Docket No. 96N-0417

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

Part 1 of 3:

General and specific comments to the Proposed Rule

August 11, 2003

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

The Dietary Supplement Health and Education Act (DSHEA) was signed into law on October 25, 1994 (Public Law 103-417). The law amended the Federal Food, Drug, and Cosmetic Act (FFDCA) in a number of ways to establish "a rational Federal framework...to supercede the current *ad hoc*, patchwork regulatory policy on dietary supplements, among other things. The law also amended the FFDCA to authorize though not require the Secretary of Health and Human Services (the Secretary) to prescribe good manufacturing practices for dietary supplements "modeled after current good manufacturing practice regulations for food," and that "may not impose standards for which there is no current and generally available analytical methodology."

A number of trade associations, including AHPA, met with the Food and Drug Administration (FDA) shortly after the passage of DSHEA and expressed interest and support for the development of current good manufacturing practice (cGMP) specific to dietary supplements. These trade associations submitted a proposal for such cGMP to FDA in November 1995 and FDA included this "Industry Draft" in an advance notice of proposed rulemaking (ANPR) for dietary supplement cGMP published on February 6, 1997. In the interim, AHPA's President, Michael McGuffin, served as an industry representative on the FDA Food Advisory Committee Working Group for Good Manufacturing Practices for Dietary Supplements from May 1998 to June 1999. By these actions AHPA has expressed support for the implementation of Federally mandated cGMP specific to dietary supplements and AHPA continues to support such action.

FDA has now 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 and these comments are addressed to the Proposed Rule.

Outline of AHPA's Comments to the Proposed Rule

AHPA has included here comments related to the following elements of the Proposed Rule:

- Modifications must be made to the Proposed Rule
- The Proposed Rule is modeled after both current food and drug cGMP
- Inclusion of dietary ingredients in the Proposed Rule
- Impact of the Proposed Rule on intrastate commerce
- Analysis of economic implications of the Proposed Rule
- Identification of key references for botanical identity
- Comments to specific sections of the Proposed Rule
- Additional comments
- Conclusions

In addition, AHPA has filed two separate comments to Docket No. 96N-0417 on this date, one of which (#2 of 3) consists of a "redline" edit of the Proposed Rule (the AHPA Proposed Revision), and the other (#3 of 3) to

address errors and misrepresentations in the March 13, 2003 *Federal Register* notice.

Modifications must be made to the Proposed Rule

As stated above, AHPA is supportive of the implementation of Federally mandated cGMP for dietary supplements. AHPA believes that the Proposed Rule, as written, properly addresses many issues that are appropriate and necessary for any Final Rule for dietary supplement cGMP. As can be seen in the AHPA Proposed Revision that is submitted as "Part 2 of 3" of AHPA's comments to the Proposed Rule, there are many provisions in which only minor revisions have been suggested or where no revisions of any kind have been requested.

At the same time, AHPA believes that certain of the provisions in the Proposed Rule must be modified and opposes implementation of this Proposed Rule without appropriate modifications.

AHPA has provided numerous comments herein. Some of these are thoughts of a general nature, addressing issues such as the inclusion of dietary ingredients in the Proposed Rule and acknowledgement that certain of the proposed provisions are modeled after existing cGMP for drugs. In addition, AHPA has provided numerous comments in which specific modifications to the Proposed Rule are suggested or requested. None of these comments, whether general or specific, is submitted lightly and AHPA has attempted to provide meaningful options for modifying the Rule to accompany each request for revision.

It is AHPA's position that the agency should seriously consider modifying the Proposed Rule to incorporate each of the suggested changes made herein. If the agency, for example, only agrees to accept AHPA's argument that the definition in §111.6 of the term "consumer complaint" be changed to "customer complaint," but rejects all other suggestion made in these comments, the resultant Final Rule would still be perceived by AHPA as an inappropriate rule for cGMP for dietary supplements.

FDA's supportive response to certain of AHPA's comments, however, is viewed by our members as more essential than the agency's response to other identified concerns, in order to assure that the Final Rule is an appropriate rule. These include but are not necessarily limited to the comments offered in regard to §§111.25; 111.35; 111.45(a); 111.50(f); 111.60(d); and 111.125. Notwithstanding the identification here of these specific sections as of highest concern to AHPA's members, AHPA does not mean to communicate that other comments are unimportant, and requests that the agency consider the merits of every comment included herein.

At the same time, AHPA must acknowledge that the agency may receive comments that include suggestions or recommendations that directly contradict those provided here. AHPA strongly encourages the agency to assure meaningful participation by stakeholders in the coming stages of this rulemaking so that any such differences can be adequately discussed.

The Proposed Rule is modeled after both current food and drug cGMP

As has been noted above and as the agency clearly acknowledged in the March 13 *Federal Register* notice, DSHEA authorized the Secretary to prescribe cGMP for dietary supplements "modeled after current good manufacturing practice regulations for food." In discussing this restriction in the preamble to the Proposed Rule, however, the agency failed to acknowledge that some elements of the Proposed Rule are obviously modeled after the cGMP for finished pharmaceuticals that is now codified in 21 CFR 211.

The agency referred to the dictionary definition of the word "model" as "[a] preliminary pattern serving as the plan from which an item not yet constructed will be produced," and provided as its reference the *Webster's II New Riverside University Dictionary*, copyright 1994. AHPA notes that the definition cited by the agency is for the word "model" when used as a noun. The statutory term is a

verb form, "modeled after," and has a meaning that is closely related to the noun definition provided by FDA.[1]

In discussing the Congressional intention represented by the words, "modeled after current good manufacturing practice for food," FDA stated, "If Congress had intended for the agency to adopt food CGMPs as the CGMPs for dietary supplements, Congress could have explicitly stated that dietary supplements were subject to food CGMPs." AHPA agrees with the agency on this point. FDA goes on to say, "The provisions in the dietary supplement CGMP proposal are modeled after food CGMPs." AHPA believes that this statement is accurate for **some** of the provisions of the Proposed Rule, but is not accurate for **all** of these provisions. In fact, many of the provisions of the Proposed Rule are "modeled after" existing cGMP for finished pharmaceuticals, and specific parts of 21 CFR 211 clearly served as the "preliminary pattern" for some of these provisions.

AHPA does not believe, however, that it is wholly inappropriate to adopt certain manufacturing practices for dietary supplements that are more nearly modeled after drug cGMP than food cGMP. In fact, the Industry Draft submitted by several trade associations in 1995 proposed at that time that certain of the provisions in drug cGMP be included in dietary supplement cGMP. An example of such a provision is the requirement proposed in the Industry Draft of a quality control unit with specific responsibilities and authority, a proposal that was modeled after 21 CFR 211.22. The Industry Draft also proposed that written procedures be established for numerous manufacturing procedures, and these proposals were similarly modeled after specific sections in 21 CFR 211. No provision exists in food cGMP for either a quality control unit with specific

[1] One could argue that the usual meaning and common definitions of the verb form, and also many common definitions of the noun form, have much narrower meanings than FDA's interpretation. Although AHPA has not been able to locate the exact reference cited by the agency, the *Riverside Webster II Dictionary*, Revised Edition, page 443 (1996; New York: Berkley Books) defines the noun "model" as, among other definitions, "A pattern on which something not yet produced will be based," and "One serving as an example to be emulated or imitated." This reference defines the verb "model" as, among other definitions, "To construct or plan, esp. after a model." Similarly, *The American Heritage Dictionary of the English Language*, 3rd edition, page 1160 (1992; Boston: Houghton Mifflin) provides the following definitions for the verb form: "To plan, construct, or fashion according to a model;" "To make conform to a chosen standard."

responsibilities and authority or for any written procedures. AHPA notes that FDA has also proposed provisions related to a quality control unit and to two written procedures in the Proposed Rule, but because no such provisions exist in food cGMP it is not accurate to state that these particular provisions are modeled after food cGMP.

As one of the organizations that submitted the Industry Draft, AHPA implicitly endorsed the inclusion of some provisions that are found in drug cGMP but not in food cGMP. AHPA believes, however, that some of the provisions in the Proposed Rule that are modeled after drug cGMP are inappropriate and further believes that FDA's legal authority is limited with regard to the creation of provisions in dietary supplement cGMP that are too closely modeled on cGMP for finished pharmaceuticals.

AHPA will provide specific comments later in this document as to those provisions in the Proposed Rule that are perceived as inappropriately modeled after cGMP for finished pharmaceuticals.

Inclusion of dietary ingredients in the Proposed Rule

DSHEA clearly authorizes the Secretary to prescribe good manufacturing practices for dietary **supplements** but not for dietary **ingredients**. AHPA is not aware of any other Federal law that specifically authorizes the establishment of cGMP for dietary ingredients.

AHPA notes that the cGMP in manufacturing, packing, or holding human food, as established in 21 CFR 110, explicitly includes "raw materials and ingredients" in the definition of "food" in that regulation. Thus, cGMP for food is relevant to both ingredients and finished foods. This is consistent with the statutory definition of "food" which includes "articles used for components of any such article [of food]." 21 USC 321(f)(3). On the other hand, the cGMP in manufacturing, processing, packing, or holding of drugs, as established in 21 CFR 210, and the cGMP for finished pharmaceuticals, as established in 21 CFR 211, do not purport to regulate raw materials or ingredients that are included in

drugs, even though the statutory definition of "drug" includes "articles intended for use as a component of any articles [of drug]...." 21 USC 321(g)(1)(D).

The Proposed Rule is identified as relevant to both dietary ingredients, i.e., specifically defined components of dietary supplements, and to dietary supplements. The statutory definition of "dietary supplement," unlike those for "food" and "drug" does not include components. 21 USC 321(ff). Notwithstanding AHPA's firm view that there is no specific authority for the establishment of cGMP for components of dietary supplements, i.e., dietary ingredients, and cognizant of the absence of consistency in the cGMP regulation of foods and drugs, AHPA supports the inclusion of dietary ingredients in cGMP for dietary ingredients and dietary supplements.

It must be noted, however, that although the Proposed Rule properly addresses many issues that are appropriate and necessary for any Final Rule for dietary ingredient cGMP, as can be seen in the AHPA Proposed Revision submitted as "Part 2 of 3" of these comments, AHPA believes that certain of the provisions in the Proposed Rule must be modified and opposes implementation of this Proposed Rule, for both dietary supplements and dietary ingredients, without appropriate modifications.

As noted earlier, AHPA believes that the agency should seriously consider modifying the Proposed Rule to incorporate each of the suggested changes made herein in order to make the Final Rule appropriately applicable to dietary supplements. If the agency accepts only those proposed revisions that address minor issues and rejects all other suggestion made in these comments, the resultant Final Rule would still be perceived by AHPA as an inappropriate rule for cGMP for dietary supplements and for dietary ingredients.

AHPA also wishes to acknowledge that it is aware that at least one other organization has expressed a position that opposes the inclusion of dietary ingredients in the Proposed Rule. While this may appear to represent a lack of agreement by the various industry representatives, the agency must keep in mind that AHPA also opposes the implementation of the Proposed Rule, for both dietary ingredients and dietary supplements, without appropriate modifications.

AHPA can not speculate as to whether the opposition expressed by others to including dietary ingredients in cGMP for dietary supplements would be mitigated by appropriate modifications to the Proposed Rule. As AHPA has suggested earlier in these comments, AHPA strongly encourages the agency to assure meaningful participation by stakeholders in the coming stages of this rulemaking so that issues such as these can be adequately discussed.

Impact of the Proposed Rule on intrastate commerce

AHPA notes that FDA discussed, in the March 13, 2003 *Federal Register* notice (68 FR 12166-7), its authority under the Public Health Services (PHS) Act to "issue and enforce regulations that, in the Commissioner's judgment, are necessary to prevent the introduction, transmission, or spread of communicable diseases from one State to another." FDA also noted, "Because this authority is designed to eliminate the introduction of diseases from one State to another, the Commissioner may exercise the authority over the disease-causing substance within the State where the food is manufactured, packaged, or held." In this introductory commentary on this matter, the agency concluded, "Thus, the agency is invoking its authority under the PHS Act in this proposed rule to prevent the spread of communicable disease from dietary ingredients or dietary supplements in intrastate and interstate commerce."

FDA discussed the relationship between dietary supplements and the PHS Act later in the March 13 notice (68 FR 12180), stating, "Dietary supplements may be regulated under the PHS Act to the extent necessary to prevent the introduction, transmission, or spread of communicable diseases in intrastate and interstate commerce." The agency provided the specific examples of products that contain "animal-derived ingredients," which "may carry infective agents that may not be able to be identified or that may be resistant to inactivation."

Nothing in these statements clearly articulates whether FDA believes that the Final Rule will be, in its entirety, binding on manufacturers, packers and holders of dietary supplements who are engaged solely in intrastate commerce,

nor has the agency requested comment on this topic. AHPA does not believe that FDA's authority for current good manufacturing practice for dietary ingredients and dietary supplements can extend to intrastate commerce except in the limited situation where communicable diseases may be involved. In any situation in which FDA needs to exercise its authority over any disease-causing substance within the State where a dietary ingredient or dietary supplement is manufactured, packed or held, it can and should act under its authority as granted by the PHS Act.

AHPA requests that the agency clearly state that the Final Rule is generally relevant only to interstate commerce and that its authority to apply final cGMP for dietary ingredients and dietary supplements in intrastate commerce is limited to those issues that are directly related to its authority under the PHS Act.

AHPA also wishes to point out that, while FDA stated in this discussion that it is "... not aware of dietary supplement manufacturers' current procurement and handling practices of [animal-derived] dietary ingredients, nor the extent to which such dietary ingredients may be used," the agency certainly should be aware of such practices and such extent. FDA has inspected and continues to inspect dietary supplement manufacturers who utilize animal-derived dietary ingredients and has programs directing how these inspections are to be performed. In addition, the FDA has been in communication with the dietary supplement industry on this subject for over a decade and AHPA and others submitted a substantial written report to FDA between June and December 2001[2].

Analysis of economic implications of the Proposed Rule

AHPA is concerned that the agency's discussion of the economic implications of the Proposed Rule may have significantly underestimated the costs that firms will bear in implement the Final Rule. This concern is based on

[2] "Dietary Supplement Industry: Self-Report Forms on Sourcing of Bovine Ingredients." Survey designed and compiled jointly by trade associations representing the dietary supplement industry: American Herbal Products Association; Consumer Healthcare Products Association; Council for Responsible Nutrition; National Nutritional Foods Association; Utah Natural Products Alliance. In 5 volumes. Submitted to FDA, June – September 2001.

information that has been provided by a number of AHPA member companies that have calculated the costs that they believe are associated with the Proposed Rule.

FDA estimated that the annual compliance costs for the Proposed Rule would range from $38,000 for very small firms to $61,000 for small firms and $47,000 for large firms. One very small firm, however, 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. In addition, 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. Each of these smaller firms has thus estimated costs about five to ten times greater than FDA's estimate. 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. AHPA does not at this time know to what degree the information provided by these few firms is representative of the industry.

AHPA is also concerned that other aspects of the agency's economic analysis may be in need of review. For example, in seeking to understand current industry practices, FDA has relied on information obtained from a survey of 238 companies that was conducted from November 1999 to February 2000. AHPA does not know whether this 3 year old information represents current industry practices and does not believe that FDA can represent this information as such. To begin with, a certain percent of the companies that responded three years ago are no longer in business. Also, it is possible that a number of business practices have changed in the intervening time.

In addition, certain of the information from that survey was presented inaccurately by FDA. For example, the agency reported, "36 percent of recently surveyed dietary supplement establishments do not follow any good manufacturing models for their products." 68 FR 12221. In fact, only 63 of the

238 respondents (26.5%) responded "no" to the question, "Does this plant follow a published GMPs model for the dietary supplement products produced at this plant?" In calculating the 36% reported by FDA, all of the sixteen companies who either stated that the question was "not applicable" or who did not answer the question were apparently included in those firms that "do not follow and good manufacturing models." Further challenging even the correctness of describing the 63 "no" responses as absent a cGMP model were these companies' responses to a follow up question that asked why cGMP was not followed. At least 29 of these 63 companies provided responses that indicated that the reason that they do not follow a published cGMP for products "produced at this plant" is that they did not produce products. Examples of such responses included: "It is not a manufacturing facility;" "All products distributed are produced by other companies;" "Not a plant;" "We don't manufacture;" etc.

Also in need of review are many 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.

For all of the reasons given here, AHPA has contracted with a firm that has expertise in economic analysis. In support of this contractor's efforts, an electronic request was submitted 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. This FOIA request was fulfilled on August 7, 2003.

No attempt has been made in the intervening days to evaluate this newly received data but AHPA believes that this information will greatly assist our understanding of the agency's economic assumptions and calculations. AHPA therefore submitted, on August 5, 2003, a request to the Dockets Management Branch for an extension of time for a period of 30 days after the fulfillment of this FOIA request. AHPA has now been informed that the agency will accept additional information from AHPA until September 9, 2003. It is therefore AHPA's

intention to submit additional information related to the economic impact of the Proposed Rule to the Dockets Management Branch not later than September 9, 2003.

Identification of key references for botanical identity

The requirement in proposed §111.35(e)(1) to establish a specification for identity for all received dietary ingredients, coupled with the various requirements that are related in some way to testing to assure that identity specifications are met (e.g., §§111.35(h); 111.35(l); and §111.60), has significant implications for the need to identify reliable resources of appropriate tests. This may be especially true for botanical ingredients.

Each of the specific options for testing that are identified at §111.35(l), i.e., organoleptic, microscopic and chemical tests, have relevance for botanical identity. In order for any of these tests to accurately identify a botanical ingredient, an appropriate analytical method must either be identified or developed for that ingredient.

AHPA wishes to make the agency aware of organizations that have established themselves as important resources in the development, review, and publication of analytical methods that are relevant to one or more of these specific analytical methodologies and that can be used in identifying a number of the more important herbal ingredients in trade. In addition, AHPA requests that FDA broadly disseminate this information to assure that the industry generally is familiar with these resources.

AHPA knows that FDA is already familiar with AOAC International and the United States Pharmacopeia (USP) as publishers of "standard compendial methods." 68 FR 12169. AOAC is actively engaged in developing methods for chemical analysis of several herbs, and USP currently lists methods for chemical analysis of nineteen botanical that are used as dietary ingredients. The monographs that USP has published also provide some additional information on certain macroscopic and microscopic characteristics.

AHPA considers the standards established by the following organizations to be scientifically valid: the American Herbal Pharmacopoeia (AHP), the European Pharmacopoeia (EP), and the World Health Organization (WHO). Combined, these three organizations have developed standards for more than 100 different botanicals as reflected in their currently completed monographs. The monographs of AHP and WHO contain methods of identification not contained in other sources, such as accurate morphological and microscopic descriptions. AHPA notes that non-chemical analyses, such as organoleptic and microscopic analyses, are extremely important, and often times more useful, in determining plant identity. Thus, methods or references that are relevant to these methodologies are essential.

Additionally, each of the monographs of these organizations have been developed and reviewed according to rigorous guidelines and subjected to international peer review prior to their adoption.

AHPA has found the AHP monographs to be among the most useful and scientifically credible sources of information about botanical ingredients, including information on identity testing and quality control parameters. Unlike other authoritative sources, AHP monographs provide numerous illustrations and photographic images detailing the gross and microscopic characteristics of each botanical, along with detailed chromatographic imagery relevant to chemical analysis. This information provides a valuable resource for assuring identity and quality of botanical ingredients, as a production sample received by a firm can be tested with the various methods and references published in these texts. AHP monographs also provide information regarding optimal harvest times and handling and drying conditions. These parameters are valuable for botanical ingredient quality control and are not addressed by any of the identified compendial sources.

The information in the AHP, EP, and WHO monographs is extremely valuable to AHPA members in complying with cGMPs and should be recognized as such by FDA as scientifically credible resources for identifying botanical dietary ingredients. Such recognition would provide AHPA members and other

manufacturers with clearer guidance to assist in accessing internationally recognized standards for more than 100 botanicals.

Comments to Specific Sections of the Proposed Rule

In order to evaluate the degree of acceptance of the Proposed Rule on manufacturers and marketers of dietary supplements, AHPA conducted five regional meetings with numerous of its members and several non-member companies between May 22 and June 12, 2003. A total of 94 individuals from 65 companies attended one of these meetings. The participating individuals included about six persons who are or represented consultants, academics or analytical labs. All of the other attendees represented companies that manufacture and/or market dietary ingredients and/or dietary supplements.

Based on the input received from this broad cross-section of the industry, AHPA has prepared a "redline" draft revision of the Proposed Rule (the "AHPA Proposed Revision") that incorporates the identified concerns. The AHPA Proposed Revision is enclosed here and is presented as an integral part of these comments. The balance of AHPA's comments in this section are directly related to and explain the rationale for each of the changes proposed in the AHPA Proposed Revision.

Section 111.3

- AHPA notes that the definition for "component" given in §111.3 includes "dietary ingredients as described in section 201 (ff) of the Act." Nevertheless, the Proposed Rule uses the terms "component, dietary ingredient;" "component or dietary ingredient;" "component and dietary ingredient;" and similar terms through the document. AHPA recommends that these terms be replaced throughout with the word "component." It should be noted that these suggested changes have not been made in the AHPA Proposed Revision.
- AHPA suggests that the definition for "consumer complaint" be changed to "customer complaint." AHPA believes that the common meaning of the

word "consumer" refers to the end product consumer. *The American Heritage Dictionary of the English Language*, 3rd edition,[3] defines consumer as, "One that consumes, especially one that acquires goods or services for direct use or ownership rather than for resale or use in production and manufacturing" (emphasis added).

By limiting the definition to complaints by consumers, the Proposed Rule implies that any complaint that involves a possible failure of a dietary ingredient or dietary supplement to meet any of its specifications by any other person, for example by a manufacturer who purchases dietary ingredients or a retailer who purchases products for resale, would be excluded under the Proposed Rule. AHPA believes that such complaints by persons other than finished-product consumers should be addressed in the final rule.

- The terms "batch" and "lot" are defined so that they are in some sense related ("Lot means a batch, or a specific identified portion of a batch...") but different terminology is given as to their meaning. On the one hand, a batch is defined as "intended to meet [certain] specifications" while a lot, which by the given definition can be a batch, is defined as "intended to have [certain] uniform" qualities, including identity, purity, quality, strength and composition.

  AHPA believes that the inconsistencies in these definitions are confusing. Further, AHPA believes that the terminology in the definition of batch should be used for both of these terms, i.e., that a lot should be defined as, "a batch, or a specific identified portion of a batch intended to meet specifications for identity, purity, quality, strength, and composition; or, in the case of a dietary ingredient or dietary supplement produced by continuous process, a specific identified amount produced in a specified unit of time or quantity in a manner that is intended to meet specifications for identity, purity, quality, strength, and composition."

[3] Soukhanov, AH, executive editor. 1992. *The American Heritage Dictionary of the English Language*, Third Edition, page 405. Boston: Houghton Mifflin Company.

- AHPA proposes that the definition of "sanitize" be modified and that an additional definition be given for "sanitizing agent." This proposal is based on a concern that the current definition implies that there will be a reduction of 5 logs (i.e., a 99.999 percent reduction) each and every time a sanitizing agent is used, even on an already clean and nearly sanitary surface.

  AHPA also does not believe that the agency's proposal to borrow the definition of a sanitizing agent from the FDA Food Code is appropriate or is consistent with the statutory mandate to model this cGMP after food cGMP. To include the proposed FDA food Code definition in this regulation, as opposed to, for example, some guidance that might be provided by the agency some time in the future would create a regulatory standard for dietary supplements that goes beyond not only current food regulations but also the current cGMP for drugs.

  AHPA therefore proposes that the term sanitize be defined to mean " to adequately treat equipment, containers, utensils, or any other dietary product contact surface by applying a sanitizing agent on cleaned food contact surfaces," and that the term sanitizing agent be defined to mean "cumulative heat or chemicals that, when applied on cleaned food contact surfaces reduce microorganisms of public health significance to a level that is adequate to prevent risks to public health and substantially reduce the numbers of other undesirable microorganisms, but without adversely affecting the product or its safety for the consumer."

Section 111.6

- AHPA requests that the process of dehydration of raw agricultural commodities be specifically included as one of the exclusions in §111.6. Dehydration of botanicals is a common farm practice for those botanicals that are harvested for use in dietary supplements and in fact the majority of botanical ingredients in dietary supplements are in dehydrated form. Farmers and harvesters of these ingredients need not, and should not be

bound by the cGMP that is relevant to manufacturers, packers, and holders of dietary ingredients and dietary supplements.

- Another common practice of farmers and harvesters that produce botanicals used in dietary supplements is size reduction (grinding, milling, etc.) of the raw agricultural commodities produced. AHPA requests that persons that grind or mill the raw agricultural commodities that they produce be excluded from the Final Rule, by adding language such as, "or to size reduction (e.g., grinding, milling, or chopping) of a raw agricultural commodity that is conducted by the same person who harvests the commodity."

  In making this request, AHPA does not mean to request that firms that are engaged in grinding, milling, or chopping of botanicals that are harvested by any other firm or person should be excluded from the Final Rule, and in fact AHPA members who are engaged in such businesses have expressed their belief that they should be made to conform to the Final Rule.
- There are numerous academic institutions that provide training for therapeutic disciplines that use, for example, herbal formulas in their practice. AHPA believes that the Final Rule should specify that it does not apply, "to academic institutions that provide training in dispensing of nutritional or herbal products and formulas related to courses in therapeutic disciplines that provide such products and formulas as a part of their therapy, for example, naturopathy, herbalism, traditional Chinese medicine, and acupuncture." Such institutions do not offer the products that are produced in their training into broad commerce but such products may be made available in a clinical setting associated with the institution[4].

[4] This issue might be moot if the agency intends the Final Rule to be relevant only to interstate commerce. On the other hand, AHPA believes that the agency defines as interstate commerce the activities described here if the academic institution purchases any of its herbal ingredients in interstate (or international) commerce. If the agency does, in fact, define such activity as interstate commerce, AHPA continues to believe that the requested exclusion be allowed. Also, see AHPA's comments above, "Impact of the proposed rule on intrastate commerce."

AHPA believes that an exclusion to the Final Rule should be clarified so as to assure that such institutions are not reduced to proving training about herb identification with photographs or other tools, but will be able to continue to use herbal specimens to assure proper training.

- Numerous health care providers offer (i.e., dispense to) their patients dietary supplements. Many health care providers also provide an on-site service that consists of producing and/or blending herbal or nutritional formulas that are specifically formulated for an individual patient. AHPA believes that the Final Rule should specify that it does not apply, "to clinics where health care providers practice and where nutritional or herbal products or formulas are produced or mixed for dispensing to persons under the direct care of the health care providers." Such clinics do not offer the products that are produced and/or mixed for persons under their direct care into broad commerce[5]. AHPA believes that an exemption from the Final Rule should be clarified so as to assure that such health care providers can continue to offer a valuable service to their patients.

Section 111.10

- The Proposed Rule would, at §111/10(a)(1), correctly exclude persons who are ill or is otherwise a source of microbial contamination, from work that might contaminate products. AHPA believes, however, that the specific language in this subparagraph is too broad in stating that such person be excluded "from working in any operation." Rather, such person may be suitable for performing, for example warehouse or administrative work.

  AHPA Therefore requests that this language be modified to communicate that it would be acceptable for such person to work so long as they will not be a vector for microbial contamination, and suggests that the words, "in any operations involving direct contact with components,

[5] See above footnote as this is equally relevant to this issue.

including dietary ingredients, dietary supplements, equipment or product contact services," be added after the word "operations."

Section 111.12

- The Proposed Rule states in §111.12(b) that the qualifications for all personnel engaged in manufacturing, packing and holding dietary ingredients and dietary supplement must include both "training and experience" (emphasis added). AHPA notes that this requirement differs from the current good manufacturing practice for foods, as codified in 21 CFR 110, in two particulars, and reminds FDA that its statutory authority explicitly states that cGMP for dietary supplements be modeled after food cGMP. First, 21 CFR 110 addresses the "education and training" only of those personnel "responsible for identifying sanitation failures or food contamination," and second, that such personnel "have a background of education or experience, or combination thereof " (emphasis added).

  AHPA has no comment as to the stated intention of the Proposed Rule to extend qualification requirements to all personnel, and in fact supports this extension. AHPA does not, however, believe it to be appropriate to require both training and experience for all employee positions. AHPA believes that the logical implication of such duplicative requirements can be interpreted to mean a person with training as a Ph.D. in pharmacognosy who has no work experience for an herbal supplement manufacturer (training but no experience) would not be considered qualified, or that a person who had decades of experience in identifying plants but had no academic degrees (experience but no training) would not be considered qualified. AHPA believes that any combination of training or experience that provides the requisite qualifications for personnel engaged in manufacturing, packing or holding dietary ingredients and dietary supplements should be recognized.

  AHPA therefore requests that 111.12(b) be changed to read, "Each person engaged in manufacturing, packaging, or holding must have the

training or experience, or a combination thereof, to perform the person's duties."

Section 111.13

- For exactly the same reasons as articulated in the last comment, AHPA requests that 111.13(b) be changed to read, "You and the supervisors you use must be qualified by training or experience, or a combination thereof, to supervise."

Section 111.15

- The Proposed Rule at §111.15(b) would establish a requirement related the quality of cleaning and sanitizing agent that is similar to requirements in the cGMP for food. AHPA notes, however, that food cGMP specifies that a firm's compliance under this requirement can be verified by means that include purchase of such substances under a supplier's guarantee or certification.

  AHPA therefore requests that the following sentence, that is, the same sentence found in 21 CFR 110.35(b), be added at the end of this subparagraph: "Compliance with this requirement may be verified by any effective means including purchase of these substances under a supplier's guarantee or certification, or examination of these substances for contamination."
- Pest control and the exclusion of animals and pests is addressed in §111.15(c)(1) and (2). While AHPA supports such requirements, it must be acknowledged that dietary ingredients are sometimes manufactured in extensive, highly automated facilities in which large tanks and vessels are interconnected via piping. In these cases "the physical plant" and "the equipment in the plant" may converge so that some or much of the equipment is effectively located outdoors. The existing language would seem to imply that such equipment must be enclosed in a separate structure in order to prevent animals and pests from contacting the outside

of the sealed equipment. In fact, such an enclosure is not necessary to prevent adulteration as long as the equipment is properly sealed.

AHPA therefore proposes the addition of the word "interior" before the word "area" in §111.15(c)(1) and the words "interior area of your" prior to the word "physical" in §111.15(c)(2) in order to clarify that it is the interior of the structures that must be protected.

- The Proposed Rule at 111.15(d)(2) would establish a requirement that, "Water that contacts dietary supplements, components, dietary ingredients, or any contact surface must at a minimum comply with the National Primary Drinking Water regulations prescribed by the Environmental Protection Agency under 40 CFR part 141 and any state and local government requirements."

AHPA agrees that such requirement is appropriate for water that contacts dietary supplements or contact surfaces, as such water may directly affect the cleanliness of a dietary supplement in a form in which it will be consumed. AHPA does not, however, believe such a requirement is either necessary or feasible for components, including dietary ingredients. AHPA notes that the current good manufacturing practice for foods, at 21 CFR 110.37, requires only that water supplies that contact food (defined to include ingredients and raw materials) be "safe and of adequate sanitary quality." This is consistent with the statutory basis for cGMP for foods, i.e., that food has not been prepared "under unsanitary conditions whereby it may have become contaminated with filth, or whereby it may have been rendered injurious to health." 21 USC 342(a)(4). AHPA believes that a similar definition must be applied in the Final Rule for components, including dietary ingredients.

Components, including dietary ingredients, are not in a form in which they will be consumed and are subject to further processing prior to consumption. AHPA therefore requests that §111.15(d)(2) be modified to read, "Water that contacts dietary supplements or any contact surface must at a minimum comply with the National Primary Drinking Water

regulations prescribed by the Environmental Protection Agency under 40 CFR part 141 and any state and local government requirements; water that contacts components, including dietary ingredients, must be safe and of adequate quality to ensure the non-adulteration of finished products in which the component is included as an ingredient."

- The Proposed Rule at 111.15(j) requires the assignment of one or more employees to supervise overall sanitation. These supervisors are required by the Proposed Rule to be "qualified by training and experience to develop and supervise sanitation procedures" (emphasis added).

  For exactly the same reasons as articulated in AHPA's comment to §111.12 of the Proposed Rule, AHPA requests that 111.15(j) be changed to read, "You must assign one or more employees to supervise overall sanitation. These supervisors must be qualified by training or experience, or a combination thereof, to develop and supervise sanitation procedures."

Section 111.20

- The Proposed Rule requires that a physical plant permit the use of proper precautions to prevent mixups and prevent contamination. §111.20(c) provides an example of one such feature that a firm "must use" as "computerized inventory controls."

  AHPA believes that inventory controls that are not computerized may be equally valuable for the purposes described in this paragraph. AHPA therefore requests that the word "computerized" be changed to "adequate."

- The Proposed Rule requires that a physical plant be designed and constructed in a manner that prevents contamination, and, at §111.20(d)(1), that such design and construction include, "Floors, walls, and ceilings that are of smooth and hard surfaces that can be adequately cleaned and kept clean and in good repair" (emphasis added).

  AHPA believes that the specificity of this requirement establishes a conundrum for certain manufacturers' requirements to conform to other

Federal regulations. For example, in order to maintain noise levels in a grinding room that comply with the occupational noise standards established by the Occupational Safety and Health Administration (see OSHA Technical Manual, Section III, Chapter 5), a firm might, among other things, design the grinding room with a ceiling that is not smooth but still cleanable in order to lessen the machinery noise. Such firms should be allowed to simultaneously conform to both OSHA and FDA requirements.

AHPA notes that such specific surfaces are not required by the cGMP for foods codified in 21 CFR 110. AHPA further notes that even in the current good manufacturing practice for finished pharmaceuticals, and specifically in 21 CFR 211.42(c)(10)(i), "smooth, hard surfaces" are only mandated for floors, walls and ceilings in facilities used for aseptic processing, and even this requirement is modified with the term, "as appropriate." There is no logical reason why the entire facility in which dietary ingredients and dietary supplements are manufactured, packed, or held should be required to be constructed of smooth, hard surfaces when there is no such broad requirement for finished pharmaceuticals.

AHPA therefore requests that the words "that are of smooth and hard surfaces" be deleted from this paragraph.

- The Proposed Rule also requires, at 111.20(d)(4), that a physical plant "must include... [f]ans and other air-blowing equipment to be located and operated in a manner that minimizes the potential for microorganisms and particulate matter to contaminate components, dietary ingredients, dietary supplements, or contact surfaces."

  AHPA believes that there are instances in which fans are not necessary to minimize the potential contamination described above. The Proposed Rule as written would mandate that fans be installed even when they are not necessary. AHPA therefore requests that this paragraph be rewritten to state, "Fans and other air-blowing equipment, if such are necessary, to be located and operated in a manner that minimizes the

potential for microorganisms and particulate matter to contaminate components, dietary ingredients, dietary supplements, or contact surfaces."

- The Proposed Rule requires, at 111.20(d)(5), that a physical plant "must include... [e]quipment that controls temperature and humidity."

AHPA believes that there are instances in which temperature- and humidity-controlling equipment is not necessary to assure that dietary ingredient and dietary supplements are properly manufactured, packed and held. The Proposed Rule as written would mandate that such equipment be installed even when not necessary. AHPA notes that there is no specific requirement for use of such equipment required in cGMP for foods and that the requirement for such equipment in facilities that manufacture, pack or hold finished pharmaceuticals is specifically limited to a mandate that they "be provided when appropriate" (see 21 CFR 211.46(b)).

AHPA therefore requests that this paragraph be rewritten to state, "Equipment that controls temperature and humidity if such equipment is necessary to prevent adulteration," or "Equipment that controls temperature and humidity shall be provided when appropriate."

Section 111.25

- The Proposed Rule at §111.25(b)(1) would require that all instruments and controls used in manufacturing or testing a component, including a dietary ingredient, or a dietary supplement, be calibrated; specifically mandated scheduling for such calibration is described in §111.25(b)(2).

AHPA does not believe that every instrument and control used in manufacturing or testing products must be calibrated in order to assure that a product meet its specifications. For example, though a processor may use a sieve or a compressor in the manufacturing of a dietary supplement, standard industry practices do not include calibration of these instruments, nor is calibration necessarily required to assure that a

product meets established specifications. Similarly, there is no reason to calibrate an electronic scanning system used by a manufacturer and additional examples can be identified. AHPA also notes that the cGMP for drugs mandates calibration only for automatic, mechanical and electronic equipment (see 211.68(a)).

AHPA also believes that this regulation should clearly express flexibility to allow a contractor or the manufacturer of certain instruments to perform calibration services on behalf of a firm. Calibration of many kinds of specialized and refined instruments, such as manometers or mass standards, must be performed by the appropriate experts.

AHPA therefore suggests that the phrase "or have calibrated" be added immediately following the existing word "calibrated," and that the following phrase be added at the end of §111.25(b)(1): "and that are critical to achieving specifications established in paragraph 111.35." Conforming language will then need to added to §111.25(b)(2).

AHPA is also concerned that the detailed schedule for calibration described in §111.25(b)(2) is unnecessarily proscriptive and that other schedules than the one that would be required by this part could be equally effective in assuring the proper operation of calibrated instruments and controls.

Section 111.30

- AHPA believes that this entire section is redundant to other sections, in almost every detail, and could be removed without any meaningful effect. For example, §111.30(a)(1) and (2) require that all automatic, mechanical and electronic equipment be designed or selected to ensure that product specifications are consistently achieved and operate satisfactorily within the operating limits required by the process. These requirements are already established by §111.25(a)(1) and more specifically by §111.25(a)(1)(v), which states that all equipment, whether or not automatic, mechanical or electronic, but specifically including equipment

used in automatic, mechanical and electronic systems, must be suitable for the intended use of the equipment. It is apparent that the intended use of equipment used to manufacture, pack or hold a product is to operate satisfactorily within operating limits, and by extension, to consistently meet the product's specifications. While AHPA is aware that separate regulations are proscribed in cGMP for finished pharmaceuticals in 21 CFR 211.68 for automatic, mechanical and electronic equipment used in the manufacture of drug products, AHPA notes that the drug regulations for all equipment, as stated in §§211.63, 211.65, and 211.67, consisting of 324 words, is much less detailed that the corresponding paragraph in the Proposed Rule, i.e., §111.25, consisting of 1052 words, despite FDA's efforts to present the Proposed Rule in "simplified language."

Nevertheless, AHPA offers the following comments to proposed §111.30.

- AHPA believes that the requirements proposed in §111.30(a) and (b)[6] should be limited to automatic, mechanical or electronic equipment that actually affect product specifications. In a modern manufacturing facility, most if not all equipment used to manufacture, package, label or hold any food product is automatic, mechanical, or electronic. For example, a forklift, used in the holding of dietary ingredients and dietary supplement, is certainly mechanical. A forklift should not be required however, to be designed or selected in a manner that ensures that product specifications are met, as would be required in proposed §111.30(a)(1), or to be calibrated, as would be required in §111.30(b)(1), as the forklift does not affect product specifications.

  AHPA therefore requests that the requirements envisioned in §111.30(a) and (b) be specifically limited to automatic, mechanical or electronic equipment that "affects the specifications of a dietary ingredient

[6] AHPA questions why §111.30 is separated into two subparagraphs, (a) and (b), when there is no meaningful difference between these subparagraphs.

or dietary supplement" by adding such language in both of these paragraphs.

- It is AHPA's view that the specific language used in §111.30(a)(1) and (2) has the effect of establishing unnecessarily stringent and expensive validation requirements on equipment design, selection, and capability, and that this language represents a *de facto* "IQ/OQ/PQ" (installation qualification / operational qualification / performance qualification) requirement. Emphasis should instead be directed to actual use and actual operation. AHPA therefore requests that, in §111.30(a)(1) the words, "Design and select equipment to ensure" be replaced with the words, "Use equipment that ensures;" and that, in §111.30(a)(2) the words, "is capable of operating" be replaced with the word, "operates."
- The regulation proposed in §111.30(b)(5) would require that backup files of software program and data entered into computer systems be made and kept.

  AHPA notes that many software programs are in a near constant state of revision and believes that it is not a common business practice for a firm in any industry to maintain records of outdated software programs, at least if the firm is still able to access data that was entered with an outdated software program that can still be accessed with a revised program. AHPA also notes that, although the cGMP for finished pharmaceuticals, at 21 CFR 211. 68(b), requires the maintenance of certain backup files of date entered into computer systems, it does not require the maintenance of backup files of software programs.

  AHPA therefore requests that the words "software programs and" be stricken both times they appear in §111.30(b)(5).

  AHPA also believes that the requirement for maintenance of backup files of data entered into computer systems should be limited to that data that is entered into computer systems that are relied upon for compliance with cGMP. AHPA believes that the paragraph as written implies that a firm must make and keep backup files of data entered into,

for example, computers on which personnel payroll records are maintained, and believes that no such requirement should be implied.

AHPA therefore requests that the words "your computer system" should be replaced with the words "any of your computer systems that are relied upon for compliance with this part."

Section 111.35

- Proposed §111.35(b) requires that a production and process control system "be designed to ensure" absence of adulteration. For reasons similar to the rationale offered in the comments provided above to §111.30(a)(1) and (2), AHPA requests that the words "be designed to" be removed, and that firms simply be required to make the required assurance.
- FDA has proposed in §111.35(d) to restate and, in some instances, provide new interpretations for existing regulations that govern food additives, color additives, and other issues. AHPA believes that the entire paragraph at §111.35(d) is redundant and unnecessary. This paragraph states, in essence, "other parts of existing Federal regulations that are binding on manufacturers of dietary supplements continue to be Federal regulations that are binding on manufacturers of dietary supplements."

  It is no more or less sensible to include this paragraph in cGMP for dietary ingredients and dietary supplements than it would be to expand it, for example, by stating, "Any substance that is a new dietary ingredient within the meaning of section 413 of the Act the intended use of which results in its becoming an ingredient of a dietary supplement, must be the subject of premarket notification consistent with Sec. 190.6 of this chapter." There would be absolutely no reason to add such a part to this new regulation as it would not make the existing regulation at 21 CFR 190.6 any more or less binding on a firm.

  It is no more or less sensible to include this paragraph in cGMP for dietary ingredients and dietary supplements than it would be to include

significantly similar language in the cGMP for foods, for example by adding a new section to 21 CFR 110 that redundantly states that food additive, prior sanction and color additive provisions that currently apply to the manufacture of foods continue to apply to the manufacture of foods. There would be absolutely no reason and it would be nonsensical to suggest such a revision to the cGMP for food – it is equally unreasonable and nonsensical to propose the inclusion of §111.35(d) to cGMP for dietary ingredients and dietary supplements.

AHPA requests that this entire paragraph be withdrawn.

AHPA can not speculate as to whether FDA will accept the request that paragraph §1111.35(d) be excluded in its entirety. In the event that any part of this redundant requirement remains, however, AHPA offers the following additional thoughts on proposed §111.35(d)(3) in the matter of color additives as the agency has, by stating this proposal, offered an interpretation of the existing regulation.

The agency has proposed to limit the use of color additives in dietary supplements to those that are "subject to a listing that, by the terms of that listing, includes the use in a dietary supplement." It is AHPA's position that the terms of this proposed regulation is to restrictive. If this proposed regulation were to be applied literally only seven colors could be used for dietary supplements as it is only these colors that specifically that they may be "safely used for coloring foods (including dietary supplements)." These colors are: FD&C Blue No. 1 (listed at §74.101); FD&C Blue No. 2 (listed at §74.102); FD&C Green No. 3 (listed at §74.203); FD&C Red No. 3 (listed at §74.303); FD&C Red No. 4 (listed at §74.340); FD&C Yellow No. 5 (listed at §74.705); and FD&C Yellow No. 6 (listed at §74.706).

Since all of these color regulations were promulgated prior to the enactment of DSHEA, however, we believe it is artifactual because DSHEA's definition of dietary supplement did not exist. A more logical approach for the Proposed Rule in this matter would be to apply it to all

colors that are currently listed as "safely used for the coloring of foods generally." This interpretation would allow the use in dietary supplements of each of the following: annatto extract (in §73.30); dehydrated beets (in §73.40); canthaxanthin (in §73.75); caramel (in §73.85); β-Apo-8'-carotenal (in §73.90); β-carotene (in §73.95); cochineal extract and carmine (in §73.100); toasted partially defatted cooked cottonseed flour (in §73.140); fruit juice (in §73.250); vegetable juice (in §73.260); carrot oil (in §73.300); paprika (in §73.340); paprika oleoresin (in §73.345); riboflavin (in §73.450); saffron (in §73.500); titanium dioxide (in §73.575); turmeric (in §73.600); and turmeric oleoresin (in §73.615).

This reading is, in AHPA's view, the most reasonable, against the background of the purpose of the Color Additives Amendments and DSHEA. There is one additional rationale for this position, FDA has correctly noted that any ingredients that are approved or GRAS for food use, not simply dietary supplement use, as to which there would be very few, may be used as "other ingredients" in dietary supplements. In addition, AHPA believes that colors permitted for ingested drugs should also be included for dietary supplements in tablet, capsule and gelcap form. Since each of the following colors is approved for use in drugs for ingestion, they should be permitted for use in dietary supplements in tablet, capsule and gelcap form. These are: annatto extract (in §73.1030); canthaxanthin (in §73.1075); caramel (in §73.1085); β-carotene (in §73.1095); synthetic iron oxide (in §73.1200); and titanium dioxide (in §73.1575).

- Numerous requirements for the establishment of specifications are set out in proposed §111.35(e). AHPA believes that clarification as to the operations that are subject to the specifications that are addressed in this subparagraph must be provided. It is not realistic or appropriate to require a firm to establish specifications for the entire manufacturing process if that firm is only responsible for certain elements of that process. Rather, their requirements must be limited to those under their control. In addition,

AHPA does not believe that FDA intended to relieve packagers from establishing specifications for the identity, and as necessary, for the purity, and insofar as claimed, the quality, strength or composition of dietary ingredients and dietary supplements they package, nor does AHPA believe such requirements should be missing in this rule. AHPA therefore requests that the words "the manufacturing process" be changed to "your manufacturing and packaging process."

- §111.35(e)(1) of the Proposed Rule would require the establishment of specifications for the "identity, purity, quality, strength and composition" of components, including dietary ingredients, and of dietary supplements that are received by manufacturers, packers and holders of dietary ingredients and dietary supplements.

  The specific language proposed in this paragraph is obviously modeled after cGMP for finished pharmaceuticals. For example, 21 CFR 211.100(a) requires "written procedures for production and process control designed to assure that the drug products have the identity, strength, quality, and purity they purport or are represented to possess" (emphasis added). The term, "identity, strength, quality, and [or "or"] purity" is repeated nineteen times in 21 CFR 211, in reference to issues such as, for example, testing and approval of components, containers and closures; in-process materials; expiration dating; warehouse procedures; equipment construction and maintenance; the responsibilities of the quality control unit; and qualifications of supervisors. This term is not found in the cGMP for food.

  It is AHPA's strong belief that the term "identity, purity, quality, strength and composition" must have limited applications in the Final Rule and that this term must be, in many of the uses for which it is included in the Proposed Rule, modified and separated into its individual attributes. It may also be necessary to define each of these separate attributes.

  AHPA believes that it is appropriate and acceptable to establish a requirement, as proposed in §111.35(e)(1), for a specification of the

identity of components, including dietary ingredients, and dietary supplements that are received by a manufacturer[7].

AHPA also believes it is appropriate and acceptable to establish a specification for purity of such ingredients and products, insofar as such specification is necessary to assure that components and dietary supplements are not contaminated with substances having public health significance.

With regard to each of the other attributes identified by FDA and modeled after drug cGMP, AHPA believes that specifications for quality, strength and composition of components and dietary supplements received by a manufacturer should only be required for the quality, strength and composition that a component or dietary supplement is purported to possess. This would provide the same requirement that is currently established for drug products and processing.

As is obvious by the emphasized citation to 21 CFR 211.100(a) above, the unmodified requirements in the Proposed Rule to establish specifications for all five of these attributes establish a demand on components, including dietary ingredients, that are used in dietary supplements, and dietary supplements themselves that goes beyond the current requirements in cGMP for finished pharmaceuticals. This is certainly unnecessary and it can not be fairly argued that such requirements are "modeled after" food cGMP.

AHPA believes that, aside from the facts that such unmodified requirements are unnecessary and go beyond the agency's authority, they are also confusing. AHPA believes that the proposals related to specifications of identity, purity, quality, strength and composition are often nonsensical for botanical dietary ingredients and that the agency has

[7] Whether the requirements for the establishment of specifications discussed here should be made for all firms that pack dietary supplements is less clear, and AHPA does not believe that a firm that is involved only in holding a supplement, for example a finished product distributor or retailer, should be required to set such specifications for the packaged goods they receive.

attempted to shove the round peg reality of these ingredients into the square box requirements of drugs.

The agency has not defined any of these five terms but has provided commentary in the March 13, 2003 *Federal Register* notice. In discussing the proposed definition of "batch," (the first instance in the Proposed Rule in which the term "identity, purity, quality, strength and composition" is used), the agency stated, "The phrase 'identity, purity, quality, strength, and composition,' means that the production on a batch-by-batch basis is consistent with the master manufacturing record and is what it is represented on the label to be (identity); is without impurities and is the desired product (purity); is the identity, purity, and strength for its intended purpose (quality); is the concentration, that is, the amount per unit of use intended (strength); and is the intended mix of product and product-related substances (composition)." 68 FR 12176.[8]

Using this guidance from the notice, and as an example, §111.35(e)(1) as written would require that a manufacturer of peppermint leaf tincture establish specification for the peppermint leaf it receives, including its identity; its purity; its quality; its strength; and its composition. There is no stated or implied option for any of these specifications. The clear implication of this language is that specifications for each of these attributes must be established. Thus, it appears as if such manufacturer would need to state that the ingredient's identity is peppermint leaf (*Mentha ×piperita*). Specifications for purity might include, or might not include, a maximum tolerance for peppermint stems, other foreign organic matter, and ash, and could also include limits for heavy metals or for pathogens that are known to occasionally contaminate peppermint leaf.

A specification for strength of peppermint leaf could arguably be the percentage of menthol (though that is not related to the language offered by FDA: "concentration, that is, the amount per unit of use intended;" but

[8] AHPA finds each of these definitions imprecise and will communicate separately suggestions that can provide more clarity.

AHPA is not clear as to the meaning of those words). Such a specification can be related to the "strength" of a peppermint leaf extract, but there are means other than quantifying one flavor constituent to identify strength. Also, if it is this kind of specification that is proposed, what is the strength of burdock root? ...of ophiopogon tuber? ...of any number of other herbal ingredients for which there is no readily identified constituent that denotes strength?

Another interpretation of the proposed requirement to specify strength could be met by requiring "98% peppermint leaf" (assuming that there is 2% stem) but such a specification would be redundant to that suggested here for purity, and would not meaningfully address the ingredient's strength.

Still another interpretation for strength could be related to the concentration of the peppermint leaf, **if** it is received as a powdered extract. In such a scenario it is logical and appropriate to establish a specification for strength, for example, 3:1 extract of peppermint leaf. If this is the purpose for which FDA has proposed that strength be stated, it must clarify its purpose, and it must not establish a requirement for the strength of a dietary ingredient for which there is no rational requirement (peppermint leaf) just because it can identify an ingredient for which there is such a rational requirement (peppermint leaf powdered extract, 3:1).

AHPA is concerned that at the same time that FDA has proposed to require specifications for "quality," as differentiated from "identity, purity and strength," the agency has not actually articulated such differentiation. This is evident in the identification in the March 13, 2003 notice of quality as "the identity, purity, and strength for its intended purpose." Nevertheless, AHPA can conceive of quality attributes that might be claimed for a product that are not specifically related to identity, purity or strength (color; taste; etc.). AHPA does not oppose a requirement for specifying quality, but believes this requirement must be limited to quality

attributes that an ingredient is purported to possess, that is, to the same limitation that is established in this regard for drugs

Finally, AHPA also believes that a specific requirement for specifying composition must be limited to composition attributes that an ingredient is purported to possess. Without such limitation on this requirement, what is to prevent an assumption that the specified composition of peppermint must identify all of the elements of its chemical makeup, or even its DNA? AHPA believes that the intention of this requirement is probably limited to "composed ingredients," that is, ingredients that consist of more than one ingredient, as opposed to more than one innate constituent (for example, Peppermint Water is composed of water and peppermint oil) – but that is not what this part of the Proposed Rule actually says.

To summarize this example of peppermint leaf received by this hypothetical manufacturer, the "specification sheet" could read:

- Identity: Peppermint leaf (*Mentha piperita*)
- Purity: Not more than 2% of stems more than 3 mm in diameter and other foreign matter
- Quality: 98% pure peppermint leaf
- Strength: 98% pure peppermint leaf
- Composition: Peppermint leaf

As is obvious by this example, the proposal to establish these five specifications for all dietary ingredients will not meaningfully contribute to any assurance of product quality and will not protect the public health. The rule as written would require the establishment of specification that will, in many cases, be meaningless.

AHPA has been informed that, in response to questions posed in public meetings with FDA personnel since the publication of the Proposed Rule, FDA personnel have stated that, since the specifications required in this part are to be established by the firm that receives components,

including dietary ingredients, and dietary supplements, the more troubling concerns or nonsensical examples given here would not actually cause any concerns, as a firm could choose to set no specifications or could set specifications simply for the sake of conforming to the rule. AHPA sincerely hopes that these comments have been misreported. While AHPA has not yet located transcripts of any of these meetings, if this is an accurate representation of the agency's position at a public meeting it is not consistent with the Proposed Rule. The Proposed Rule at §111.35(e)(1) is quite specific: "Specifications must be established for... the strength and composition of... dietary ingredients... you receive." That does not say, "if you think you should," rather it demands that these specifications be set.

For all of the reasons given here, AHPA strongly requests that FDA reword §111.35(e)(1) as follows: "The identity and, where necessary to assure that components or dietary supplements are not contaminated with substances having public health significance, the purity of components, including dietary ingredients, or dietary supplements that you receive. Specifications must also be established for quality, strength and composition of components and dietary supplements you receive if specifications for these attributes are necessary to assure accurate representation of the received components, including dietary ingredients, or dietary supplements or of manufactured or packed products in which these received components or dietary supplements are subsequently included."

- Consistent with the immediately preceding comments, AHPA requests that the requirements for establishment of specifications for in-process controls, as stated in §111.35(e)(2), be reworded to take into account that specifications for attributes of quality, strength and composition should not be required for a product that does not purport to possess such attributes, as follows: "The in-process controls in the master manufacturing record where control is necessary to ensure the identity or purity, or, if

established for the product that is the subject of the master manufacturing record, the quality, strength, and composition of dietary ingredients or dietary supplements."

- Consistent with the above commentary to §111.35(e)(1), AHPA requests that the requirements for establishment of specifications for manufactured dietary ingredients and dietary supplements, as stated in §111.35(e)(3), be reworded to take into account that specifications for attributes of quality, strength and composition should not be required for a product that does not purport to possess such attributes, as follows: "The identity and, where necessary to assure that dietary ingredients are not contaminated with substances having public health significance, the purity of the dietary ingredients or dietary supplements that you manufacture. Specifications must also be established for quality, strength and composition of dietary supplements and dietary supplements you manufacture if specifications for these attributes are necessary to assure accurate representation of the manufactured dietary ingredients or dietary supplements or of manufactured or packed products in which these manufactured dietary ingredients or dietary supplements are subsequently included.
- §111.35(f) of the Proposed Rule would establish requirements for monitoring of in-process control points, the purpose of which would be the assurance that the "specifications established under paragraph (e) of this section," (i.e., of §111.35(e)), and apparently all of them, are met, and to detect unanticipated adulteration.

  AHPA agrees that the intention of this paragraph is sound but finds some of the details to be nonsensical. There is no monitoring that can logically be undertaken in-process to ensure that the specifications have been met for the identity, for example, of ingredients that are no longer identifiable at an in-process stage. In addition, any such requirement, if it were feasible, would be redundant, as §111.35(h) specifies that a firm must ensure, through testing or examination, that all established specifications are met.

AHPA believes that the purpose of in-process monitoring should be to ensure that the specifications established for in-process controls and for finished products are met, and requests that §111.35(f) be restated as, "You must monitor the in-process control points, steps, or stages to ensure that specifications established under paragraph (e)(2) and (e)(3) of this section, as appropriate to ensure that specifications established in (e)(3) are met and to detect any unanticipated occurrence that may result in failure to meet finished product specifications."

- The first sentence of §111.35(g) states a requirement for assurance, through testing or examination, that all established specifications have been met. As this regulation is now proposed, it is applicable to all established specifications set in §111.35(e)[9], that is: all specifications for identity, purity, quality, strength and/or composition that are required to be established by §111.35(e)(1) for all components, including dietary ingredients, and dietary supplements that a firm receives; and all such specifications that are required to be established by §111.35(e)(2) for in-process controls; all such specifications that are required to be established by §111.35(e)(3) for all manufactured dietary ingredients and dietary supplements; and all such specifications that are required to be established by §111.35(e)(4) for labeling and packaging.

AHPA has no opposition to the requirement in the first sentence in the Proposed Rule at §111.35(g) that a firm ensure that specifications are met and in fact supports the clear imposition of such requirement in cGMP for dietary ingredients and dietary supplements. The balance of this paragraph, however, presents significant concerns for AHPA and its members. AHPA is particularly, but not exclusively, opposed to those

[9] AHPA is not certain that FDA intended to establish a requirement that envisions an option implying that, for example, testing to ensure that an ingredient's specifications are met can occur after the production of a finished product in which the ingredients is included. Nevertheless, the regulation at §111.35(g) does, in fact, identify "each specification that you established under paragraph (e)" (emphasis added), which includes all of the specification for ingredients, in-process controls, and labels and packaging. It is possible that any such implication for testing finished products to ensure that raw material specification are met was inadvertent, and the agency does not intend to establish such a requirement. In that event, certain of the comments provided here may not be relevant.

elements of this paragraph that would prescribe that two and apparently only two acceptable means would be allowed by which a firm can ensure that specifications are met; and is opposed to any requirement that specifications for ingredients and in-process controls be ensured by testing finished products; and is opposed to any requirement that fails to acknowledge that dependable and accurate assurances that specifications have been met can be made by means other than testing or examination, for example, by implementing process controls or by accepting a meaningful certificate of analysis provided by a supplier provided that the reliability of the supplier's analysis is verified.

Proposed §111.35(g) would establish "[S]pecific testing requirements" related to the mandate to ensure, through testing or examination, that specifications are met. There are two specific testing requirements that are delineated in this paragraph, one consisting of the testing of each finished batch of a product, as described in §111.35(g)(1), and the other consisting of a combination of testing of ingredients and of in-process testing, as described in §111.35(g)(2). These two requirements are not presented as options; rather, the first stated requirement (hereinafter, "the default finished product testing requirement") is required to be used, except for those specifications that a firm "document[s] cannot be tested on the finished batch...because there is no scientifically valid analytical method available." The testing requirement delineated in §111.35(g)(2) (hereinafter "the backup testing requirement") would only be allowed in the event that the quality control unit determines that the default finished product testing requirement cannot be used.

The Final Rule must not establish the unrealistic demand that the only means by which a firm can ensure that specifications have been met are by either the default finished product testing requirement, or, when allowed, the backup testing requirement. To begin with, the default finished product testing requirement could not reasonably achieve the stated purpose of ensuring that "each specifications that you established

under paragraph (e)" of §111.35 has been met, as it is not reasonable to think that specifications established for ingredients (in §111.35(e)(1)) or for in-process controls (in §111.35(e)(2)) can be ensured by testing or examining a finished product that includes such ingredient or that was subjected to such in-process controls. It is not physically possible, for example, for any test that might be undertaken in conformity with the default finished product testing requirement to ensure that many specifications that might be established for the strength[10] of an herbal dietary ingredient (for example, an ingredient identified as "rose hips extract, strength - 3:1 concentration") have been achieved. There is no test that will measure the concentration ("strength") of this ingredient after a product containing this ingredient is made and consideration of such testing borders on the nonsensical. The paragraph as it is currently written, however, would require the burdensome process of the quality control unit engaging in a process to "determine" and "document" that this strength specification for this ingredient can not be ensured by testing the finished product in which it is included, even though any such expectation is nonsensical. Any requirement that a firm must either test finished products to ensure that specifications that are established for ingredients or for in-process controls are met or determine and document that such an illogical approach "cannot be completed" must be removed in the Final Rule.

On the other hand, it can be argued that it is at least sensible to identify the default finished product testing requirement for a finished batch of a manufactured product (whether dietary ingredient or dietary supplement) as an acceptable means to ensure that the specifications that have been established for that product, in conformity with §111.35(e)(3), have been met. Even for finished products, however, AHPA is opposed to any requirement that refuses to acknowledge that dependable and

[10] AHPA offers this only as an example and does not believe this to be a unique or rare example; on the contrary, it is AHPA's position that the implied requirement to ensure that specifications for raw materials and in-process controls are met by testing finished products is almost always nonsensical.

accurate assurances that specifications have been met can be made by means other than testing or examination of each and every finished batch for each and every established specification. The narrowness of these specific requirements is unnecessarily restrictive and, in fact, would prevent companies from using other means of ensuring that specifications are met that are more effective and more efficient.

AHPA strongly believes that the specific testing requirements in §111.35(g)(1) and (2) must be significantly modified. AHPA believes that the agency has failed to provide in the Proposed Rule a meaningful rule for ensuring that specifications have been met, though, as stated above, AHPA supports the imposition of a requirement that a firm ensures that specifications have been met.

AHPA suggests that a more effective approach to ensuring that specifications are met would be to establish separate requirements for such verification for each of the four separate categories in which FDA has proposed a requirement for establishing specifications, i.e., for goods received as identified in §111.35(e)(1); for in-process controls as identified in §111.35(e)(2); for manufactured goods as identified in §111.35(e)(3); and for labels and packaging as identified in §111.35(e)(4). AHPA therefore suggests that proposed §111.35(e) be replaced in its entirety as follows:

> (g) You must ensure that each specification that you established under paragraph (e) of this section is met. Specific requirements are as follows:
>
> (1) For specifications established under paragraph (e)(1) of this section you must
>
> (i) perform testing on each shipment lot of components, including dietary ingredients, or dietary supplements received to determine whether specifications are met;
>
> (ii) conduct at least one test to verify that the specifications for identity of a dietary ingredient are met;
>
> (iii) in lieu of the testing required by subparagraph (i) of this paragraph, a guarantee or certificate of analysis may be

accepted from the supplier of a component, including a dietary ingredient, or of a dietary supplement, provided that

a. the certificate contains all of the information necessary to determine whether specifications have been met, including but not limited to a description of the test or scientifically valid analytical method that was used to make such determination; and

b. you establish the reliability of the supplier's analyses.

(2) For specifications established under paragraph (e)(2) of this section you must perform testing in-process in accordance with the master manufacturing record where control is necessary to determine whether specifications for identity, purity, quality, strength and composition are met.

(3) For specifications established under paragraph (e)(3) of this section you must

(i) establish and follow written process controls that ensure that such specifications are met; or

(ii) test each finished batch of the dietary ingredient or dietary supplement produced before releasing for distribution to determine whether established specifications for identity, purity, quality, strength, and composition are met, provided that there are scientifically valid analytical methods available to conduct such testing.

(4) For specifications established under paragraph (e)(4) of this section you must examine or test upon receipt and before use each shipment lot of labels and packaging that may come into contact with dietary ingredients or dietary supplements to determine whether specifications are met.

AHPA believes that each part of the revision proposed above is rational and would serve to ensure that all specifications established by a firm for their ingredients, in-process controls, manufactured goods and labels and packaging are met.

AHPA's proposed subparagraph (g)(1) would require that a firm ensure that specifications established under §111.35(e)(1) (i.e., related to components, including dietary ingredients, and dietary supplements that a firm receives) be met. Such verification would be accomplished by

performing testing on each shipment lot of received goods, except that AHPA has proposed that at least one test be performed to verify that specifications for identity of a dietary ingredient; and has proposed that a certificate of analysis (C of A) be acceptable in lieu of testing and under certain prescribed circumstances, except that a C of A could not be accepted for the required test for identity.

AHPA notes that the proposed requirement to perform testing on each shipment lot of received goods is modeled after the backup testing requirement in §111.35(g)(2)(i) of the Proposed Rule, and in fact uses nearly the same language as that proposed subparagraph. AHPA's proposal to require at least one test for identity repeats the requirement that was proposed in the Industry Draft for raw materials as published in the 1997 ANPR. Similarly, the proposal for the acceptability of a C of A in lieu of testing refers to part of the Industry Draft, except that AHPA has attempted here to articulate a minimum requirement for the content of a C of A that would be allowed for the proposed purpose[11].

A factor to keep in mind in evaluating the role and usefulness of a C of A that complies with an established standard is the fact that FDA has stated its intention to establish this cGMP to include dietary ingredients. This means that every supplier of a dietary ingredient will have established specifications for and ensured that all specifications were met for every dietary ingredient they sell. There is no reason to require that every action taken by a supplier to ensure that specifications are met in the goods that they sell should be repeated by the buyer for the same lot of the same goods upon purchase. Certificates of analysis accompanying such ingredients would be able to provide all of the information necessary to show that specifications have been met. Any unwillingness by FDA to find a meaningful role for sound certification documents will result in duplicative testing.

[11] AHPA encourages FDA to review the June 25, 1999 Draft Report of the Food Advisory Committee Dietary Supplement Working Group on Ingredient Identity Testing Records and Retention, and especially Appendix E: Desirable Elements of a Certificate of Analysis.

AHPA's proposed subparagraph (g)(2) would require that a firm ensure that specifications established under §111.35(e)(2) (i.e., related to in-process controls in the master manufacturing record where such control is necessary in relation to meeting specifications) be met. This verification would be accomplished by performing testing in-process in accordance with the master manufacturing record. AHPA notes that the proposed requirement to perform the suggested in-process testing is modeled after the backup testing requirement in §111.35(g)(2)(ii) of the Proposed Rule, and in fact uses nearly the same language as that proposed subparagraph.

AHPA's proposed subparagraph (g)(3) would require that a firm ensure that specifications established under §111.35(e)(3) (i.e., related to dietary ingredients and dietary supplements that a firm manufactures) be met. Such verification would be accomplished either by establishing and following written process controls that ensure that the specifications for the manufactured product are met, or by the testing of each finished batch of a manufactured dietary ingredient or dietary supplement.

AHPA has thus proposed that the regulation in the matter of a firm's obligation to ensure that specifications are met provide an option to the requirements proposed by FDA in this matter. AHPA recognizes that this suggested revision is a significant departure from the rule proposed here by FDA and strongly believes that such departure is not only necessary, but is proper and will better serve the interest of the public in assuring that product specifications are met. Note that AHPA is not proposing that process controls that do not ensure that finished product specifications are met be allowed, and does not intend, in proposing this option, to create a loophole that will in any manner tolerate goods that do not meet their stated specifications.

AHPA's proposed subparagraph (g)(4) would require that a firm ensure that specifications established under §111.35(e)(4) (i.e., related to labels and packaging that may come in contact with dietary ingredients

and dietary supplements) be met. Such verification would be accomplished by examining or testing each shipment lot of labels and such packaging to determine that specifications have been met, such examination or testing to occur before use of the labels and packaging. AHPA notes that the requirement proposed here to examine or test labels and packaging in this manner is modeled after the similar rule in the cGMP for finished pharmaceuticals, and specifically after 21 CFR 211.122(a), which states, "[L]abeling and packaging materials shall be... examined or tested upon receipt and before use in packaging or labeling of a drug product."

AHPA recognizes that the proposal made here to replace §111.35(g) as it was presented in the Proposed Rule is a significant departure from FDA's approach as published in the March 13, 2003 *Federal Register* notice. In addition, AHPA has not had sufficient time while preparing these comments to discuss the suggestions made here with other industry organizations. AHPA therefore requests that the agency be prepared to receive additional comments on this particular part of the rule.

- §111.35(i)(2) specifies that a firm will need to conduct a material review of any failure to meet specifications. AHPA has no issue with this proposed requirement, but suggests that the first clause of this subparagraph ("Review the results of the monitoring required by this section") is both unnecessary and can be read as narrowing the intention of the rule in this matter. The only required monitoring for in the Proposed Rule is that established in §111.35(f) related to monitoring of in-process control points, steps or stages, and such monitoring will not necessarily find all failures in specifications, for example specifications related to raw materials or labels. AHPA requests that these words be removed.
- AHPA believes that the testing requirements proposed in §111.35(k) for testing of contaminants that may adulterate a product is unnecessarily broad, as it would require testing or examination of components, including

dietary ingredients, and dietary supplements for "those types of contamination that may adulterate or may lead to adulteration" (emphasis added).

AHPA notes that the cGMP for food defines the term "microorganism" somewhat broadly ("yeasts, molds, bacteria, and viruses, and includes but is not limited to, species having public health significance"). There is not, however, any regulation in the food cGMP that requires testing or examination for each and every potential contaminant, whether or not a microorganism, that is remotely possible to be present. Similarly, the cGMP for finished pharmaceuticals requires examination only for those components and packaging "that is liable to contamination with filth, insect infestation, or other extraneous adulterant" (21 CFR 211.84(d)(5)).

AHPA also believes that there should be no implication in the Final Rule of a "zero tolerance" for any contaminant for which such an absolute requirement is needed. AHPA notes, for example, that FDA has established tolerable levels for heavy metals such as lead in certain color additives that are listed for safe use in foods generally (e.g., 10 ppm lead and 3 ppm arsenic for annatto extract; 21 CFR 73.30(b)(1)). There is no reason for testing for these heavy metals to be required at a level greatly lower that the tolerance level. Similar consideration should be given when evaluating testing of contaminants in dietary ingredients and dietary supplements.

AHPA also believes that FDA must establish that a certificate of analysis (C of A) be acceptable in lieu of the testing required in this paragraph and under certain prescribed circumstances. There is no reason to require that every test performed by a supplier to ensure that specifications related to contamination are met in the goods that they sell should be repeated by the buyer for the same lot of the same goods upon purchase. Certificates of analysis accompanying such ingredients would be able to provide all of the information necessary to show that

specifications have been met and AHPA notes that 21 CFR 211.84(d)(2) provides significant leeway for assuring the purity of drug components through the use of a properly corroborated supplier's certification. Any unwillingness by FDA to find a meaningful role for sound certification documents for dietary ingredients and dietary supplements will result in duplicative testing for contamination for these goods.

Based on the comments here, AHPA requests that language similar to that found in the drug cGMP and that provides some attention to the level of a contaminant be placed in the Final Rule at this part, as follows:

> "You must
> (i) test or examine components, including dietary ingredients, and dietary supplements for those types and levels of contamination for which there is information or evidence that suggests that these may be present in an amount or at a level that may adulterate or may lead to adulteration of the finished product in which the components and dietary supplements are used. You must use an appropriate scientifically valid method for the test or examination. The types of contamination of concern may include, but are not limited to, the following:
>
> (1) Filth, insects, or other extraneous material;
> (2) Microorganisms; and
> (3) Toxic substances.
>
> (ii) In lieu of the testing required by subparagraph (i) of this paragraph, a guarantee or certificate of analysis may be accepted from the supplier of a component, including a dietary ingredient, or of a dietary supplement, provided that
>
> (1) the certificate contains all of the information necessary to determine whether specifications have been met, including but not limited to descriptions of the specific test or scientifically valid analytical method that was used to make such determination; and
>
> (2) you establish the reliability of the supplier's analyses.

- AHPA views §111.35(n) as completely redundant to §111.35(i), to which it refers. AHPA suggests that this paragraph be removed.
- As discussed in the comments for §111.12 of the Proposed Rule, and for exactly the same reasons as articulated in those comments, AHPA

requests that 111.35(o)(6) be changed such that the words, "qualified by training and experience" be changed to read "qualified by training or experience, or a combination thereof.

Section 111.37

- The quality control unit would be required by §111.37(b)(6) to review and approve processes for calibrating instruments and controls. There are some instruments and controls, however, that are calibrated by the manufacturer and it is not realistic or necessary to require a manufacturer or packager to repeat this work to assure that there is accuracy. AHPA therefore requests that the following words be added to the end of this subparagraph: "except when the equipment's manufacturer has already done so."
- Representative samples of each lot of various commodities, including components, including dietary ingredients; dietary supplements; packaging; and labels, would be required to be collected by §111.37(b)(11)(i), and would be required by §111.37(b)(12) to be kept for a period of three years.

AHPA has no objection to these requirements for the most part, but has been informed by numerous of its members that the requirement for keeping packaging is problematic and potentially expensive in terms of storage space costs. AHPA also notes that there is no comparable retention requirement for any food ingredient, packaging, or label, and that such requirements for drugs are limited to active ingredients and finished pharmaceuticals.

There is no rational reason to make any requirement for retention of samples related to dietary ingredients or dietary supplements. AHPA therefore requests that the word "packaging" be stricken from §111.37(b)(11)(i).

AHPA also notes that the term "representative sample" is defined in §111.3, but that the term "reserve sample" is not. AHPA assumes that

each place in the Proposed Rule where the agency used the term "reserve sample," both in §111.37 and in §111.50(h), and in §111.83 or "representative reserve sample" the term "representative sample" was intended. AHPA suggests that this be clarified.

AHPA also requests that some retention period of less than three years be specifically authorized for components, including dietary ingredients, and dietary supplements that have a shelf life that is less than 3 years. AHPA notes that an exception for retention of the ingredients identified as "compressed medical gases" is specifically exempted from sample retention requirements in the cGMP for drugs. AHPA is aware that some companies may use, for example, nitrogen gas to provide better packaging of dietary supplements.

AHPA requests that the agency acknowledge that it may not be tenable, or even necessary, to retain all ingredients in dietary supplements and the supplements themselves, for the arbitrary period of three years. AHPA therefore requests that §111.37(b)(12) be modified by adding after the words, "3 years from the date of manufacture," the following words: "except that samples of components, including dietary ingredients, and dietary supplements that are perishable in less than 3 years must be kept for a period of time that is reasonable associated with the component's or supplement's shelf life."

Section 111.45

- The agency has proposed in §111.45(a) that a manufacturer must prepare and follow a written master manufacturing record in order to "ensure uniformity from batch-to-batch."

The implications of the word "uniformity" in this usage can be extended to an assumption that two batches would be exactly the same, down to the minutest level. *The American Heritage Dictionary of the English Language*, 3rd edition[12], page 1952, defines "uniform" as, "Always

[12] See footnote #3.

the same, as in character or degree, unvarying," and as, "Unvaried in texture, color, or design." There is nothing in current Federal law that authorizes, and little in the centuries of use of herbal products, that supports "uniformity from batch-to-batch" for most of these products. In the example discussed earlier, the implication of uniformity for a peppermint leaf tincture would be that each batch contains exactly the same concentration of menthol, and of chlorophyll, and of every other constituent that is transferred from the raw plant material to the finished product. Unless the marketer of such product makes such representation, the agency must not make such a requirement.

There is, however, clearly a need to require that a master manufacturing record be written and followed in a manner that assures that a dietary supplement product meets its specification. AHPA therefore strongly requests that the language in the last clause of the first sentence in §111.45(a) be changed to, "to ensure that specifications are met from batch to batch."

AHPA also notes that the actual language of proposed §111.45(a) states that a master manufacturing record would be required for "each batch size." AHPA does not believe these words to be important, or event necessary, to establish the meaning of this proposed rule, and asserts that these words add confusion for at least certain manufacturers of herbal products. Firms that manufacture small lots of herbal tinctures from fresh (i.e., not dehydrated) wild-harvested materials will often plan the specific batch size around the particular amount of raw material that is harvested over two days or a week. This amount might be 15 pounds for one batch, 50 for the next and 100 for the next, and the separate harvest lots can not be stored for combining with later harvests to arrive at a specifically mandated, and artificial, batch size. But each of the production lots can, in fact, conform to a consistent master manufacturing record that is developed in a proportional format rather than on a fixed quantity. Thus, the 15 pound lot of harvested material might be combined with 3 pounds

of other dietary ingredients and extracted in 1.5 gallons of ethanol; the 50 pound lot would be manufactured to the same proportion, i.e., with 10 pounds of the same additional dietary ingredients and extracted in 5.0 gallons of ethanol; and the 100 pound lot, similarly would be combined with 20 pound of the other ingredients and extracted in 10 gallons of ethanol. These are clearly following the same master manufacturing record. AHPA reiterates its request that the words, "and for each batch size" be removed from this sentence, or add the words, "as appropriate."

- Proposed §111.45(b)(5) would require that a master manufacturing record "explain[s]" any intentional excess amount of a dietary ingredient in a dietary supplement. AHPA believes it to be sufficient to require only that the excess amount be identified and notes that the comparable language in the cGMP for finished pharmaceuticals states, "A statement concerning any calculated excess of component."

  AHPA requests that the words, "that explains" in this paragraph be changed to the word, "of."

Section 111.50

- For exactly the same reasons as articulated in AHPA's comment to §111.12 of the Proposed Rule, AHPA requests that 111.50(e)(4) be so that the identity of the person required to be identified in this paragraph be identified as "qualified by training or experience, or a combination thereof."
- Proposed §111.50(c)(4) would require that the date and time of the maintenance, cleaning, and sanitizing of the equipment and processing lines used in producing the batch be included in batch production records.

  Many firms that manufacture dietary supplements maintain records that are specific to all of their cleaning operations related to equipment and production lines in which date and time of all cleaning operations are recorded. There is no need to require that records maintained in any such extant system be duplicated in batch records.

AHPA therefore requests that the following words be added at the end of this subparagraph: "...except that such records, if maintained in a written cleaning log, are not required to be duplicated in the batch production record."

- Proposed §111.50(f) would forbid the reprocessing of any dietary ingredient or dietary supplement that is "rejected because of contamination with microorganisms of public health significance or other contaminants, such as heavy metals." The *de facto* implication of this restriction, if fully enforced, would not allow any herbal ingredient that contains an unacceptable amount of any microorganism of public health significance or any other contaminant.

  AHPA finds this proposal to be unacceptable and unnecessary, and in fact does not believe that the agency intends to establish such a prohibition. AHPA is aware that companies that import ginseng from China have worked to develop processes for the removal of pesticides that contaminate ginseng at the time of import. Under the Proposed Rule, as written, this would no longer be allowed.

  AHPA is aware that the agency has a long-standing policy to prohibit blending of a contaminated lot with an uncontaminated lot in order to reach a particular specification. AHPA believes that it is that practice that the agency actually intends to establish for dietary supplements, and AHPA supports such an intention.

  AHPA therefore recommends that the agency rewrite the second sentence of this paragraph to read, "You must not reprocess by a process of dilution a dietary ingredient or dietary supplement if it is rejected because of contamination with microorganisms of public health significance or other contaminants of public health significance, such as heavy metals.

Section 111.60

- §111.60(d) would establish a requirement that the "appropriate validated testing method" be identified and used for each established specification for which testing is required to determine whether the specification is met.

  In analytical chemistry, the term "validated" has a specific meaning related to the process by which an analytical method is corroborated. A validated method is one in which it has been demonstrated that certain performance characteristics or parameters function in an acceptable manner. According to Reference number 76, as identified by FDA in its discussion of test method validation in the March 13, 2003 *Federal Register* notice (see 68 FR 12209), and also published by FDA,[13] these parameters for chromatographic analytical methods include: accuracy; detection and quantitation limits; linearity; precision; range; recovery; robustness; sample solution stability; specificity / selectivity; and specifications and tests related to system suitability. This FDA published document is identified as the agency's current thinking, as of its 1994 publication date, on the validation of chromatographic methods. While AHPA is aware of the existence of another draft document that the agency has published on this matter, to the best of AHPA's knowledge the document identified as Reference number 76 provides evidence of the agency's thinking on the meaning of the word validation for the purposes of this rulemaking. In addition, AHPA is aware that this list of validation parameters is not unique to this publication and that validation of a method is generally related to substantiation of performance of these parameters.

  AHPA therefore assumes that FDA's proposal at §111.60(d) to require that a firm identify and use appropriate validated testing methods means that the only methods that will be allowed when testing to determine whether specifications have been met will be those methods in which the parameters described above have been examined. AHPA is

[13] Analytical Methods Technical Committee of the Chemistry Manufacturing Controls Coordinating Committee of the Center for Drug Evaluation and Research (CDER) at FDA. November 1994. "Reviewer Guidance – Validation of Chromatographic Methods."

aware of the agency's statement in its discussion of test method validation in the March 13, 2003 *Federal Register* notice that "[T]est method validation determines whether a... test method is accurate, precise, and specific for its intended purpose." 68 FR 12208. AHPA does not believe, however, that this statement reflects the agency's intention in regard to §111.60(d), or FDA could have explicitly stated that a firm must identify and use the appropriate testing method that is accurate, precise and specific for the purposes of determining that each established specification for which testing is required is met.

AHPA strongly opposes such strict limitation on allowable testing methods. To begin with, the attempted application of test method validation performance parameters is unnecessary when applied to many commonly used test methods, such as accurate and well-designed organoleptic analysis for identification of botanical ingredients. Under §111.35(e) a firm will have established a specification for, among other things, the identity of each botanical it uses. Current industry practice uses numerous generally available testing methods for identity (dependent on numerous factors, including the form of the herb – whether cut, powdered, or processed) to assure compliance with established specifications. These include gross organoleptic analysis (e.g., examination to assure conformity to known morphological features of entire plant parts; smell or flavor, as appropriate; etc.); microscopic analysis; and chemical analysis including numerous chromatographic methods (e.g. TLC, HPLC, GC, etc.). Validation by substantiating the performance of the parameters identified here is not meaningful or applicable to any of these commonly employed methods except for the chromatographic methods.

AHPA also notes that FDA's authority in prescribing cGMP for dietary supplements is limited, in that such cGMP "may not impose standards for which there are no current and generally available analytical methodology." If FDA insists that only validated testing methods are used for determining that established specifications are met, FDA will have

imposed standards for which there are very few generally available methodologies. In fact, for many dietary ingredients and dietary supplements, no such validated testing methods are generally available as analytical methodologies.

For all of the reasons given above, AHPA requests that the words "appropriate validated" in §111.60(d) be changed to "scientifically valid". AHPA also notes that the issue of appropriate testing methodologies is also addressed in proposed §111.35(h), which states, "You must use an appropriate test or examination to determine whether your specifications are met. An appropriate test is one that is a scientifically valid analytical method" (emphasis added). Thus, the agency's acceptance of AHPA's request in this matter would have the effect of producing consistency between these paragraphs.

Section 111.85

- The agency has proposed in §111.85(b) to establish a specified protocol for salvaging returned goods that consists of two steps, one of inspection to assure that proper storage conditions were maintained during the returned product's transit time, and the other to require testing that demonstrates that all specifications are met.

AHPA supports this approach for goods that are returned because the customer for the goods (or that recipient's customer, etc.) observed or opined that the product did not meet the specifications that it was represented to possess. There are many cases, however, where products are returned for purely commercial reasons (e.g., product was shipped to an incorrect location; the customer purchased more than was needed and has a guaranteed return policy; etc.). In such cases, inspection to assure proper storage is an appropriate requirement, but there is neither a need nor should there be a requirement that testing be conducted to reevaluate compliance with specifications, so long as such returns are in the same packaging and bear the same closures as when they were originally

shipped. AHPA believes that any such unnecessary requirement will result in the majority of such commercially reasoned returns being discarded even though they are compliant with all specifications.

AHPA therefore requests that §111.85(b) be rewritten to establish two different requirements, one that included testing for goods that are returned by a person who claims or suggests that the product failed to meet any specification, and another, consisting only of inspection, for returns for which no such concern is expressed by the person who returns the goods. AHPA's proposed language is as follows:

(b) You must not salvage returned dietary ingredients and dietary supplements

1. for which no claim or suggestion is made by the person that returns the goods that the dietary ingredient or dietary supplement has failed to meet any specification, unless
   i. evidence from their packaging (or, if possible, an inspection of the premises where the dietary ingredients and dietary supplements were held) indicates that the dietary ingredients and dietary supplements were not subjected to improper storage conditions; and
   ii. the returned dietary ingredient or dietary supplement is in the same packaging with the same closures as when you distributed the product, unless tests demonstrate that such dietary ingredients or dietary supplements that is returned in other packaging or with other closures meet all specifications for identity, purity, quality, strength, and composition; or
2. for returns for which a claim or suggestion is made by the person that returns the goods that the dietary ingredient or dietary supplement has failed to meet any specification, unless:
   i. Evidence from their packaging (or, if possible, an inspection of the premises where the dietary ingredients and dietary supplements were held) indicates that the dietary ingredients and dietary supplements were not subjected to improper storage conditions; and
   ii. Tests demonstrate that the dietary ingredients or dietary supplements meet all specifications for identity, purity, quality, strength, and composition.

Section 111.125

- The final paragraph in the Proposed Rule, §111.125(c), refers to the agency's inspection and copying authority for records that are required under this entire section. AHPA requests that the agency clarify and acknowledge that such authority is limited to its authority under the Public Health Security and Bioterrorism preparedness and Response Act of 2002 (PL 107-188), and that the agency has no such authority under the FFDCA.

Additional comments

AHPA is aware that FDA has requested comments in numerous places throughout the preamble to the Proposed Rule and offers comments on certain of these.

Written procedures

The agency requested comments as to whether written procedures should be required in relation to certain provisions and operations other than the few such requirements proposed by FDA. The Proposed Rule has limited requirements for written procedures to those for calibrating instruments and controls and related to the written instructions that would be required in master manufacturing records. When AHPA and others submitted the Industry Draft in 1995, written procedures were proposed for seven operations: for cleaning and maintaining equipment and utensils; for certain operations related to raw materials; for certain operations related to appropriate tests and/or examinations of finished products; for reprocessing operations; two separate written procedures for certain operations related to labels and packaging; and for handling and dealing with complaints.

FDA has stated that it is not requiring written procedures "in order to limit the burden to manufacturers," but, as noted above, requested comments on whether written procedures should be required for certain operations. 68 FR 12165 and 12170. AHPA reiterates here its support, as stated in the 1995 Industry Draft, for the establishment of those written procedures that were

proposed in the Industry Draft. Moreover, AHPA is receptive to extending such requirements to additional cGMP operations and believes that, in many cases, a requirement for written procedures will actually save costs by reducing training time for personnel. In fact, many companies, including small and large companies, already use written procedures extensively. In addition, AHPA notes that it is difficult to imagine how the quality control unit will carry out its obligations under §111.37(b)(1) to "approve or reject all processes, specifications, controls, tests, and examinations, and deviations from or modifications to them..." if these processes, specifications, controls, tests and examinations are not subject to written procedures.

AHPA therefore requests that the agency identify all operations where written procedures need to be established in order for the cGMP to be internally consistent and to assure that dietary ingredients and dietary supplements are properly manufactured, packaged and held, and to, at some time prior to publication of a Final Rule, identify its thinking as to those operations for which written procedures might be established in a Final Rule.

Product dating

The agency requested comments as to whether expiration dating should be required for dietary ingredients and dietary supplements and at one point in this discussion stated that its reference to "expiration dating" included expiration dating, shelf-life dating, or best if used by dating. 68 FR 12203. The agency stated that expiration dating had not be proposed at this time because there is insufficient scientific information available to determine the biological activity of certain products and such information would be necessary to determine an expiration date, and because testing methods are evolving. 68 FR 12203-4.

AHPA agrees that expiration dating should not be required at this time as a function of cGMP but believes that firms should be allowed to place a product use date, such as a shelf-life date or a best if used by date, on their products to provide useful information to customers and consumers. AHPA notes that, for some botanical products the idea of expiration is not rational, for example, when does goldenseal root offered for sale in a capsule "expire" and become

something other than goldenseal root? On the other hand, if goldenseal root capsules are labeled to contain 4% berberine, some understanding of the stability of that alkaloid will be required in order to assure that the product is accurately labeled throughout its shelf-life – which of course argues that a shelf-life date must be included on the label to prevent adulteration by mislabeling.

The agency also stated in the preamble to the Proposed Rule, "...if you use an expiration date on a product, you should have data to support that date." 68 FR 12204. AHPA agrees that data to support such labeling is often needed, for example when expiration dating refers strictly to a date prior to a product's expiration or prior to a date on which quantified label claims will no longer be met. AHPA does not believe, however, that the same degree of data is needed to support shelf-life dating or best if used by dating, as these label messages may only recommend the time limit within which a dietary ingredient or dietary supplement should be used for best quality[14]. In the example given above, a firm may choose to place a 3 year best if used by date on its goldenseal root capsule which is labeled with no information on the berberine content of the product. There is no rational reason to require data to support that date.

Conclusions

AHPA appreciates the opportunity to provide these comments to the Proposed Rule for current good manufacturing practice in manufacturing, packing, and holding dietary ingredients and dietary supplements hopes that the agency will treat these comments seriously. AHPA has offered here numerous comments of both a general and of a specific nature and reiterates here its belief that the Proposed Rule must be modified and its opposition to implementation of the Proposed Rule without significant modifications.

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 is submitted as "Part 2 of 3" of AHPA's

[14] FDA defines "Best if used by" date as "A calendar date on the packaging of a food product, which represents the recommended time limit a food should be used within for best flavor or quality." Accessed from http://www.cfsan.fda.gov/~dms/a2z-b.html#bestby, August 11, 2003.

comments to the Proposed Rule 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.

Included in the above comments AHPA has encouraged the agency to assure meaningful participation by stakeholders in the coming stages of this rulemaking process. AHPA acknowledges that the comments provided here and by other organizations have significantly challenged numerous of the most important elements of the Proposed Rule, for example those parts that address ensuring that specifications are met. AHPA does not believe that the honest and honorable differences of opinions with the agency's proposal that have been identified by this process will be meaningfully resolved without active and forthright communication between the agency as regulator and the industry as the regulated class. There must be established a forum to communicate the agency's perception of these and other comments long before the publication of a Final Rule and AHPA reiterates here it strongest encouragement to FDA to consider how it can sponsor such a forum.

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