient market incentives to use controls to prevent adulteration and misbranding" of their products. The agency goes on to say that absent the Proposed Rule consumers "cannot be assured that...these products are not adulterated or misbranded." 68 FR 12220.

AHPA can not overstate the degree to which these statements distort the facts. The damage done to the reputation of any firm that markets an adulterated

product provides a real market incentive to companies that sell any consumer goods, including dietary supplements. However, FDA should not assume that market incentives are required to prevent companies marketing adulterated and misbranded products. Any such product is already blatantly illegal, a fact of which the agency must certainly be aware, and the threat of FDA enforcement should provide a real disincentive to market such products. Yet this entire section of the agency's analysis is filled with statements that imply that FDA is currently unable to enforce against adulterated or misbranded dietary supplements.

AHPA has already attempted to communicate in the August 11th Comments its concerns about the numerous and significant errors and misrepresentations contained in the March 13, 2003 *Federal Register* notice in which the Proposed Rule was published. Rather than expand those earlier comments to articulate the specific errors and misrepresentations in this section, AHPA reiterates here its belief that FDA must expend real and significant efforts to overcome the misperceptions that may have resulted from the erroneous implications of the many misstatements in this discussion of the Proposed Rule, and also repeats its support for the establishment of cGMP specific to dietary supplements.

Analysis of benefits

The agency conducted several analyses to attempt to estimate the benefits of the Proposed Rule. Ultimately the agency estimated that mean annual benefits can be calculated to be $218 million, consisting of:

- $39 million from fewer illnesses associated with product recalls
- $66 million from fewer illnesses associated with rare catastrophic events
- $3 million from fewer product recalls
- $109 million from reduced consumer search time

In each of these categories the agency selected somewhat random but arguably reasonable criteria to calculate a benefit. Some specific commentary on three of these four areas of benefit follows.

Benefit from fewer illnesses associated with recalls. FDA presented a table (Table 8) detailing recalls that were associated with dietary supplements between 1990 and 1999 and that were linked to poor manufacturing processes. Calculations for the health benefits for preventing illnesses that are potentially associated with these recalls were presented in Table 9, which estimated that the health benefit for preventing illnesses associated with Class 1 recalls would average $60,000; that those associated with Class 2 recalls would average $5,000; and that the total annual benefit would be $39 million.

The agency stated 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." 68 FR 12228. Though the agency requested comments on this assumption, AHPA is not offering comments on this assumption but is merely reporting the assumption. AHPA does note, however, that it must be emphasized that the agency identified every one of the illnesses presented in Table 8 only as a "potential" illness. The agency stated that "with a few exceptions, no evidence explicitly links illnesses to these [poor] manufacturing practices." In other words, except for those exceptions, none of these potential illnesses actually represents an illness that was reported to the agency and it is possible that none of these potential illnesses actually occurred.

In addition to the agency's arbitrary assignment of a single illness for each recall, FDA cited a reference (Ref. E16: Walker, AM. "The Relation Between Voluntary Notification and Material Risk in Dietary Supplement Safety," Harvard School of Public Health [sic][1], March 9, 2000). The agency stated that it had

[1] Dr Walker is affiliated with Harvard School of Public Health. This document was not, however, published by this institution, as is apparently implied by the citation. Rather, this document was solicited by FDA and provided to FDA by Dr Walker directly.

relied upon this document to establish a multiplier of 100, as the agency stated that Walker had "determined that for dietary supplements, reported illnesses represent at best approximately 1 percent of total illnesses." Ibid. In fact, Walker did not present his conclusion as a "determination," but rather as an "estimate," and, importantly, he also stated, "...the rate of reporting of drug and vaccine adverse events, even in countries where there are well-advertised and effective systems for identifying events, is very low. **It is probably no more than one percent**, except when the event is readily recognized, severe, and clearly related to the exposure in the mind of the treating physician" (emphasis added). Any citation of Walker's work should disclose not only his conclusions about dietary supplements but also his conclusions regarding the similarly low rate of reporting for adverse events associated with drugs and vaccines.

Given the importance of this 100-fold multiplier in estimating the costs related to illnesses associated with recalls, AHPA is troubled that Dr. Walker's speculation is the only reference that the agency has identified to substantiate this number. AHPA believes, in fact, that the agency has no other information to substantiate this number and that almost any other number might be as accurate as this estimate.

In attempting to quantify the benefit of reduced illness associated with product recalls, the agency went on to state that it received reports on an annual basis averaging 13 class 1 and class 2 recalls over the 10 year period from 1990 to 1999. Based on the assumed proxy of one single illness for each recall and utilizing the multiplier of 100, the agency concluded, "the total number of unreported illnesses per year is approximately 1,300." Ibid. In fact, Table 8 identifies 51 class 1 recalls and 61 class 2 recalls, for a total of 112 recalls and an annual average of 11 rather than 13. FDA did not provide references to these recalls so additional specific review of any recall has not been attempted for these comments.

Even this calculation of 11 annual recalls may be an overestimate of the average number of recalls associated with manufacturing issues. For one thing,

the event that led to the largest number of recalls was due to contamination of L-Tryptophan by a single Japanese manufacturer, resulting in 48 recalls. The illness associated with this contamination, eosinophilia-myalgia syndrome (EMS), occurred in 1989. Assuming therefore that these recalls must have occurred in 1990, the average number of class 1 and class 2 recalls in the subsequent 9 years is calculated to be only 7 in each year. Similarly, the 33 recalls reported for digitalis, presumably in 1997 or 1998, have skewed the average. Because FDA did not provide references to the recalls reported in Table 8, AHPA has not had an opportunity to review these in detail. It can be speculated, however, even without such review, that the median number of annual recalls is probably in the area of three to four.

Another specific factor that may have artificially exaggerated the potential benefit related to a reduction in recalls is that the agency has calculated health costs for EMS associated with the 1989 L-Tryptophan contamination in both Table 8 and in Table 10, discussed below. While it may be reasonable to assume that not all cases of EMS were reported to FDA and were therefore not included in Table 10, it is not reasonable to use the same multiplier of 100 as was used generally, as the agency expended significant efforts in publicizing the public health concern associated with this event.

AHPA must also question the accuracy of FDA's assumptions with regard to the most serious of the potential illnesses included in Table 8 and the related calculations presented in Table 9. It is difficult to believe, for example, that if 15 deaths had actually occurred in association with each of the reported recalls associated with *Klebsiella pneumonia* and selenium poisoning that all such deaths would have been unreported and that health authorities would not have associated these deaths, or at least some of them, with the reported recall. These were both Class 1 recalls and, as such, were broadly reported to the medical community and to health authorities throughout the country. It is simply not feasible that these "potential" deaths were actual but unreported deaths, yet the costs associated with these in Table 8 are substantial. AHPA has

recalculated the average health benefit for preventing illnesses associated with Class 1 recalls, as presented in Table 9, by revising the assumptions made by FDA as follows:

- 100 percent of the potential illnesses related to the recall associated with *Klebsiella pneumonia* are classified as severe and none are classified as deaths;
- 50 percent of such illnesses associated with the selenium recall are classified as serious and none are classified as deaths (the 50 percent that FDA classified as "low doses" are not altered).

The revised average estimate of health benefits for a Class 1 recall is $32,000 when recalculated with the above modified assumptions, and the recalculated benefit for all recalls is revised to $23 million. Similarly, FDA has estimated that 3 percent of the one hundred persons who were potentially ill from the single recall associated with undeclared ephedra would have died. AHPA can find no reference to support such a supposition and in fact believes such a projection to be unsupportable. If these three cases are reclassed as "other" under this event, the average estimate of health benefits for a Class 1 recall will be further reduced to $29,000 and the benefit for all recalls would be revised to $21 million.

Of additional concern is the fact that there are three recalls that are not included in Table 8 but that do appear in one of the spreadsheets provided by FDA in response to AHPA's FOIA (identified by FDA as "Health Benefits_ DSGMP") and included in the calculations presented in Table 9. These are specifically one Class 1 and one Class 2 recall associated with botulism and one Class 1 recall associated with lead poisoning. Because FDA did not provide any references to assist in identifying any of the recalls included in either Table 8 or this spreadsheet, AHPA can make no determination as to whether these three recalls were erroneously excluded from Table 8 or erroneously included in the spreadsheets, and thus, erroneously included in the calculations presented in

Table 9. If the latter is the case, the information in Table 9 would be recalculated to be:

- Health benefit for preventing illness associated with a Class 1 recall: $21,000
- Health benefit for preventing illness associated with a Class 2 recall: $5,000
- Annual health benefits, recall base: $16 million[2]

Finally, AHPA believes that FDA's assumption that recalls will reduce to zero as a result of the implementation of a Final Rule is not credible. AHPA notes that the agency provided no information to support this overly optimistic assumption. Also, AHPA is aware, and knows that the agency is aware, that there are greater than zero recalls each year for foods and for drugs even though each of these classes of goods are required to be manufactured according to good manufacturing practices. The agency can not assume that the Proposed Rule will reduce recalls to zero, yet it is exactly that assumption that was used in calculating this benefit.

In summary, AHPA is concerned that the benefit quantified from a reduction in illnesses associated with product recalls my have been overstated. First, as mentioned above, FDA provided specific details for an average of only 11 recalls each year rather than 13 and the annual average for the past nine years is believed to have been only 7 recalls, while the median number of recalls is even lower. The agency may have also overestimated unreported illnesses associated with EMS and may have exaggerated the percentage of unreported deaths associated with Class 1 recalls for *Klebsiella pneumonia*, selenium

[2] AHPA also notes that there is an additional inconsistency between this spreadsheet and Table 8. Table 8 reports that there were 41 Class 2 recalls associated with EMS whereas the spreadsheet referenced here does not identify these recalls but instead includes 41 Class 2 recalls for lead poisoning. AHPA can not speculate as to which of these is accurate. However, because the cost associated with EMS is greater than the cost associated with lead poisoning, and because the data in the spreadsheet was used to calculate the information presented in Table 9, further adjustments may need to be made to the numbers given here. In the event that these were in fact EMS recalls, AHPA has tentatively calculated the correct values for the three numbers bulleted above as $21,000; $11,000; and $20 million, respectively.

poisoning, and undeclared ephedra, and may have inadvertently included recalls for botulism and for lead poisoning that should not have been included in this estimation of benefits. If all of these concerns are taken into account, the total benefit that can be associated with a reduction in illnesses from recalls is less than half of the $39 million that the agency has calculated. Finally, the agency has not substantiated its assumption that 100 percent of recalls should be expected to be avoided under the Proposed Rule and so should not assume that 100 percent of the associated costs can be included as a benefit.

Benefit from fewer illnesses associated with rare catastrophic events. The agency provided information in Table 10 related to costs associated with the EMS outbreak of 1989, which was calculated to be just under $2 billion. 68 FR 12232.

In analyzing the potential benefit from preventing such an event in the future, the agency then made several speculative assumptions. With no data to substantiate or support an estimate of the lower bound for such an event, the agency "assumed [it] would be 50 years." Also, "[f]or lack of data" the agency "assumed a uniform probability distribution... of once in 30 years" and therefore calculated that a potential annual benefit could be calculated as $66 million by dividing the $2 billion cost associated with the 1989 EMS event by 30 years. Finally, the agency acknowledged, "We do not know how likely rare events are, nor do we actually know the likelihood of reducing these events by the proposed regulation." Ibid. In other words, there is no more or less information to support any other assumption as to the next time a rare catastrophic event might occur, such as next week or sometime in the 22nd century, and there is no evidence to suggest that the Proposed Rule would, in fact, in any way alter such date.

The agency specifically recognized that their "lack of information about such events creates significant uncertainty about the social costs and the health benefits from reducing their impact." While AHPA appreciates such frankness, it remains to be observed that there is a real possibility that the annual health

benefit FDA quantified as $66 million, representing 30 percent of the total projected benefit, could in fact be zero.

Benefit from reduced consumer search time. Exactly one half of the summarized annual benefit that was projected by FDA consists of $109 million from reduced search time in obtaining dietary supplements. In calculating this amount, the agency made numerous assumptions that must be questioned, including:

- The basic assumption that there is currently an expense universally associated with dietary supplement quality that now "costs" consumers search time;
- The assumption that adoption of a Final Rule will actually affect consumer search time;
- The population estimates used in calculating this benefit;
- The agency's use of arbitrary values for the fraction of consumer search time devoted to quality and the potential reduction in search time due to new cGMP.

In introducing this topic FDA states that consumers must search for products made with good manufacturing practices "because they cannot take such practices for granted when purchasing dietary supplements." 68 FR 12233. FDA provided 3 references to substantiate "large variations in product quality" for dietary supplements. Ibid. None of these references, however, are from peer-reviewed sources. One of them, the April 2000 edition of *D Magazine* (a monthly Dallas area journal), included several statements that should have led FDA to question its reliability as a source of information in establishing a Federal rule. For example, the article claimed that an analytical laboratory engaged by the magazine to test dietary supplements "serves as an FDA reference for making these supplements," and that the lab's analytical method "is considered so reliable that the FDA has requested a copy of our test results for its research into

the industry." To the best of AHPA's knowledge there is no such thing as an "FDA reference" for making dietary supplements and in fact this claim is nonsensical. The lab also apparently used an incorrect analysis in at least one test, as it identified the lack of "any trace of ginseng at all" in a product that was labeled to contain Siberian ginseng (*Eleutherococcus senticosus*) – an herb that does not purport to contain ginseng.

The other two references cited by FDA were a four year old article in *Consumer Reports* that provided results of its tests of two types of herbal products and a visit to the web site of ConsumerLab.com in March 2000. Without commenting on the credibility or lack of credibility of these references, AHPA notes that these citations are dated and may not in any manner represent current issues.

Even if these references or other references can substantiate that there are issues related to product quality that might be addressed by good manufacturing practices, FDA has not substantiated that there is currently an expense associated with searching for dietary supplements that is associated with product quality. The agency simply stated as if it were an established fact that if there were uniform quality control practices, presumably associated with the adoption of new cGMP, "[c]onsumers could more reasonably assume that all products are free from contamination and have the identity, purity, strength, quality and composition stated on the label." 68 FR 12234. But this is an equally good argument for full enforcement by FDA of the current regulations that govern dietary supplements, as it is not allowed, under current rules, to sell contaminated dietary supplements or products that do not meet any label claim.

To reiterate the first two points made in the bulleted outline at the beginning of this section of AHPA's comments, there is nothing in the introduction of FDA's analysis of supposed benefits from lessened search costs that either establishes that there is a search cost at this time that is associated with issues that are related to good manufacturing practice, nor is there any meaningful presentation that shows that the adoption of the Proposed Rule

would reduce such a cost if it in fact exists. Rather, the agency has made statements that have no substantiation, or that are supported only by questionable or outdated references. Nevertheless, AHPA must provide additional comments to the calculations that FDA made to quantify this purported benefit.

FDA employed three different models to measure the direct benefit of any reduced search time that might be attributed to implementation of a Final Rule. FDA presented information about these models in Table 11 and calculations based on this information in Table 12. 68 FR 12235-6. AHPA believes that each of these three models made assumptions that are inaccurate and unsubstantiated and that resulted in a significant overestimation of the benefit associated with reduced consumer search time.

To begin with, in two of the models, FDA estimated that the entire U.S. adult population of 205 million would be positively affected by this purported savings. But the agency also provided a reference in other discussions that estimated the population of supplement users to be only 160 million. 68 FR 12224. FDA acknowledged that it used the total adult population rather than just the adult consumers of dietary supplements "because the shopping time studies are for all adults." AHPA does not believe that this statement is accurate or that it is appropriate to calculate a benefit for shoppers who do not shop.

Even the 160 million users of dietary supplements identified by FDA probably overestimates the population that should be used in calculating this benefit. Some of these are presumably children who will not be searching for dietary supplements that are purchased by a parent. Furthermore, the Food Policy Institute has informed AHPA that in partnered households it is more likely that only one adult will actually do the shopping and that census reports suggest that there are approximately 107 million households in the United States. Even if it is assumed that every household in the U.S. includes one adult who searches for dietary supplements the cost of their searching would be approximately 52 percent (107 million divided by 205 million) of the amount calculated by FDA. If

the average annual benefit of $109 million that FDA calculated from the three models it examined is adjusted by this factor, the actual benefit would be $57 million.

But even this amount is based on assumptions that are not well substantiated and that are, in fact, arbitrary. The agency defined three different variables that affected two or more of the models and provided estimates of these variables. Here follow the information provided by FDA on these variables, including the statements provided by the agency to support their assumptions:

- Ratio of search time to shopping time: 40 to 100 percent (with 70 percent used in calculations). "We... converted shopping time to search time by assuming that search time equaled 40 to 100 percent of shopping time." 68 FR 12236.
- Fraction of total search time devoted to searching for quality: 10 to 30 percent (with 20 percent used in calculations). "We assumed that 10 to 30 percent of pure search time involves quality searches." Ibid.
- Potential reduction in search time attributable to CGMP regulations: 1 to 50 percent (with 33 percent used in calculations). "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[3] 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

[3] Table 11 identifies this range as between 15 and 50 percent in the "use of time model." Both the text accompanying the Table and the spreadsheet obtained by AHPA under FOIA, however, state this range to be 1 to 50 percent and it is this also broader range that is identified in Table 11 for the "grocery store model."

that products will contain what the label claims, then perhaps search time for quality will decline by that percentage." Ibid.

Thus, FDA has provided absolutely no references to substantiate their estimates of the ratio of search time to shopping time or of the fraction of total search time devoted to searching for quality. As an aside and with regard to the first of these, AHPA can not conceive of an instance in which that could be 100 percent. While there are references provided for the last variable, these are at best speculations by pharmacists as reported in a trade journal and at worst the exact same references that were identified above, i.e., the April 2000 edition of *D Magazine*; a four year old article in *Consumer Reports*; and a March 2000 visit to the website of ConsumerLab.com. For all of the reasons articulated in the earlier discussion of these references, AHPA does not believe that these unreviewed references constitute a sound basis for the economic analysis of Federal rulemaking. Further, AHPA must reiterate that, if it happens that the information attributed to these references is accurate, the agency has made an equally valid evaluation of the benefit that consumers would gain in reducing search time if FDA would fully enforce the current regulations that govern dietary supplements, as it is not allowed, under current rules, to sell dietary supplements that do not meet any label claim.

AHPA does not have any additional information that can be used to support these or any other estimates for these variables. Given the significant ranges that FDA has applied to these, however, AHPA believes it is important to highlight the calculations that would result if the lowest range of each of these is, in fact, the best estimate of these variables. If, in fact, the ratio of search time to shopping time is only 40 percent, the fraction of total search time devoted to searching for quality is only 10 percent, and the potential reduction in search time attributable to cGMP regulations is only 1 percent, then the average annual benefit attributable to search cost savings, as calculated from the three models provided by FDA, would be less than $2 million. This is a remarkably large

difference from the $109 million estimate that FDA has provided and, in AHPA's view and in light of the absence of any real substantiation of the variables used in FDA's calculations, must be considered in any meaningful economic analysis of the Proposed Rule.

Summary of analysis of benefits. FDA provided an overall estimate of an annual economic benefit of $218 million that might be associated with implementation of the Proposed Rule. AHPA has presented information here that questions the methodology and accuracy of this estimate. AHPA believes that the benefit resulting from fewer illnesses associated with product recalls may be only $16 million, or even less if less than 100 percent of recalls are avoided, rather than the $39 million estimated by FDA; that there may be no actual benefit that results from fewer illnesses associated with rare catastrophic events, rather than the $66 million calculated by the agency; and that savings associated with reduced consumer search time may be less than $2 million annually. AHPA did not attempt to evaluate FDA's estimate of an annual benefit of $3 million from fewer product recalls. In summary, AHPA believes that the benefit that can be assumed for the implementation of current good manufacturing practice for dietary supplements may be as little as $21 million, and could, in fact, be even less than that amount.

Analysis of costs

The agency conducted several analyses to attempt to estimate costs to industry of the Proposed Rule. The agency estimated that mean annual costs can be calculated to be $86 million with additional costs incurred in the first year in which any Final Rule is in effect.

In AHPA's August 11th Comments, concern was stated that the agency may have significantly underestimated the costs that firms will bear in implement the Final Rule. AHPA provided information at that time on the estimated costs that several member companies have provided, and specifically:

- One very small firm has informed AHPA that it has received an estimate of between $300,000 and $400,000 for the annual costs newly established by the testing requirements included in the Proposed Rule for the estimated 200 lots of botanical ingredients received each year.
- One small firm has informed AHPA that they have estimated that their annual expenses only for analytical work and for travel expenses and personnel costs associated with site visits would be between $340,000 and $540,000.
- Two large firms have stated that they expect their annual expenses related to complying with the Proposed Rule to be in excess of $2,000,000 and $5,800,000, respectively.

As stated in the August 11th Comments, AHPA does not know to what degree the information provided by these few firms is representative of the industry. In addition, AHPA has not been able to obtain additional information of this type in the interim.

If, however, the information provided by these few firms is in any way representative of the industry, costs associated with implementation of the Proposed Rule can be calculated based on FDA's stated estimate that there are 830 very small firms and 564 small firms. 68 FR 12246. As the agency has also estimated that there are a total of 1,566 firms (68 FR 12219) the number of large firms can then be determined to be 172.[4] Assuming that the cost of compliance for very small firms would be between $300,000 and $400,000; that for small

[4] AHPA notes that, although FDA consistently stated that the number of firms that would be covered by the Proposed Rule would be 1,566, it was inconsistent in its estimates as to which are very small, small, or large. For example, the estimates cited here for very small and small firms are taken from page 12246 of the March 13, 2003 *Federal Register* notice. Another breakdown is presented in Table 2, on page 12223, based on the Dietary Supplement Enhanced Establishment Database, and classifies 514 very small firms, 351 small firms, 106 large firms, and 594 of unknown size. A third estimate is provided in Table 16, on page 12242, and states that there are 740 very small firms, 766 small firms, and 60 large establishments. Extrapolation of the total annual cost to industry from the information provided by the four firms cited here would be between $783 million and $1.63 billion if calculated for 1,566 firms on the ratio or very small to small to large firms provided in Table 2; and between $602 million and $1.06 billion if calculated from the numbers of firms in each size as provided in Table 16.

firms would be between $340,000 and $540,000; and that for large firms would be between $2,000,000 and $5,400,000, the total annual cost for the dietary supplement industry would be between $785 million and $1.63 billion.

AHPA acknowledges that the cost analysis provided above is speculative as it is based on limited actual information. AHPA is aware, however, that other organizations and firms have provided cost analyses that are more detailed, and in particular that an analysis conducted by Paul H. Rubin, Ph.D. has been presented to FDA by Emord & Associates in which the estimated annual cost of implementation of the Proposed Rule was stated to be in excess of $800 million. AHPA encourages FDA to take this analysis and any other well conducted analyses seriously in reconsidering the financial impact of the Proposed Rule.

AHPA also notes that it does not believe that the excessive cost that has been suggested by the limited information provided here and the extensive information provided by others is inevitably associated with any reasonable model for dietary supplement cGMP. Rather, AHPA believes that the costs that would be associated with cGMP that are consistent with the recommendations made by AHPA in its August 11th Comments would be considerably less and would be in a range that could be borne by industry.

Impact on small businesses

FDA stated in its analysis of the economic implications of the Proposed Rule on small entities that the average burden to very small, low revenue firms (i.e., those with less than 20 employees and annual sales of less than $500,000) would be at least 8 percent of their annual revenue, and that the average burden for small, low revenue firms (i.e., those with between 20 and 499 employees and annual sales of less than $500,000) would be at least 12 percent of their annual revenue. The agency estimated that 700 firms (45% of the total 1,566 estimated by the agency to be in this trade) are in one of these two categories, and made an unreferenced assumption that 50 percent of these firms are not at risk of going out of business because they may have sales revenues from other

products and locations. With regard to the other 350 very small and small establishments with annual revenues less than $500,000, the agency identified the possibility that "a large number of these... would be unable to absorb the compliance costs and will close."

AHPA is concerned that the possible scenario of such a significant proportion of its member companies and others in the dietary supplement industry being forced to close due to the high costs associated with the Proposed Rule. AHPA's concern is related to a number of factors, including the fact that many of these companies would be forced out of business because they could not afford to meet manufacturing practices that are not necessary to assure that their products are properly manufactured, accurately labeled, and free of contamination and adulterants, even though other practices, which would be affordable, would assure all of these. AHPA reiterates here its requests, as presented in the August 11th Comments, that the agency seriously consider revising the Proposed Rule to create cGMP for dietary supplements that establishes more efficient practices with fewer unnecessary redundancies. If the agency fails to do so, many small companies that are now making high quality products will be unfairly forced out of business, and the associated loss of jobs, in many cases in rural areas, would be an unacceptable outcome not only for the dietary supplement industry but for the overall economy.

Conclusions

AHPA continues to be supportive of the implementation of federally mandated cGMP for dietary ingredients and dietary supplements. AHPA believes that the AHPA Proposed Revision that was submitted as "Part 2 of 3" of AHPA's August 11th Comments serves as an excellent model for dietary supplement cGMP and strongly encourages the agency to seriously consider this Revision as a better option to the Proposed Rule.

In the comments presented here AHPA has expressed concerns that the agency may have, in analyzing the economic impact of the Proposed Rule, overstated the economic benefits and understated the costs.

If the agency adopts the Proposed Rule as a Final Rule, AHPA agrees with the agency that a significant number of companies will go out of business. AHPA does not believe this to be an acceptable outcome, as other options, such as those suggested by AHPA in the August 11th Comments, would be equally as effective in producing all of the benefits that the Proposed Rule would achieve, but would do so at a lower cost.

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