

DOCKET NO. FDA-2017-N-5094

BEFORE

THE UNITED STATES OF AMERICA

FOOD AND DRUG ADMINISTRATION

COMMENTS OF THE

AMERICAN HERBAL PRODUCTS ASSOCIATION

ON

**FDA's Request for Comments on Evaluation of Existing Regulations
Relating to Products Regulated by
CFSAN (Center for Food Safety and Applied Nutrition)**

February 5, 2018

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I. Prefatory remarks

The American Herbal Products Association (AHPA) is the national trade association and voice of the herbal products industry. AHPA members include domestic and foreign companies doing business as growers, processors, manufacturers and marketers of herbs and herbal products, as well as non-herbal products, including conventional foods, dietary supplements, and bodycare and cosmetic products. AHPA serves its members by promoting the responsible commerce of products in these several regulatory categories.

On September 8, 2017, the Food and Drug Administration (FDA or the Agency) published several Federal Register notices in which the Agency invited input to help FDA identify existing regulations and related paperwork requirements that could be modified, repealed, or replaced, consistent with the law, to achieve meaningful burden reduction while allowing FDA to achieve its public health mission and fulfill statutory obligations. One such notice was identified as specific to products regulated by FDA's Center for Food Safety and Applied Nutrition (CFSAN)¹. The present comments are in response to this particular Federal Register notice, referred to herein as the September 8 CFSAN Notice or as Docket No. FDA-2017-N-5094.

The September 8 CFSAN Notice explains that the request for input was issued as part of the implementation of Executive Order 13771 (EO 13771), "Reducing Regulation and Controlling Regulatory Cost," and Executive Order 13777 (EO 13777), "Enforcing the Regulatory Reform Agenda."

As noted in the September 8 CFSAN Notice, EO 13771 states that the policy of the Executive Branch is to be prudent and financially responsible in the expenditure of funds, from both public and private sources, and that it is essential to manage the costs associated with complying with Federal regulations. Though not noted in the September 8 CFSAN Notice, EO 13771 clarifies that for purposes of this order, the term "regulation" or "rule" means "an agency statement of general or particular applicability and future effect designed to implement, interpret, or prescribe law or policy or to describe the procedure or practice requirements of an agency." AHPA

¹ 82 FR 42503; Docket No. FDA-2017-N-5094.

understands this to mean that the scope of EO 13771 applies to both formal regulations and to FDA-issued guidance, and the comments herein may therefore address both official rules and rulemaking as well as guidance issued in relation to products regulated by CFSAN.

As noted in the September 8 CFSAN Notice, EO 13777 established a federal policy “to alleviate unnecessary regulatory burdens” on the American people, and directs each federal agency to establish a Regulatory Reform Task Force (RRTF) with duties to evaluate existing regulations and identify those that merit repeal, replacement, or modification. The September 8 CFSAN Notice provides descriptions of the types of regulations that each RRTF is required to attempt to identify for this purpose, as stated in EO 13777, including regulations that “eliminate jobs, or inhibit job creation; are outdated, unnecessary, or ineffective; impose costs that exceed benefits; create a serious inconsistency or otherwise interfere with regulatory reform initiatives and policies; are inconsistent with the requirements of the Information Quality Act, or the guidance issued pursuant to that Act, in particular those regulations that rely in whole or in part on data, information, or methods that are not publicly available or that are insufficiently transparent to meet the standard for reproducibility; or; derive from or implement Executive Orders or other Presidential directives that have been subsequently rescinded or substantially modified.”

The September 8 CFSAN Notice provides a list of questions that the agency describes as “those that FDA is using to guide [its] initial review” of FDA regulations.” The Notice also identifies the list of question as “intended to help the public in providing comments, not to restrict the issues that may be addressed.” Certain of those questions are listed below:

- Is the regulation still current, or is it outdated or unnecessary in some way?
 - Have regulated entities had difficulties complying with the regulation? If yes, identify what entity or entities have had such difficulties and the nature of the difficulties.
 - Does the regulation impose requirements that are also provided for in voluntary or consensus standards or guidance by third party organizations (e.g., International Council for Harmonisation, International Organization for Standardization, Codex Alimentarius)? Do the entities covered by these
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standards or guidance take steps to meet the standards and to document that they meet the standards? If met, do the standards achieve the same level of public health protection as the FDA regulation? Are there entities who are not covered by these standards or guidances or who choose not to observe them?

- Does the regulation contain redundant, outdated, or unnecessary collections of information or retention of records, e.g., reporting, recordkeeping, or labeling requirements?
- Could the goal of the regulation be achieved by less costly means that would provide the same level of public health protection?

AHPA members manufacture and market conventional foods, dietary supplements and other consumer products that contain herbal ingredients. These products and ingredients all are potentially affected by one or another of CFSAN's regulations. These comments are submitted on behalf of AHPA and its members and address numerous issues relevant to CFSAN regulations, guidance documents, and enforcement practices.

II. Note on the format of these comments

FDA requested in the September 8 CFSAN Notice that comments be submitted in a specific format, as shown in Table 1 in the Notice, in order to “more efficiently review and consider comments.” The requested format identifies six specific elements; AHPA’s adherence in these comments to these elements is as follows:

- “Type of product or FDA Center regulating the product” – Each of the comments included here are relevant to products regulated by CFSAN; this fact is repeated at each separate comment in a field identified as “FDA Center regulating the product.”
- “Citation to Code of Federal Regulations and statutory citation (as applicable)” – Each of the comments included here that is relevant to a regulatory issue is related to a regulation under Title 21 of the Code of Federal Regulations (21 CFR), except for one comment that is also relevant to Title 40 of the Code of Federal Regulations (40 CFR). The specific part or section of 21 CFR or 40 CFR addressed in each comment is identified at each separate comment in a field identified as “Citation to CFR.” In addition, a few comments are relevant

to statutory issues under Title 21 of the United States Code (21 U.S.C.) and these are similarly identified in a field identified as “Statutory Citation,” or in a combined field identified as “Citation to CFR and Statutory Citation.”

- “Approved information collection and OMB Control Number (as applicable)” – None of the comments included here are relevant to FDA’s information collection activities, and no applicable OMB Control Number applies to any of these comments. For clarity, the statement “Not applicable” is inserted at each separate comment in a field identified as “OMB Control Number.”
- “Brief description of concern” – The subject of each of AHPA’s separate comments is included in a field identified as “Brief description of concern.”
- “Available data on cost or economic impact” – Although each of these comments includes a field identified as “Available data on cost or economic impact,” in most cases the comments simply states, “AHPA has no such data,” and AHPA has not conducted any formal economic research with regard to these comments.
- “Proposed solutions” – AHPA’s suggested approach to each identified concern is presented in a field identified as “Proposed solutions.”

In addition to completing each of the described elements in FDA’s requested format, AHPA has included one additional element in each of the comments included here, and so has provided, in a field identified as “Relevance to Docket No. FDA-2017-N-5094 and/or EO 13771 and/or EO 13777,” reference to either one of the questions posed by FDA in the September 8 CFSAN Notice or to a purpose described in Executive Order 13771 or 13777, and a short rationale as to why the specific comment is relevant to the cited question or purpose. In so doing, AHPA believes that each of the comments presented here is, in fact, relevant and germane to the subject matter of the Docket.

An additional formatting detail utilized throughout these comments is relevant to each instance in which AHPA proposes herein a specific amendment to an existing regulation. In all such cases AHPA identifies proposed added language in bold underline text (as **bold underline**) and proposed deleted language in strikethrough text (as ~~strikethrough text~~).

III. Issues related to regulations that affect conventional food and dietary supplement operations and farms

The following issues are specifically addressed to certain of FDA's regulations, including current good manufacturing practice regulations, that affect operations that manufacturer, package, label or hold food or dietary supplements; and to farms.

FDA should remove requirements for "written assurances" except where explicitly established by statute.

FDA CENTER REGULATING THE PRODUCT – CFSAN

CITATION TO CFR – 21 CFR Parts 1, 11, 16, 106, 110, 111, 112, 114, 117, 120, 123, 129, 179, 211, and 507

OMB CONTROL NUMBER – Not applicable.

BRIEF DESCRIPTION OF CONCERN – As follows:

FDA regulatory provisions implementing the Food Safety Modernization Act's (FSMA) Preventive Controls for Human and Animal Foods, Foreign Supplier Verification Program and Produce Safety Rule each require sellers (farmers and food processors) to obtain from their customers (downstream food processors and distributors), and buyers to obtain from their vendors, various "written assurances" on an annual or biannual basis.

With these written assurances in place, sellers are provided a certain amount of regulatory relief – relief which in many cases is essential to the continued existence of their business, since in many cases it is frankly impossible (not just inefficient or uneconomical) for the firm otherwise to comply with the applicable regulations.

However, the requirement to obtain annual written assurances is so impractical that FDA determined to delay their enforcement.² An analysis by the Grocery Manufacturers Association (GMA) determined that the written assurances requirements just under the provisions in 21 CFR § 117.136 would require

² 81 FR 57784.

individual firms to obtain thousands or even millions of assurances every year.³ This is clearly a huge expense for both the sellers and the buyers, not only to generate and exchange the documents but also to maintain them on file as required by the regulations. Furthermore, for many entities it will be impossible to obtain the required assurances (e.g., small firms who have little leverage over larger business partners, or farmers who are several intermediaries removed from the eventual food processors).

Even if the written assurances were obtainable and required only once, as opposed to annually or biannually, the burden will be significant and without any commensurate public health benefit, because these written assurances do nothing to materially improve the safety of the food supply. The written assurances are intended to assure that food safety hazards that exist in the food being sold by one company will be appropriately mitigated by a downstream firm. But the regulations already require that the existence of any hazards must be disclosed in documentation accompanying the sale of the food, and already require that food processors adequately mitigate any relevant hazards as appropriate for their products and customers, so that by the time the food reaches the final consumer all relevant hazards will have been addressed. Furthermore, the Food, Drug and Cosmetic Act (FDCA or the Act) makes any entity, including retailers, and their chief executives that knowingly or unknowingly distribute adulterated or misbranded food, strictly liable under the Act, which provides strong incentive for entities throughout the supply chain and especially those selling food to consumers to ensure the safety of the food they sell.

³ “21 CFR § 117.136 – Industry Impacts from Disclosure and Written Assurance Requirements,” Grocery Manufacturers Association, March 23, 2016. This analysis described a scenario in which one very large firm could be required to receive in excess of 1.5 million written assurances annually to comply just with § 117.136 (see presentation at slide #20) – and this is for *just one firm and just for this one rule*, not for the industry in aggregate or for other FSMA-implementing rules. AHPA notes that in describing this meeting FDA reported, “GMA estimated that [compliance with the customer provisions in the part 117 rule] could result in *hundreds or even thousands* of written assurances needed by a single distributor” (emphasis added to highlight the inconsistency with GMA’s actual reported estimate). 81 FR 57784 at 57786.

AHPA notes that the U.S. Department of Commerce (DOC) on October 6, 2017 issued a report (the DOC Report⁴) that reflects comments received from various stakeholders in response to a Request for Information (RFI) issued by that agency in March 2017 to request input to identify “the most burdensome regulations and permitting requirements” faced by U.S. domestic manufacturers and to also request “feedback on how regulatory compliance and permitting could be simplified.”

The DOC Report presents many of the issues and suggestions raised by respondents, and also presents DOC’s recommendations for streamlining the federal permitting processes and reducing the regulatory burdens that affect domestic manufacturing. Of particular relevance to AHPA’s present comments, one of the specific “priority areas for reform” recommended in the DOC Report addresses written assurances, as follows:

The Department of Health and Human Services, Food and Drug Administration (HHS, FDA) should rescind requirements to obtain written assurances from downstream customers on an annual basis, or alternatively consider revision of requirement to reduce frequency and burden.⁵

AHPA believes FDA should, and hereby requests the Agency to extend this recommendation to each of the FSMA-implementing rules that impose extensive burdens to obtain written assurances.

DATA ON COST OR ECONOMIC IMPACT – AHPA has not conducted any independent economic research with regard to the cost of providing the many written assurance that will be required to comply with FSMA-implementing rules, but conservatively estimates, based on other analyses, that these written assurances requirements will cost industry tens of millions of dollars per year. Actual costs may range much higher.

⁴ U.S. Department of Commerce. October 6, 2017. Streamlining Permitting and Reducing Regulatory Burdens for Domestic Manufacturing.

⁵ Ibid, at page 45.

PROPOSED SOLUTION – As follows:

FDA should remove regulatory requirements for farmers and food companies to exchange and maintain on file thousands and even millions of useless pieces of paper in the form of “written assurances” received from their customers and/or provided to their vendors. No replacement requirements are necessary, since other existing regulatory and legal framework adequately requires farmers, food processors, and retailers to disclose the existence of hazards that require mitigation and to ensure food safety prior to sale to consumers.

RELEVANCE TO DOCKET No. FDA-2017-N-5094 AND/OR EO 13771 AND/OR EO 13777 –

One of the questions posed by FDA in the September 8 CFSAN Notice is, “Could the goal of the regulation be achieved by less costly means that would provide the same level of public health protection?” AHPA considers the proposed solution presented above to address this question, and to represent an alternative means of thorough public health protection at a very greatly reduced cost.

FDA inspectors should cite the specific regulation associated with each observation issued on FDA Form 483

FDA CENTER REGULATING THE PRODUCT – CFSAN

CITATION TO CFR – 21 CFR Part 117

OMB CONTROL NUMBER – Not applicable.

BRIEF DESCRIPTION OF CONCERN – As follows:

[NOTE: This comment is included in AHPA’s comments to this Docket in both the Section III of the comments on issue related to regulations that affect conventional foods and dietary supplement operations as well as farms and importers, and in Section IV of the comments on issue related to cGMP for dietary supplements.]

As AHPA has observed the implementation of the dietary supplement cGMP regulations (21 CFR Part 111) since 2007, it has become aware that inspectional observations issued on FDA Form 483 in association with dietary supplement facility inspections do not normally inform recipients of the specific paragraph(s) in the regulations that are relevant to each observation or deficiency asserted. AHPA understands that this is also FDA’s practice when issuing observations on

a Form 483 in association with conventional food facility inspections. AHPA understands that Form 483s lack such information because internal Agency policy directs investigators not to disclose the regulatory bases for their observations or to quote or otherwise disclose the relevant regulatory provisions on which investigators base their observations.⁶ As a result, when a firm receives a Form 483, it is often unclear what element of the regulation FDA considers to be applicable to the observation or deficiency.

This information is necessary for transparency, accurate communication, and ease of comprehension by the regulated trade. Therefore, inclusion of such information would assist the regulated industry in coming into compliance with FDA regulations and thereby promote the public health benefits underlying their promulgation. Furthermore, inclusion of such information would help ensure that FDA food facility inspections accurately reflect the provisions of the applicable regulations.

AHPA submitted a Citizen Petition to FDA on October 17, 2013 to request the agency (1) formally rescind FDA's policy of prohibiting Agency investigators from quoting or citing the cGMP regulations upon which they base their inspectional observations within an FDA Form 483 issued to conventional food and dietary supplement facilities; and (2) revise the Agency's Inspections Operations Manual (IOM) to expressly require that Form 483s issued to conventional food and dietary supplement facilities reference each cGMP regulation to which the Agency investigator's listed observations relate.⁷

FDA issued a response to the above-cited AHPA Citizen Petition on July 23, 2014 in which the Agency denied the petition.⁸ With regard to the first action requested

⁶ See Inspections Operations Manual 5.2.3.3 (2017): "Do not quote Regulations (e.g., specific CFR sections) when listing items."

⁷ AHPA hereby incorporates by reference to the present comments that October 17, 2013 Citizen Petition, and will submit that document to the present Docket simultaneous to submission of these comments, identified as Addendum 1.

⁸ AHPA hereby incorporates by reference to the present comments that July 23, 2014 FDA response to AHPA's Citizen Petition, and will submit that document to the present Docket simultaneous to submission of these comments, identified as Addendum 2.

in the petition, i.e., to formally rescind the described FDA policy, FDA replied that “there is no such policy.” AHPA finds this statement to be disingenuous: clearly some sort of policy exists, otherwise 483s and Warning Letters would not uniformly omit information whose inclusion would so obviously be helpful to compliance.

With regard to the second action requested in the petition, i.e., to revise the IOM as described, the Agency replied that “FDA’s current practices further the Agency’s interests,” that “The IOM’s procedures promote understanding, compliance, and transparency”; and that “The IOM is consistent with the RPM’s [Regulatory Procedures Manual] ‘prior notice’ policy.”

AHPA believes the decision not to cite the link between the investigator’s observation and the applicable provision of the regulations disserves the Agency’s goal to promote “understanding, compliance, and transparency.” It is in the public interest to ensure understanding within the regulated trade by citing the regulatory provisions that apply to each observation or deficiency asserted in a 483.

AHPA acknowledges that members report that many FDA investigators provide the regulation connection to observations in the inspection closeout meeting either voluntarily or where requested by the facility representative. Nonetheless, whatever motive there might have been or be to not including that information on the FDA 483 should be abandoned in favor of the transparency requested herein.

DATA ON COST OR ECONOMIC IMPACT – AHPA has no such data.

PROPOSED SOLUTION – As follows:

AHPA suggests the Commissioner of Food and Drugs revise the Inspections Operations Manual (IOM) to require that Agency investigators include references to the underlying cGMP regulations in relation to each cGMP-related observation listed in Form 483s issued to conventional food and dietary supplement facilities.

RELEVANCE TO DOCKET No. FDA-2017-N-5094 AND/OR EO 13771 AND/OR EO 13777 –

In the September 8 CFSAN Notice FDA provides descriptions of the types of regulations that each RRTF is required to attempt to identify, including regulations

that “impose costs that exceed benefits.” In AHPA’s view, FDA’s current policy imposes an unnecessary cost on the regulated trade, and especially on small businesses, that could be readily alleviated by including references to the relevant paragraphs from cGMP regulations for each Form 483 inspectional observation. Any business, especially small businesses, would benefit from receiving as much information as possible about the regulatory basis of each Form 483 observation, so that management can clearly understand the basis for the problem and what is required to address it.

IV. Issues related to cGMP for dietary supplements (21 CFR Part 111)

The following issues are specifically addressed to certain of FDA’s current good manufacturing practice regulations that affect operations that manufacturer, package, label or hold dietary supplements.

FDA should exempt very small establishments from 21 CFR Part 111 or exercise enforcement discretion for such firms

FDA CENTER REGULATING THE PRODUCT – CFSAN

CITATION TO CFR – 21 CFR Part 111

OMB CONTROL NUMBER – Not applicable.

BRIEF DESCRIPTION OF CONCERN – As follows:

In promulgating 21 CFR Part 111 in 2007, FDA estimated that very small establishments having fewer than 20 employees or less than \$1 million in annual sales would incur costs of around \$46,000 annually to comply with the rule.⁹ AHPA believes this estimate to have been conservatively low even at the time it was published, and that the costs in 2017 are certainly higher. Many firms subject to Part 111 have annual revenues of far less than \$1 million and are unable to spend tens of thousands of dollars on compliance with this rule; AHPA is aware of a number of small firms that have been driven out of business, or forced to outsource their manufacturing, as a direct result of this rule. Since many of the

⁹ 72 FR 34752 at 34917-34918, 34938.

affected businesses are located in rural areas or small towns, this can represent significant job losses in economically depressed areas.

AHPA notes that the majority of Part 111 is directed toward ensuring quality rather than safety. AHPA furthermore notes that when 21 CFR Parts 112 and 117 were promulgated to implement provisions of the Food Safety Modernization Act, FDA made a concerted effort, at the direction of Congress, to minimize the burdens imposed on small farms and businesses by providing extensive and specific exemptions; no such effort was made, however, in promulgating Part 111.

AHPA therefore believes FDA should craft a formal policy of enforcement discretion to refrain from imposing Part 111 (as well as 21 CFR Part 117 Subparts C and G, which technically would apply in the absence of Part 111 compliance) on very small firms with less than \$250,000¹⁰ in annual sales (based on a 3-year rolling average and adjusted hereafter annually for inflation) if all of the following apply: (a) the firm complies with all local health department regulations; (b) for any purchased ingredients that are processed foods, the firm obtains and reviews the vendor's certificate of analysis for each lot to ensure the ingredient is free from contaminants that may adulterate the finished product; (c) none of the botanical ingredients used by the firm are listed in Safety Class 2a or Class 3 in AHPA's *Botanical Safety Handbook* (latest edition).

This policy will enable small firms subject to Part 111 to remain in business until they grow large enough to afford full compliance with the rule, without creating a significant public health risk.

DATA ON COST OR ECONOMIC IMPACT – AHPA has no such data.

¹⁰ For comparison, this proposed threshold is only 25% of the threshold used in the definition of "very small firms" set forth by FDA in 21 CFR § 117.3. FDA estimated in 2013 that food facilities with annual sales of up to \$250,000 numbered 46,100 facilities and produced <0.5% of all food produced in the US when measured by dollar value. 78 FR 3702. Dietary supplement manufacturers are only one type of food producer; therefore, although there may be thousands of firms that benefit from this enforcement discretion, the food produced by these firms will represent only a tiny fraction (<<0.5%) of the U.S. food supply.

PROPOSED SOLUTION – As follows:

As described above, craft a formal policy of enforcement discretion to refrain from imposing Part 111 (as well as 21 CFR Part 117 Subparts C and G, which technically would apply in the absence of Part 111 compliance) on very small firms with less than \$250,000¹¹ in annual sales (based on a 3-year rolling average and adjusted hereafter annually for inflation), under the conditions stipulated above.

RELEVANCE TO DOCKET NO. FDA-2017-N-5094 AND/OR EO 13771 AND/OR EO 13777 –

In the September 8 CFSAN Notice FDA provides descriptions of the types of regulations that each RRTF is required to attempt to identify, including regulations that “eliminate jobs, or inhibit job creation” or that “impose costs that exceed benefits.” For the reasons stated above, AHPA believes that strict enforcement of 21 CFR Part 111 in dietary supplement facilities operated by the types of small firms identified in this comment risks loss of current jobs by such firms and inhibits potential job creation if these small firms do not survive and develop into larger companies with more employees.

FDA cannot create the requirement to comply with 21 CFR Part 111 on an ad hoc basis

FDA CENTER REGULATING THE PRODUCT – CFSAN

CITATION TO CFR – 21 CFR § 111.1

OMB CONTROL NUMBER – Not applicable.

BRIEF DESCRIPTION OF CONCERN – As follows:

21 CFR Part 111, by its own terms, applies to dietary supplement manufacturers and does not apply to dietary ingredient manufacturers. 21 CFR § 111.1(a) states, “you are subject to this part if you manufacture, package, label, or hold a dietary supplement....” On the other hand, companies that perform these operations with dietary ingredients are, like conventional food ingredient operations, subject to 21 CFR Part 117.

¹¹ This threshold is consistent with the definition of “very small firms” set forth by FDA in 21 CFR § 117.3.

In the preamble accompanying the issuance of 21 CFR Part 111 as a final rule FDA states:

“...those who manufacture, package, label, or hold dietary *ingredients* (emphasis added) are not subject to the final rule. To illustrate, assume you manufacture a dietary ingredient and sell that bulk dietary ingredient to Company X. Company X then utilizes the bulk dietary ingredient in a dietary supplement. Under final §111.1(a), you would not be subject to these dietary supplement CGMP requirements because you are not manufacturing a dietary supplement, rather you are manufacturing a dietary ingredient for further incorporation into a dietary supplement by Company X.”¹²

However, FDA has created a policy of enforcing Part 111 compliance on dietary *ingredient* manufacturers under a number of circumstances. For example, the preamble to the final rule goes on to state:

“If, however, you sell herbs in bulk to Company X, and Company X simply packages the herbs into smaller units for sale as a dietary supplement, you would be subject to the dietary supplement CGMP requirements because you are manufacturing a dietary supplement that Company X is simply packaging and labeling, and not further processing into a dietary supplement. In other words, in the latter example, you would have acted as a manufacturer whose finished product is simply repackaged or relabeled.”¹³

It has long been the law that a manufacturer determines the nature of its product by labeling it as a food, drug, or dietary supplement. The actions of a subsequent manufacturer or packager utilizing a food ingredient or a “dietary ingredient” as that term is used by FDA in the first preamble quoted above, does not change the character of the ingredient as sold by the ingredient manufacturer.

AHPA does not disagree that Part 111 compliance may be useful to ensure that the ingredient manufacturer’s products meet their specifications. In fact, it is not uncommon for dietary supplement manufacturers to require their dietary ingredient vendors to comply with Part 111, so that the supplement manufacturer can confidently rely on the vendor’s representations about the ingredient.

¹² 72 FR 34752 at 34792.

¹³ Ibid.

However, such a burden must be undertaken voluntarily by the ingredient manufacturer as a response to market forces. It cannot lawfully be imposed based on a preamble statement to be applied *ad hoc* by FDA; and as a matter of regulatory transparency and sheer practicality it cannot be triggered by the actions of buyers downstream from the dietary ingredient manufacturer, the identity and actions of which the dietary ingredient manufacturer has no knowledge of or control over.

Furthermore, AHPA notes that while Part 111 compliance may be useful to ensure dietary ingredient *quality*, it is no longer needed to ensure ingredient *safety*. Since 2007 when Part 111 was published, the new food safety requirements of Part 117 have come into force and dietary ingredient manufacturers who forego Part 111 compliance are now required to ensure safety through compliance with 21 CFR Part 117 Subparts C and G. Therefore, FDA's *ad hoc* requirements for Part 111 compliance by firms that are dietary ingredient manufacturers and not dietary supplement manufacturers are no longer needed to protect the public health.

In the preamble to the final rule on Foreign Supplier Verification Programs, FDA rejects a request to include under 21 CFR § 1.511(a) and (b) certain importers that comply with Part 111, noting “Attempting to enforce compliance with the dietary supplement CGMP regulation by firms that are not legally required to comply with the regulation could present problems for the Agency if we sought to take an enforcement action against [such a firm]....”¹⁴ AHPA agrees with this analysis and believes it clearly applies to FDA's imposition of Part 111 requirements on firms that are not dietary supplement manufacturers.

Therefore, FDA must revise its policies in this area.

DATA ON COST OR ECONOMIC IMPACT – AHPA has no such data.

¹⁴ 80 FR 74226 at 74311.

PROPOSED SOLUTION – As follows:

AHPA believes the most straightforward manner to ensure regulatory clarity and proper legality in this matter, is for FDA to regulate food manufacturers solely based on the representations made on their product labels. Firms whose labels state that the dietary ingredient-containing foods they manufacture are dietary supplements should be regulated under Part 111 (and Part 117 Subpart B insofar as it does not overlap with Part 111).¹⁵ Firms whose food labels make no mention of dietary supplements should be regulated solely under Part 117.

To the extent that additional regulatory requirements are necessary to ensure product quality under circumstances where a dietary ingredient is purchased for packaging as a dietary supplement, these burdens must fall on the firm performing the packaging; they cannot retroactively fall on vendors upstream from that firm. Since the packager is the party responsible for deciding what ingredient to buy and how to process it prior to packaging, the packager is rightly the party to bear any additional burdens related to those decisions. Furthermore, the packager is the only entity with knowledge of what processing the firm intends to do, or not do, prior to packaging; and is the only entity with the information (e.g., serving size, target population, package size, packaging material, shelf life, etc.) necessary to set proper specifications for the ingredient used in the product. Therefore, if FDA believes that elements of Part 111 such as setting appropriate ingredient specifications and verifying compliance with those specifications are critical in situations where an ingredient is packaged as a supplement, FDA must place those burdens on the packager, not the ingredient vendor.

To accomplish this, AHPA suggests FDA issue a clarification to correct the cited preamble, for example by reissuing the last sentence cited above as two sentences to state:

“Similarly, if you sell herbs in bulk as a dietary ingredient to Company X and Company X repackages those herbs into smaller units for sale as a dietary

¹⁵ 21 CFR 117.5(e) provides that dietary supplement manufacturers operating in compliance with Part 111 and with 21 U.S.C. 379aa-1 are exempt from the requirements of the Part 117 Subparts C and G. Therefore, any food that contains one or more dietary ingredients, is labeled as a “dietary supplement,” and is manufactured in conformance with Part 111 and complies with 21 U.S.C. 379aa-1 must not be subjected to the additional requirements of Part 117 Subpart C or G.

supplement, you would not be subject to these dietary supplement CGMP requirements. In this scenario, Company X acts as a dietary supplement manufacturer whose manufacturing process consists of subdividing the bulk herbs into smaller portions; Company X would be required to establish specifications under §111.70 for the herbs that they repackage into smaller units for sale as a dietary supplement and to ensure that their specifications are met under §111.73 and §111.75.”

The proposed policy of determining GMP requirements based on the labeling of the ingredients in question will relieve dietary ingredient vendors from duplicative regulatory schemes and provide clarity for both FDA and the regulated trade, thereby reducing legal and enforcement costs and improving compliance.

Also, the proposed policy of placing any additional burdens necessary to ensure quality on the shoulders of the packager in question, rather than the dietary ingredient manufacturer, is necessary not only as a matter of logic and fairness but also practicality, since it is simply not possible for the dietary ingredient manufacturer to anticipate what specifications will be relevant to the dietary supplement packaged using its ingredient.¹⁶

RELEVANCE TO DOCKET No. FDA-2017-N-5094 AND/OR EO 13771 AND/OR EO 13777 –

One of the questions posed by FDA in the September 8 CFSAN Notice is, “Could the goal of the regulation be achieved by less costly means that would provide the same level of public health protection?” AHPA considers the proposed solution presented above to address this question, and to present a less costly means to meet the regulation’s goal with equal or even improved public health protection.

Definitions should be provided for the terms “manufacturing,” “packaging,” “labeling,” and “holding” in 21 CFR Part 111

FDA CENTER REGULATING THE PRODUCT – CFSAN

CITATION TO CFR – 21 CFR Part 111

OMB CONTROL NUMBER – Not applicable.

¹⁶ In cases where a distributor provides a dietary ingredient to a contract packager to be packaged without further processing, it may be appropriate for the distributor rather than the packager to bear responsibility for establishing the dietary ingredient’s specifications and confirming conformance to the specifications. This may be established contractually between the parties.

BRIEF DESCRIPTION OF CONCERN – As follows:

21 CFR Part 111 is titled Current Good Manufacturing Practice in Manufacturing, Packaging, Labeling, or Holding Operations for Dietary Supplements, but nowhere defines “manufacturing,” “packaging,” “labeling,” or “holding.”

AHPA notes that in promulgating the new rules for current good manufacturing practice, hazard analysis, and risk-based preventive controls for human foods at 21 CFR Part 117 and for animal foods at 21 CFR Part 507, the Agency provides a definition for one of these terms (“holding”) and for another similar and possibly synonymous term (“manufacturing / processing”), but does not provide definitions for the other two terms (“packaging” and “labeling”). AHPA further notes, however, that the definition for “manufacturing / processing” given for both human foods and animal foods in 21 CFR § 117.3 and 21 CFR § 507.3, respectively, includes both packaging and labeling within that definition.

FDA provided these definitions presumably because they are necessary for the regulated trade to understand and comply with the rules.

AHPA believes that definitions for these terms are likewise necessary for the dietary supplement industry, and that in fact the lack of such definitions has caused persistent compliance difficulties for the industry. However, AHPA does not believe the specific definitions provided in Parts 117 and 507 are appropriate for inclusion in Part 111 due to significant differences between these rules. AHPA proposes appropriate definitions below.

DATA ON COST OR ECONOMIC IMPACT – AHPA has no such data.

PROPOSED SOLUTION – As follows:

AHPA requests that the following definitions be added to 21 CFR § 111.3:

- Manufacturing means to conduct operations to make from one or more components a dietary supplement intended for ingestion in the form of a tablet, capsule, powder, softgel, gelcap, liquid or other form for ingestion, such as a teabag.

- Packaging means to conduct operations to place a dietary supplement into the container in which it will be sold.
- Labeling means to conduct operations to place labels on packaged dietary supplements, or to form and/or fill packages bearing such labels.
- Holding means maintaining and storing components and bulk or retail packaged dietary supplements.

It is clear from reading the preamble that accompanied issuance of final 21 CFR Part 111 that FDA believes that a company's specific operations are relevant to determining which specific sections of the rule apply to their operations. FDA makes exactly this point in the preamble by stating, "you need to comply with the CGMP requirements that apply to your operations related to the manufacture, packaging, labeling, and holding of dietary supplements" (emphasis added).¹⁷ FDA provides an example of a company that is a packager/labeler but not a finished product manufacturer, and which "would not need to comply with requirements that do not apply to it; for example, the packager/relabeler would not have to conduct testing on the finished batch of dietary supplement since it does not manufacture the finished batch of dietary supplement."¹⁸ The agency also notes, "if you are a wholesaler, you would be subject to the requirements in final §111.470 for the dietary supplements you are holding for distribution as well as other applicable requirements, such as those related to personnel, physical plant and grounds, equipment and utensils, quality control, returned dietary supplements, and product complaints."¹⁹

Because there are different obligations under 21 CFR Part 111 for different operations it is essential that the regulated trade clearly understand exactly what FDA means by each of the terms, "manufacturing," "packaging," "labeling," and "holding." It is also essential that FDA and industry mean the same thing when each of these terms is used. AHPA is concerned, for example, that FDA may believe that encapsulating a dietary ingredient is a packaging operation, whereas the industry certainly considers this to be a manufacturing operation.

¹⁷ 72 FR 34752 at 34790.

¹⁸ Ibid.

¹⁹ 72 FR 34752 at 34903.

RELEVANCE TO DOCKET No. FDA-2017-N-5094 AND/OR EO 13771 AND/OR EO 13777 –

In the September 8 CFSAN Notice FDA provides descriptions of the types of regulations that each RRTF is required to attempt to identify, including regulations that “are ... ineffective.” Clarity about the meaning of the terms “manufacturing,” “packaging,” “labeling,” or “holding” can only be accomplished if each of them is defined in the rule. Most relevant to the current comments, and to the obligation under EO 13777 for each RRTF to attempt to identify regulations that are “ineffective,” clarity as to how each of these separate operations is defined would make compliance more likely, if only because this would provide greater information to operations that must comply with the rule to understand the specific sections of the rule applicable to each specific operation, which would thus make the rule more effective.

Comments regarding the terms “identity,” “purity,” “strength,” and “composition” in 21 CFR Part 111

FDA CENTER REGULATING THE PRODUCT – CFSAN

CITATION TO CFR – 21 CFR § 111

OMB CONTROL NUMBER – Not applicable.

BRIEF DESCRIPTION OF CONCERN – As follows:

21 CFR Part 111 requires manufacturers of dietary supplements to establish specifications, and to meet these specifications, for “the identity, purity, strength, and composition of the finished batch of the dietary supplement.” The rule does not, however, define these four terms.

FDA did share certain “information” in the preamble that accompanied the issuance of the final rule to “elaborate on [FDA’s] interpretation” of these terms, as follows:

“Identity. The ‘identity’ of a dietary supplement refers to the dietary supplement’s consistency with the master manufacturing record and/or that it is the same as described in the master manufacturing record.”

“Purity. The ‘purity’ of a dietary supplement refers to that portion or percentage of a dietary supplement that represents the intended product.” FDA provides as an example that if “a dietary supplement provide[s] the amino acid L-

arginine, and you determine that 90 percent of the manufactured product is L-arginine and 10 percent of the manufactured product is D-arginine, you could describe your L-arginine product as ‘90 percent pure.’”

“Strength. The strength of a dietary supplement relates to its concentration. By concentration, we mean the quantitative amount per serving (for example, weight/weight, weight/ volume, or volume/volume). Therefore, for purposes of this final rule, strength does not refer simply to the quantity of an ingredient, rather it refers to the amount of a stated ingredient per a specified unit of measure.” In further discussing this term, FDA notes, “We do not consider the rule’s requirements on dietary supplement strength as necessarily relating to the individual constituents of such products. Whether the requirements regarding dietary supplement strength apply to one or more constituents of dietary ingredients in a dietary supplement depends on what you are manufacturing. For example, if you are manufacturing vitamin C, and your source of vitamin C is rosehips, you would establish a strength specification for vitamin C in the finished batch of the dietary supplement (e.g., ‘x milligrams (mg) of vitamin C per tablet’). Alternately, if you are manufacturing rosehips and not vitamin C from rosehips, the strength specification that you establish for the finished batch of the dietary supplement is the strength of the rosehips themselves (i.e., the concentration of rosehips in the final product, such as ‘x mg of rosehips per tablet’).”

“Composition. A dietary supplement’s ‘composition’ refers to the specified mix of product and product-related substances in a dietary supplement. For example, a dietary supplement manufactured to provide vitamin C may contain, in addition to vitamin C, a tablet coating agent and substances used as binders. The composition could be described as the percent of the dietary supplement that is vitamin C, the tablet-coating agent, and each binder.” 72 FR 34803-34804.

AHPA to some extent agrees with the above discussions insofar as they apply to finished supplements, but believes that the definitions need to be formalized and incorporated into the rule itself; that the definitions need certain refinements and clarifications; and that the term “purity” should be omitted.

It is essential that both FDA and the regulated trade clearly understand exactly what is meant by each of the terms, “identity,” “purity” (if maintained in the rule), “strength,” and “composition.” Without clear definitions it is not surprising that the trade has struggled to comply with §§ 111.70 and 111.75, and it is not surprising that enforcement may be inconsistent.

DATA ON COST OR ECONOMIC IMPACT – AHPA has no such data.

PROPOSED SOLUTION – As follows:

(a) Identity. The preamble defines the “identity” of a dietary supplement as consistency with the master manufacturing record (MMR). AHPA largely agrees with this definition (although it requires refinement to provide for deviations from the MMR where appropriate and where approved by the Quality department).²⁰

With respect to the “identity” of a dietary supplement, AHPA notes that by the terms of the definition provided, conformance to identity specifications can only be evaluated through review of the batch record; there is no scientifically valid “test” to ensure that the batch is consistent with the MMR.

However, in enforcing the requirement to set specifications for the “identity” of supplements, FDA inspectors have been known to interpret “identity” specifications to mean descriptive or quantitative characteristics such as size, weight, color, odor, taste, viscosity, chemical fingerprint, content of claimed substances, etc. AHPA does not disagree that such tests provide evidence that the product (or a component) is the intended item; but requiring these specifications is inconsistent with the definition provided in the preamble. This causes confusion among the regulated trade.

- If FDA intends to maintain that the “identity” of a supplement refers to the supplement’s consistency with the MMR, then FDA must stipulate that the identity is confirmed by the manufacturer through review of the batch record. A separate definition or at least an explanation is then needed for the “identity” of a component, since the rule requires “identity specifications” to be set for components.

- If FDA intends to maintain that “identity” specifications consist of descriptive or quantitative characteristics that, when tested or examined,

²⁰ For example, one-time use of different equipment from what is specified in the MMR; one-time use of a component that is different from what is specified in the MMR but meets sufficiently similar specifications to make it appropriate for use in the product; unforeseen reprocessing required for a particular batch; etc.

will provide evidence that a component or product is the intended item, then FDA should adjust the definition provided for the “identity” of a finished product or define “identity specifications” separately from “identity.”

(b) AHPA agrees that “strength” should be related to concentration or amount per serving, but believes FDA’s discussion of “strength” is confusing and incomplete.

- FDA begins by giving dietary supplement “strength” examples as “weight/weight, weight/volume, or volume/volume,” but makes no mention of “amount per tablet” until later in the preamble, and omits other units such as “per capsule.” Since tablets and capsules are the most common form of dietary supplements, these should be explicitly discussed at the outset along with weight/weight, weight/volume, and volume/volume.
- AHPA believes that for botanical extracts – and for other extracts from natural materials – the “strength” is often best expressed as the extract ratio.²¹ This essentially the same as expressing the concentration as weight/weight, weight/volume, or volume/volume but is in a format that uses a colon rather than a forward slash. The extract ratio is a common measure of extract “strength” familiar to industry and consumers alike; for example, the labeling regulations in 21 CFR § 101.36(b)(3)(ii)(B) specify how liquid extract ratios should be expressed. For powdered or solid extracts, the ratio should be defined as X:Y where X is the amount of starting botanical material and Y is the amount of finished extract including excipients, with X being dried botanical unless specified as fresh.²² The option of expressing the “strength” as the extract ratio should be explicitly discussed in the definition, since the ratio is a key characteristic in many instances.

²¹ While the extract ratio is appropriate for many extracts, it may not be relevant to every extract, such as those that contain a specified amount of marker or a specified amount of bioactivity per unit of weight or volume.

²² For further clarity, FDA should consider defining the “native extract ratio” as X:Y where X is the amount of botanical raw material and Y is the amount of finished extract *excluding* excipients. The native extract ratio is a common strength measurement for solid or powder extracts. For example, a 10:1 native extract containing 50% filler has a final extract ratio of 5:1.

- AHPA notes that there is no scientifically valid test for extract ratio; the extract ratio can only be determined by the extract manufacturer through review of batch records or, for downstream recipients of the extract, through review of the documents and labels accompanying a shipment.
- AHPA believes that additional examples should be provided wherein the “strength” is expressed as an amount per unit of weight or volume. For example, the strength of a Vitamin D liquid may be described as “X mg (or IU) per mL”²³; the strength of enzymes may be described as “X USP units (or other units) per g”; the strength of probiotic products may be expressed as “X billion cfu/g”; etc.
- The option of expressing “strength” in terms of percent should also be explicitly discussed. Percent is one of the most common expressions of concentration, equates to “amount of units per 100 units,” and is expressed as weight/weight, weight/volume, or volume/volume. It is therefore entirely consistent with the “strength” discussion provided by FDA in the preamble. For example, 90% ascorbic acid granules consist of vitamin C mixed with appropriate excipients to form a granule.
- FDA should clarify that “strength” is relevant only with respect to dietary ingredients, not excipients. The “strength” of a vitamin C tablet is properly described as the amount of vitamin C per tablet; the amounts of excipients per tablet are not part of the strength. FDA mentions in the preamble that it is not necessary to establish specifications for the strength of excipients, at least if such a specification is not necessary to ensure the finished dietary supplement specifications are met²⁴; AHPA is aware of no case in which such a specification would be necessary. Furthermore, this exemption should be stated in the rule itself, not the preamble.

²³ AHPA recognizes that use of IU in nutrition labeling is being phased out; nevertheless, many supplements and ingredients that supply Vitamin A, Vitamin D, or Vitamin E are currently described in terms of IU.

²⁴ 72 FR 34752 at 34848.

(c) Composition. AHPA agrees with FDA's discussion of "composition" but finds it to be inartfully expressed. In particular, the phrase "product and product-related substances," for which an example is given where vitamin C is the "product" and various excipients are the "product-related substances," is quite confusing since per normal usage, the "product" of a manufacturing process is the totality of the material or item resulting from the manufacturing process, not some subcomponent of the final material. In FDA's example, the "product" is vitamin C tablets, not vitamin C.

The composition of a dietary supplement would be more clearly defined in a manner such as, "The formula for the dietary supplement, in which each ingredient²⁵ is identified and the level of each ingredient is expressed as a percent."²⁶

AHPA notes that there is no generally available, scientifically valid test for many elements of the composition (unless each ingredient consists of a single molecular entity that is easily separated from the other ingredients and readily measured, which is almost never the case). In general, the composition can only be determined through review of batch records. Furthermore, AHPA notes that no other FDA-regulated ingestible product category is required to perform testing (or to write a justification to omit such testing) for the content of every ingredient - not conventional foods, not infant foods, and not drugs. There is no good reason, public health or otherwise, for dietary supplements to be singled out for such an onerous burden.

As a result, the rule should be modified to stipulate that composition specifications for dietary supplements are to be confirmed through review of properly-completed batch records.

²⁵ AHPA uses the term "ingredient" here rather than "component," because components include process aids and process aids do not appear, at a defined level or at all, in the finished product.

²⁶ The term "formula" can then be used in describing § 111.210(b) through (e), which are currently written in a manner that is quite confusing to many in the regulated trade.

(d) Purity. The term “purity” as described by FDA is either redundant to “strength” and/or “composition” or is irrelevant.

In the example provided by FDA, a dietary supplement containing 90% L-arginine and 10% D-arginine is sufficiently described by stating the “strength” as “90% L-arginine” and the “composition” as “100% arginine.”²⁷ As another example, a 1000-mg dietary supplement containing 500 mg calcium carbonate, 300 mg ascorbic acid, 180 mg cellulose, and 20 mg silica is sufficiently described by stating the “strength” as 500 mg calcium carbonate per tablet and 300 mg ascorbic acid per tablet and the “composition” as 50% calcium carbonate, 30% ascorbic acid, 18% cellulose, and 2% silica. To additionally describe the product as “50% pure calcium carbonate,” “30% pure ascorbic acid,” “18% pure cellulose,” and/or “2% pure silica” is at best redundant and at worst confusing.

Insofar as FDA intends “purity” to be used to describe different forms of a dietary ingredient within a single component (e.g., a naturally occurring mixture of L and D isomers of arginine), AHPA can still find no example where a purity specification is needed in addition to strength and composition. A powder dietary supplement that contains 90% L-arginine and 10% D-arginine, and for which the serving size is 1 g, has a strength of 900 mg L-arginine per g and a composition of “100% arginine”; there is no additional benefit to specifying the “purity” as “90% L-arginine.” If in fact “10% D-arginine” is critical to the supplement’s specifications, this can be established as an additional “strength” specification.

Furthermore, use of the term “purity” in this context is extremely confusing to the regulated trade. “Purity” most commonly refers to freedom from contaminants, not to the percentage of a target ingredient.

As a result of the above, “purity” should be removed from the regulation.

²⁷ If a company then wants to describe its product as “90% pure L-arginine,” this claim is readily substantiated through the strength and/or composition specifications. A separate “purity” specification is not needed.

If FDA maintains “purity” in the regulation, FDA needs to clarify how “purity” differs from “strength,” and should stipulate that “purity” is not always relevant and therefore specifications should be set only where it is relevant.

RELEVANCE TO DOCKET No. FDA-2017-N-5094 AND/OR EO 13771 AND/OR EO 13777 –

In the September 8 CFSAN Notice FDA provides descriptions of the types of regulations that each RRTF is required to attempt to identify, including regulations that “are ... ineffective.” Clarity about the meaning of the terms “identity,” “purity,” “strength,” “composition” and “contaminants that may adulterate” can only be accomplished if each of them is defined in the rule. Most relevant to the current comments, and to the obligation under EO 13777 for each RRTF to attempt to identify regulations that are “ineffective,” clarity as to how each of these separate specification is defined would make compliance more likely, if only because this would provide greater information to operations that must comply with the rule to understand the specific requirements to set these specifications, which would thus make the rule more effective.

Master manufacturing records should be able to declare a range of batch sizes

FDA CENTER REGULATING THE PRODUCT – CFSAN

CITATION TO CFR – 21 CFR § 111.205

OMB CONTROL NUMBER – Not applicable.

BRIEF DESCRIPTION OF CONCERN – As follows:

21 CFR § 111.205 describes the requirement to establish a written master manufacturing record (MMR), and states:

- (a) You must prepare and follow a written master manufacturing record for each unique formulation of dietary supplement that you manufacture, and for each batch size, to ensure uniformity in the finished batch from batch to batch.

AHPA understands why FDA believes a different MMR may be appropriate for different batch sizes, because in many cases the quantity of each component must be accurately recalculated for each batch size in order to maintain the correct proportions. Also, batch sizes that differ greatly may require use of different equipment or other changes.

However, as described below, AHPA believes these concerns do not apply in every case, and even where they do apply, there are other means to ensure quality and consistency. Therefore, the requirement to create a MMR for every batch size is cumbersome, impractical, and overly prescriptive.

- (a) Some AHPA members prepare and follow MMRs that are written to cover various batch sizes within a known range. This is especially true for herbal products that are manufactured from agricultural products that are grown by or on a contractual basis for the manufacturer, and where the exact yield of a crop from which such agricultural products are manufactured varies from one harvest to another. Thus, one harvest may yield 73.5 pounds of an herb and the next may yield 128 pounds. The MMR for a tincture produced from that herb must necessarily be sufficiently flexible to deal with such variations in the quantity of the herbal starting material. If a separate MMR is required for each individual batch size, companies will be required to maintain numerous MMRs for what is actually a single product. This creates a tremendous recordkeeping and filing burden, especially with respect to revision control.

AHPA provided a similar communication in comments filed on August 11, 2003 in response to the proposed rule on dietary supplement cGMP. AHPA is aware that FDA discussed such comments in the preamble that accompanied issuance of the final rule, wherein the agency “disagreed with these comments” and declared that it was “not making the suggested changes to proposed §111.45(a),” which was the predecessor section for final §111.205(a).²⁸

AHPA continues to believe FDA’s unwillingness to reconsider a revision in this paragraph will create a scenario wherein a single product may have a different MMR each and every time it is manufactured. Yet the stated purpose of a MMR is to “ensure uniformity in the finished batch from batch to batch.” This phrase is nearly illogical when only one batch of each “formula” is ever produced, as could be the case if a new MMR is required for every batch size.

²⁸ 72 FR 34752 at 34882.

As described in the proposed solution presented below, AHPA believes it should be possible to create an MMR that covers a defined range of batch sizes so long as the (a) relative proportions of all components in the formulation, (b) equipment, (c) in-process specifications, and (d) packaging components used all remain the same for all sizes within the range, and so long as each batch record created from the MMR is reviewed and approved prior to use by quality control personnel to ensure accuracy and appropriateness (e.g., to ensure any ingredient quantities were calculated correctly based on the proportions specified in the product formula).

- (b) In some manufacturing environments, the size-dependent manufacturing specifications are established on the basis of a defined lot size rather than a defined batch size. For example, consider a facility in which the manufacture of one batch of product involves producing, during a specified period of time and under one manufacturing record, a series of identical lots of a defined mixture which are then combined to become the finished batch (e.g., by using the lots as the feed for a continuous manufacturing process). In such cases it is more appropriate for the MMR to be established on the basis of the lot size rather than the batch size. The batch size may vary based on how many lots are combined to make the batch, but different batch sizes do not require a separate MMR because there are no process parameters (such as ingredient quantities or equipment settings) that change based on the batch size.

Therefore, in these cases the regulation should provide flexibility for MMRs to be established based on a fixed lot size rather than a fixed batch size.

- (c) Packaging operations typically do not include process parameters that vary based on batch size; furthermore, it is typical for each packaging batch to be a different size. The batch size may be slightly different due to minor variations in the output of each manufacturing batch or significantly different because a different batch size was manufactured. It may also differ because one manufactured batch is packaged under a number of different, smaller packaging batches in varying quantities.

In any case, since there are typically no process parameters such as ingredient quantities or equipment settings that vary based on the packaging batch size, it is both onerous and pointless to require a separate MMR for each packaging batch size.

DATA ON COST OR ECONOMIC IMPACT – AHPA has no such data.

PROPOSED SOLUTION – As follows:

AHPA requests this detail in the rule be amended to allow a written master manufacturing record to be prepared for a range of lot or batch sizes, and that flexibility be provided such that the requirement may apply to either lots or batches as appropriate to the facility's operations. To accomplish this, AHPA requests that the rule be amended to replace current § 111.205(a) with the following:

(a) You must prepare and follow a written master manufacturing record for each unique formulation of dietary supplement that you manufacture, and for each **lot or** batch size, to ensure uniformity in the finished batch **product** from **lot to lot and** batch to batch, **except that a master manufacturing record may cover a range of lot or batch sizes so long as the (a) relative proportions of all components in the formulation, (b) equipment, (c) in-process specifications, and (d) packaging components used all remain the same for all sizes within the range, and so long as each batch record created from the master manufacturing record is reviewed and approved prior to use by quality control personnel to ensure accuracy and appropriateness. Alternately, in cases where ingredient quantities and other manufacturing parameters vary based on lot size rather than batch size, master manufacturing records may cover a range of batch sizes wherein the lot size fixed but the number of lots per batch may vary. For packaging operations, a separate MMR is not required for each batch size so long as there are no process parameters that vary based on the batch size.**

RELEVANCE TO DOCKET No. FDA-2017-N-5094 AND/OR EO 13771 AND/OR EO 13777 –

In the September 8 CFSAN Notice FDA provides descriptions of the types of regulations that each RRTF is required to attempt to identify, including regulations that “are ... ineffective” or “impose costs that exceed benefits.” For the reasons stated above AHPA believes the regulation as currently written at 21 CFR § 111.205(a) to require a separate master manufacturing record for each batch size

of a dietary supplement is both ineffective and imposes unnecessary costs on certain dietary supplement manufacturers. AHPA further believes these issues can be readily corrected by accepting AHPA recommended revision.

Supplement manufacturing should be allowed in a facility with only one employee

FDA CENTER REGULATING THE PRODUCT – CFSAN

CITATION TO CFR – 21 CFR § 111.210

OMB CONTROL NUMBER – Not applicable.

BRIEF DESCRIPTION OF CONCERN – As follows:

FDA's cGMP rule for dietary supplements requires at 21 CFR § 111.210(h)(3)(ii) that a minimum of two persons are needed to perform certain manual operations that involve the weighing and addition, and verifying the weight and addition, of components in a dietary supplement. AHPA believes this to be unnecessarily prescriptive, and believes there are certainly other means by which the weight or volume and the addition of components can be verified.

More specifically, 21 CFR § 111.210 pertains to master manufacturing records and § 111.210(h) requires written instructions in a master manufacturing record to include:

“(3) Specific actions necessary to perform and verify points, steps, or stages in the manufacturing process where control is necessary to ensure the quality of the dietary supplement and that the dietary supplement is packaged and labeled as specified in the master manufacturing record.

(i) Such specific actions must include verifying the weight or measure of any component and verifying the addition of any component; and

(ii) For manual operations, such specific actions must include:

(A) One person weighing or measuring a component and another person verifying the weight or measure; and

(B) One person adding the component and another person verifying the addition.”

DATA ON COST OR ECONOMIC IMPACT – AHPA has no such data.

PROPOSED SOLUTION – As follows:

AHPA requests the rule be revised to allow manufacturing operations that consist of just one person and that use manual operations to have additional options to verify the weight or measure and addition of components. AHPA notes that FDA allows in its cGMP rule for manufacturing infant formula, at 21 CFR § 106.50(b), for a manufacturer to “establish controls to ensure that each raw or in-process ingredient required by the master manufacturing order is examined by one person and checked by a second person or system” (emphasis added), and further clarifies that this “checking” by a second person or system must ensure, among other things, “that the correct weight or measure of the ingredient is added to the production unit.”

Consistent with this detail in the infant formula cGMP rule, AHPA requests that the following amendment to replace current § 111.210(h)(3)(ii):

“(ii) For manual operations, such specific actions must include:

(A) One person weighing or measuring a component and another person verifying the weight or measure; and

(B) One person adding the component and another person **or system or procedure** verifying the addition.”

Such a “system” might consist of, for example, re-measuring of components by the same person to verify the weight or volume of each, or weighing or measuring the remaining inventory of each component after a batch is assembled to verify that the proper ingredients and quantities were dispensed. As another example, each ingredient dispensed for a batch may be labeled with a sticker which is transferred into the batch record at the time the ingredient is added to the batch; addition of the proper ingredients could then be confirmed through review of the batch record at a later time or date. These are just examples of the types of steps a company may take to verify proper ingredient quantities and additions.

RELEVANCE TO DOCKET NO. FDA-2017-N-5094 AND/OR EO 13771 AND/OR EO 13777 –

The September 8 CFSAN Notice cites in EO 13771 that order's admonishment that it is "essential to manage the costs associated with complying with Federal regulations," and also provides descriptions of the types of regulations that each RRTF is required to attempt to identify, including regulations that "impose costs that exceed benefits." AHPA believes that it is obvious that current § 111.210(h)(3)(ii), since it would necessarily require a very small dietary supplement manufacturer with only one employee to hire a second employee on at least a part time or occasional basis, badly manages the costs for such a firm to comply with this rule and imposes a cost that exceeds the benefit of requiring extra staffing for this single regulatory function. This is especially obvious in light of the fact that FDA makes no such requirement for manufacturers of infant formula, but instead allows "a system" to be established to verify the weight or measure of ingredients in a product. AHPA believes it is inappropriate for this specific regulation to impose requirements that would immediately exclude any firm that employs only one person, even if such a firm is in complete compliance with every other element of 21 CFR Part 111.

FDA should discontinue the practice of imposing manufacturing cGMP requirements under 21 CFR Part 111 on "own label distributors"

FDA CENTER REGULATING THE PRODUCT – CFSAN

CITATION TO CFR – 21 CFR Part 111

OMB CONTROL NUMBER – Not applicable.

BRIEF DESCRIPTION OF CONCERN – As follows:

There is no cGMP regulation in 21 CFR Part 111 that establishes any specialized obligations for a company that sells supplement products under its own brand that are manufactured and/or labeled by one or more other firms. Since the rule was promulgated, FDA has come to describe such companies as "own label distributors" although the rule nowhere defines such a term, and the Agency has come to enforce novel cGMP requirements for such firms and their contract manufacturers although the rule nowhere sets forth such requirements. In doing so, FDA has created an onerous and impractical regulatory environment both for "own label" distributors and contract manufacturers and has acted in direct contravention to the requirements of 21 U.S.C. 342(g) and 374(a)(1).

In the preamble to this cGMP regulation, FDA stated:

“A manufacturer who contracts with a person to do packaging and labeling, but who later distributes the packaged and labeled product, is ultimately responsible for the dietary supplement it releases for distribution. The manufacturer would be responsible for the CGMP requirements for the operations that it performs, including those related to the release of the product for distribution.”²⁹

Since at least as far back as 2011, has FDA cited this preamble to the regulation in warning so-called “own label” distributors that they must comply with various parts of the cGMP with regard to products manufactured for them by contract manufacturers, such as maintaining master manufacturing records, batch manufacturing records, raw material testing records, etc. These obligations, however, are nowhere spelled out in the cGMP regulations for any type of distribution company, and in fact cannot as a practical matter be implemented by a firm engaged in distribution rather than manufacturing.

Most recently, after rephrasing but quoting the preamble noted above and citing FDCA case law regarding the Act’s strict liability provisions, FDA stated in a November 14, 2017 Warning Letter to Mannatech Incorporated, that:

“In particular, the Act prohibits a person from introducing or delivering for introduction, or causing the delivery or introduction, into interstate commerce a dietary supplement that is adulterated under section 402(g) for failure to comply with dietary supplement CGMP requirements (see 21 U.S.C. 342(g) and 331(a)). Thus, a firm that contracts out some or all of its operations must establish a system of production and process controls to ensure the quality of the dietary supplement and that the dietary supplement is packaged and labeled as specified in the master manufacturing record (21 CFR 111.55). The quality control personnel must ensure that the manufacturing, packaging, labeling, and holding operations ensure the quality of the dietary supplement and that the dietary supplement is packaged and labeled as specified in the master manufacturing record (21 CFR 111.105).”³⁰

²⁹ 72 FR 34752 at 34790.

³⁰ Posted online at <https://www.fda.gov/iceci/enforcementactions/warningletters/2017/ucm585515.htm>; accessed November 30, 2017.

Thus, from the preamble to a regulation, to a summary of that preamble, to strict liability case law, to the general provisions of the Act, FDA in this and similar Warning Letters leaps to impose on distributors various cGMP provisions that are plainly directed to manufacturers. This is contrary to the mandate of the very section of the law cited by FDA, 21 U.S.C. 342(g) which states in subparagraph (2) that:

“(2) The Secretary may by regulation prescribe good manufacturing practices for dietary supplements. *Such regulations shall be modeled after current good manufacturing practice regulations for food* (emphasis added) and may not impose standards for which there is no current and generally available analytical methodology. *No standard of current good manufacturing practice may be imposed unless such standard is included in a regulation promulgated after notice and opportunity for comment in accordance with chapter 5 of title 5, United States Code* (emphasis added).”

FDA’s assertions in Warning Letters regarding the specific cGMP responsibilities of “own label” distributors under the cGMP regulations appear to be made up on an *ad hoc* basis as inspections occur. AHPA members report a variety of cGMP documentation requests from inspectors and successful responses, including simply to refer the inspector to the contract manufacturer, to provide batch records and/or ingredient testing records from the contract manufacturer, and to provide a quality agreement with the contract manufacturer. In other cases, FDA has desisted in their requests for these documents when pushed by the “own label” distributor to cite where in the regulation such a burden is imposed on the distributor (a question which FDA is unable to answer, since no such provisions exist).

There are a number of very basic problems with FDA’s “own label” distributor practice. First, it is directly contrary to 21 U.S.C. 342(g) as described above. Dietary supplement firms are subject to a wide variety of requirements under the Act, but it does not follow that all such requirements are subject to review by FDA during a cGMP inspection. Rather, FDA’s authority during a dietary supplement cGMP inspection is limited to those requirements promulgated in the dietary supplement GMPs. Second, the Act’s prohibition on distribution of adulterated dietary supplements applies to all distributors, not just “own label” distributors, and

therefore cannot form the basis for requirements uniquely imposed on “own label” distributors. Third, AHPA is not aware of any similar requirement for any other category of “own label” food distributors to comply with such FDA demands during a cGMP inspection.

Last but not least, this practice by FDA is onerous and impractical because an “own label” distributor does not and cannot have the detailed knowledge necessary to create, evaluate, or justify to FDA documents such as master manufacturing records, batch records, ingredient specifications, etc.³¹ Only the manufacturer has the prerequisite knowledge of the applicable facilities, equipment, processes, procedures, etc. that is necessary to establish these documents or evaluate their adequacy.

In many cases, FDA during inspection of an “own label” distributor will demand that the distributor obtain these documents within 24 hours from the contract manufacturer.³² This has proven extremely disruptive to the contract manufacturers’ operations, since they must pull key staff from their normal functions to compile and then discuss the documents with FDA. Since any one contract manufacturer may process supplements on behalf of hundreds or even thousands of distributors, the manufacturer can find itself disrupted day after day by waves of these demands. This is inefficient both for FDA and for the manufacturer; it would be a far better use of resources to schedule FDA inspections on-site at the manufacturing facility on a more frequent basis, not least because the adequacy of the documents can be accurately evaluated only with a complete understanding of the circumstances existing at the facility in which they are used. Finally, AHPA notes that FDA demands to review the contract manufacturer’s documents during an inspection of the “own label”

³¹ It may be appropriate for the “own label” distributor to bear responsibility for ingredient specifications and/or testing in those cases where the distributor supplies its own ingredients for the contract manufacturer to use. In other cases, however, the distributor will typically not have the requisite knowledge of the effect of the manufacturer’s processing steps on the strength, purity, or freedom from contaminants of the ingredients.

³² The contract manufacturer typically will not allow the distributor to maintain these documents on file ahead of time, since they may contain extensive confidential, proprietary, or trade secret data, and since the adequacy of the documents cannot be evaluated in a context divorced from the facility in which they are used.

distributor fail to provide the contract manufacturer with the protections of 21 U.S.C. 374(a)(1), which require FDA to present a Notice of Inspection to the facility (in this case, the contract manufacturer) prior to demanding access to the facility's records, and the corresponding protections regarding confidential treatment for proprietary and confidential information within those records.

AHPA does not disagree that distributors including "own label" distributors bear responsibility under the law for the dietary supplements they distribute. AHPA furthermore does not disagree that in some circumstances, especially where responsibility for the quality and safety of the finished product is divided amongst multiple parties, a formal quality agreement or other contract may be useful to clearly delineate responsibilities and liabilities among the parties. AHPA encourages FDA to respect the terms of such agreements or other contractual arrangements between the parties.

However, AHPA strongly objects to FDA's attempts to impose extralegal obligations on "own label" distributors or any other regulated entity, and strongly object to FDA's practice of demanding during the course of cGMP inspections that facilities produce documents related to the operations of a different facility that is not currently the subject of inspection.

DATA ON COST OR ECONOMIC IMPACT – AHPA has no such data.

PROPOSED SOLUTION – As follows:

FDA should direct the Office of Dietary Supplement Programs and its Human and Animal Food investigators as well as investigators generally to discontinue the practices of imposing manufacturing cGMP requirements under 21 CFR Part 111 on "own label" distributors, and of demanding that distributors being inspected by FDA must produce documents from their contract manufacturers.

If FDA believes that quality agreements or other steps should be required of "own label" distributors then FDA must proceed with notice and comment rulemaking to clearly define such entities and establish such requirements.

RELEVANCE TO DOCKET No. FDA-2017-N-5094 AND/OR EO 13771 AND/OR EO 13777 –

One of the questions posed by FDA in the September 8 CFSAN Notice is, “Could the goal of the regulation be achieved by less costly means that would provide the same level of public health protection?” Because FDA already has full authority to inspect and require compliance with all of the sections of 21 CFR Part 111 relevant to the operations of the manufacturing and labeling facilities that provide dietary supplements to “own label” distributors under contract, and because any duplicative inspection of “own label” distributors is completely redundant, the solution AHPA has proposed here represents an alternative means to ensure public health protection at a greatly reduced cost and in a manner that complies with the requirements and limitations imposed on FDA by the Act.

Properly completed batch records should be acknowledged as adequate for confirmation of specifications in the absence of existing analytical methods

FDA CENTER REGULATING THE PRODUCT – CFSAN

CITATION TO CFR – 21 CFR § 111.75

OMB CONTROL NUMBER – Not applicable.

BRIEF DESCRIPTION OF CONCERN – As follows:

The FDCA authorizes establishment of good manufacturing practice regulations for dietary supplements, now codified at 21 CFR Part 111, and specifies, “Such regulations shall be modeled after current good manufacturing practice regulations for food and may not impose standards for which there is no current and generally available analytical methodology” (emphasis added).³³

In relation to the above highlighted statutory restriction against imposing new standards, it is very rare for valid test methods to currently exist and be generally available for chemically complex food ingredients, such as animal or botanical ingredients, or for a unique and chemically complex matrix, such as a supplement that includes numerous herbal ingredients, with or without other additional dietary ingredients.

³³ 21 U.S.C. § 342(g)(2).

However, despite the clear language in the FDCA, during inspections of firms under 21 CFR Part 111, FDA consistently pushes supplement manufacturers to implement expensive chemical testing, such as chromatographic analysis, to confirm the presence and quantity of chemically complex ingredients, such as ingredients derived from animals or botanicals, as established in finished products specifications. But generally available, scientifically valid tests for chemically complex materials rarely exist, especially when the ingredient is used in unique or chemically complex product matrices.³⁴ Development and validation of the necessary methods costs thousands to tens of thousands of dollars, depending on the extent of validation performed, which is totally inconsistent with the statutory mandate and any other food regulation, and has no commensurate public health benefit to justify it.

An alternate response to FDA's push for chemical testing is for firms to try to prove that no scientifically valid chemical test method exists anywhere for the specific product, as required by 21 CFR § 111.75(d). This exercise is time-consuming and ultimately futile, since it's impossible to prove a negative. Some companies have attempted to provide evidence of the lack of available methodologies by contacting multiple laboratories to confirm they have no method for the ingredients in question in the product in question; however, the law requires that test methods be generally available (not the proprietary property of individual laboratories), and attempts to prove the absence of available methods cause pointless busywork for both the laboratories and the regulated trade.

In other food labeling contexts, FDA has formally acknowledged that reliance on batch records is an accurate and practical method for assuring that finished food products meet required compositional specifications for ingredients that are

³⁴ It might be argued that rather than testing for a broad chemical profile, the requirement for chemistry testing may be satisfied by testing for individual "marker" compounds that are characteristic of the chemically complex ingredient. However, even where test methods exist for such marker compounds, the test may not produce valid results in a finished food product due to matrix interferences from other ingredients in the food. Furthermore, marker compound tests are easily fooled by spiking the marker into the food through addition of tiny quantities of purified marker chemicals – most of which are readily and cheaply available these days from foreign chemical suppliers. As a result, marker testing cannot reliably prove whether the intended chemically complex ingredient (e.g., botanical) is present at the intended level in the product.

chemically complex or for which no validated test method exists, such as soy protein, dietary fiber, added sugars and certain types of Vitamin E.³⁵

Therefore, rather than continue to push for chemical testing to confirm that supplement specifications are met even where no current and generally available analytical methodology exists, FDA should amend 21 CFR Part 111 in a manner consistent with the principles it has established previously for foods containing soy protein, dietary fiber, etc. The regulations should acknowledge that, where no current or generally available test method exists, batch records are always presumed to be an adequate and effective method for determining whether a dietary supplement complies with finished product label claims or finished product specifications for identity, purity, strength, composition, or nutritional content.

DATA ON COST OR ECONOMIC IMPACT – AHPA has no such data.

PROPOSED SOLUTION – As follows:

FDA should revise 21 CFR § 111.75(d)(1) to provide that properly completed batch production records are an adequate and effective method for determining whether product specifications are met, for example as follows:

(d)(1) You may exempt one or more product specifications from verification requirements in paragraph (c)(1) of this section if—

(i) You determine and document that the specifications you select under paragraph (c)(1) of this section for determination of compliance with specifications are not able to verify that the production and process control system is producing a dietary supplement that meets the exempted product specification; **or**

³⁵ See for example 64 FR 45934 and 79 FR 11956. In the former FDA states, "...calculation of the soy protein content based on information contained in manufacturers' records is an accurate and practical method for assuring that products bearing the proposed health claim meet the requirement for the qualifying level of soy protein." In the latter FDA states, "The information contained in manufacturers' records is an accurate and practical method for assuring that the nutrient declarations comply with section 403(q) of the FD&C Act." In 21 CFR § 101.9(g)(10), FDA stipulates that manufacturers may rely on databases, formulae, recipes, or batch records to confirm the content of various nutrients. In addition, FDA provides for use of similar documentation to substantiate nutrient content to support health claims in regulations such as 21 CFR §101.82(c)(2)(ii)(B).

(ii) and there ~~There~~ is no current scientifically valid method for testing or examining such exempted product specification at the finished batch stage in the finished product matrix generally available as an AOAC method or in an authoritative English language pharmacopoeial reference.

(2) In such a case—

(i) You may rely on information in your batch records as an accurate and practical method for assuring that the subject specifications are met; and

(ii) you ~~You~~ must document why, for example, any component and in-process testing, examination, or monitoring, and any other information, will ensure that such exempted product specification is met without verification through periodic testing of the finished batch; and

~~(2)~~ **(3)** Your quality control personnel must review and approve the documentation that you provide under paragraphs (d)(1) and (2) of this section.

RELEVANCE TO DOCKET No. FDA-2017-N-5094 AND/OR EO 13771 AND/OR EO 13777 –

The September 8 CFSAN Notice cites in EO 13771 that order's admonishment that it is "essential to manage the costs associated with complying with Federal regulations," and also provides descriptions of the types of regulations that each RRTF is required to attempt to identify, including regulations that "impose costs that exceed benefits." The absence of an option to use properly completed batch records to confirm that specifications for a manufactured dietary supplement has been met greatly increases the costs that are implied, and in fact often directed by FDA inspectors, to develop new chemical analytical methods for every unique dietary supplement.

The September 8 CFSAN Notice also states as a central purpose to assist FDA in identifying "existing regulations and related paperwork requirements that could be modified, repealed, or replaced, consistent with the law..." (emphasis added). As documented in this specific comment, the law – that is, the FDCA – is quite clear that FDA may not impose cGMP standards for which there is no current and generally available analytical methodology, and AHPA's recommendation here seeks only to make the requirements at 21 CFR § 111.75 consistent with this law.

Analytical variability should be taken into account for Class I nutrients

FDA CENTER REGULATING THE PRODUCT – CFSAN

CITATION TO CFR – 21 CFR §§ 101.9 and 101.36

OMB CONTROL NUMBER – Not applicable.

BRIEF DESCRIPTION OF CONCERN – As follows:

Under current FDA regulations, foods must be formulated to provide not less than 100% of the labeled quantity of any Class I nutrient,³⁶ and reasonable excesses of Class I nutrients are permitted in accordance with good manufacturing practice.³⁷ The regulations furthermore provide that FDA must take the variability of the analytical method into account when determining compliance with labeled amounts of Class II nutrients (naturally occurring nutrients), but makes no similar provision with respect to Class 1 nutrients.³⁸

Dietary supplement manufacturers typically compensate for the potential variability of Class I nutrient analyses by using a larger overage of the nutrient in question. However, this may not be possible if the labeled amount is close to the threshold at which safety concerns may arise (e.g., for potassium or selenium). As a result, manufacturers are at risk of having their products deemed misbranded due purely to analytical variability.

AHPA is not aware of any principled reason why consideration of analytical variability should be extended to Class II nutrients but not to Class I nutrients. AHPA therefore recommends that 21 CFR § 101.9(g)(4)(i) be correspondingly amended.

DATA ON COST OR ECONOMIC IMPACT – AHPA has no such data.

³⁶ 21 CFR §§ 101.9(g)(4)(i) (added nutrients) and 101.36(f)(1).

³⁷ 21 CFR §§ 101.9(g)(6) and 101.36(f)(1).

³⁸ 21 CFR §§ 101.9(g)(4)(i) and (ii).

PROPOSED SOLUTION – As follows:

21 CFR § 101.9(g)(4)(i) should be amended by adding the sentence, “*Provided*, That no regulatory action will be based on a determination of a nutrient value that falls below this level by a factor less than the variability generally recognized for the analytical method used in that food at the level involved.”

RELEVANCE TO DOCKET No. FDA-2017-N-5094 AND/OR EO 13771 AND/OR EO 13777 –

One of the questions posed by FDA in the September 8 CFSAN Notice is, “Could the goal of the regulation be achieved by less costly means that would provide the same level of public health protection?” AHPA considers the proposed solution presented above to address this question, and to present a less costly means to meet the regulation’s goal with equal public health protection.

A batch, lot or control number should be affixed to finished dietary supplement labels

FDA CENTER REGULATING THE PRODUCT – CFSAN

CITATION TO CFR – 21 CFR § 111.415

OMB CONTROL NUMBER – Not applicable.

BRIEF DESCRIPTION OF CONCERN – As follows:

21 CFR §111.415 describes procedures to include in filling, assembling, packaging, labeling, and related operations to ensure the quality of the dietary supplement, including:

- “(f) Assigning a batch, lot or control number to:
 - (1) Each lot of packaged and labeled dietary supplement from a finished batch of dietary supplement; and,
 - (2) Each lot of dietary supplement, from a finished batch of dietary supplement, that you distribute to another person for packaging or labeling.”

In the preamble that accompanied accompanying issuance of this section of 21 CFR Part 111, the Agency states: “We do not require you to affix this batch, lot, or control number to the immediate container or the product label” (72 FR 34901) and in fact there is not a requirement in this regulation to affix such an identifying mark on the immediate container of label of a finished dietary supplement.

AHPA requests that this regulation should be revised to require that each such “batch, lot, or control number” be affixed to or otherwise marked on the dietary supplement package that is distributed for sale to consumers.

DATA ON COST OR ECONOMIC IMPACT – AHPA has no such data.

PROPOSED SOLUTION – As follows:

AHPA requests that the rule be amended to replace current 21 CFR § 111.415(f) with the following:

(f) Assigning a batch, lot or control number to, **and affixing or otherwise marking the batch, lot or control number to or on the immediate container or the product label of:**

- (1) Each lot of packaged and labeled dietary supplement from a finished batch of dietary supplement; and,
- (2) Each lot of dietary supplement, from a finished batch of dietary supplement, that you distribute to another person for packaging or labeling.

RELEVANCE TO DOCKET No. FDA-2017-N-5094 AND/OR EO 13771 AND/OR EO 13777 –

One of the questions posed by FDA in the September 8 CFSAN Notice is, “Could the goal of the regulation be achieved by less costly means that would provide the same level of public health protection?” AHPA believes that virtually all supplement labels already provide a batch, lot or control number, so there would be no or very little additional costs to the trade to provide this information on labels. On the other hand, significant additional costs would be borne if a supplement marketer encounters the need for a recall and if the specific lot subject to such recall cannot be easily identified by consumers in possession of the subject product. In such a scenario, the company could need to recall all lots of the subject product, thus increasing their financial burden. In addition, the health of consumers in possession of the subject product may be compromised if they are not aware that the recall applies to the specific lot in their possession.

FDA inspectors should cite the specific regulation associated with each observation issued on FDA Form 483

FDA CENTER REGULATING THE PRODUCT – CFSAN

CITATION TO CFR – 21 CFR Part 111

OMB CONTROL NUMBER – Not applicable.

BRIEF DESCRIPTION OF CONCERN – As follows:

[NOTE: This comment is included in AHPA's comments to this Docket in both the Section III of the comments on issue related to regulations that affect conventional foods and dietary supplement operations as well as farms and importers, and in Section IV of the comments on issue related to cGMP for dietary supplements.]

As AHPA has observed the implementation of the dietary supplement cGMP regulations (21 CFR Part 111) since 2007, it has become aware that inspectional observations issued on FDA Form 483 in association with dietary supplement facility inspections do not normally inform recipients of the specific paragraph(s) in the regulations that are relevant to each observation or deficiency asserted. AHPA understands that this is also FDA's practice when issuing observations on a Form 483 in association with conventional food facility inspections. AHPA understands that Form 483s lack such information because internal Agency policy directs investigators not to disclose the regulatory bases for their observations or to quote or otherwise disclose the relevant regulatory provisions on which investigators base their observations.³⁹ As a result, when a firm receives a Form 483, it is often unclear what element of the regulation FDA considers to be applicable to the observation or deficiency.

This information is necessary for transparency, accurate communication, and ease of comprehension by the regulated trade. Therefore, inclusion of such information would assist the regulated industry in coming into compliance with FDA regulations and thereby promote the public health benefits underlying their promulgation. Furthermore, inclusion of such information would help ensure that

³⁹ See Inspections Operations Manual 5.2.3.3 (2017): "Do not quote Regulations (e.g., specific CFR sections) when listing items."

FDA food facility inspections accurately reflect the provisions of the applicable regulations.

AHPA submitted a Citizen Petition to FDA on October 17, 2013 to request the agency (1) formally rescind FDA's policy of prohibiting Agency investigators from quoting or citing the cGMP regulations upon which they base their inspectional observations within an FDA Form 483 issued to conventional food and dietary supplement facilities; and (2) revise the Agency's Inspections Operations Manual (IOM) to expressly require that Form 483s issued to conventional food and dietary supplement facilities reference each cGMP regulation to which the Agency investigator's listed observations relate.⁴⁰

FDA issued a response to the above-cited AHPA Citizen Petition on July 23, 2014 in which the Agency denied the petition.⁴¹ With regard to the first action requested in the petition, i.e., to formally rescind the described FDA policy, FDA replied that "there is no such policy." AHPA finds this statement to be disingenuous: clearly some sort of policy exists, otherwise 483s and Warning Letters would not uniformly omit information whose inclusion would so obviously be helpful to compliance.

With regard to the second action requested in the petition, i.e., to revise the IOM as described, the Agency replied that "FDA's current practices further the Agency's interests," that "The IOM's procedures promote understanding, compliance, and transparency"; and that "The IOM is consistent with the RPM's [Regulatory Procedures Manual] 'prior notice' policy."

AHPA believes the decision not to cite the link between the investigator's observation and the applicable provision of the regulations disserves the Agency's goal to promote "understanding, compliance, and transparency." It is in the public

⁴⁰ AHPA hereby incorporates by reference to the present comments that October 17, 2013 Citizen Petition, and will submit that document to the present Docket simultaneous to submission of these comments, identified as Addendum 1.

⁴¹ AHPA hereby incorporates by reference to the present comments that July 23, 2014 FDA response to AHPA's Citizen Petition, and will submit that document to the present Docket simultaneous to submission of these comments, identified as Addendum 2.

interest to ensure understanding within the regulated trade by citing the regulatory provisions that apply to each observation or deficiency asserted in a 483.

AHPA acknowledges that some members report that many FDA investigators provide the regulation connection to observations in the inspection closeout meeting either voluntarily or where requested by the facility representative. Nonetheless, whatever motive there might have been or is now in place to refrain from including that information on the FDA 483 should be abandoned in favor of the transparency requested herein.

DATA ON COST OR ECONOMIC IMPACT – AHPA has no such data.

PROPOSED SOLUTION – As follows:

AHPA suggests the Commissioner of Food and Drugs revise the Inspections Operations Manual (IOM) to require that Agency investigators include references to the underlying cGMP regulations in relation to each cGMP-related observation listed in Form 483s issued to conventional food and dietary supplement facilities.

RELEVANCE TO DOCKET No. FDA-2017-N-5094 AND/OR EO 13771 AND/OR EO 13777 –

In the September 8 CFSAN Notice FDA provides descriptions of the types of regulations that each RRTF is required to attempt to identify, including regulations that “impose costs that exceed benefits.” In AHPA’s view, FDA’s current policy imposes an unnecessary cost on the regulated trade, and especially on small businesses, that could be readily alleviated by including references to the relevant paragraphs from cGMP regulations for each Form 483 inspectional observation. Any business, especially small businesses, would benefit from receiving as much information as possible about the regulatory basis of each Form 483 observation, so that management can clearly understand the basis for the problem and what is required to address it.

A 10-year review of 21 CFR Part 111 is in order under the Regulatory Flexibility Act

FDA CENTER REGULATING THE PRODUCT – CFSAN

STATUTORY CITATION – 5 U.S.C. § 610

OMB CONTROL NUMBER – Not applicable.

BRIEF DESCRIPTION OF CONCERN – As follows:

Section 610 of the Regulatory Flexibility Act requires federal agencies to review regulations that have a significant economic impact on a substantial number of small entities within 10 years of their adoption as final rules.⁴²

21 CFR Part 111 was adopted as a final rule in June 2007, and in issuing the rule FDA reported, “this final rule will have a significant economic impact on a substantial number of small entities.”⁴³ The Agency also reported in that same June 2007 rulemaking its analysis of economic effects of the rule on small entities its use of an economic model that predicted at that time that, “as a result of the final rule, 140 very small and 32 small dietary supplement manufacturers⁴⁴ will be at risk of going out of business. The model estimates the number of workers in those firms to be about 2,250.”⁴⁵

Despite 21 CFR Part 111 having been issued as a final rule just over 10 years ago, and despite FDA having acknowledged that the rule will have a significant economic impact on a substantial number of small entities and estimated that over 2,000 jobs could be lost due to the rule, FDA has not to the best of AHPA’s knowledge initiated a process to review 21 CFR Part 111.

As of 2018 FDA continues to find gaps in compliance with 21 CFR Part 111 by dietary supplement firms. AHPA believes these gaps are not entirely the fault of

⁴² 5 U.S.C. § 610.

⁴³ 72 FR 34752, at 34938.

⁴⁴ The total number of very small and small supplement manufacturers are estimated elsewhere in the preamble to the final rule to be 774 and 526, respectively. Thus FDA estimated at that time that the final rule could risk 18 percent of very small businesses and 6 percent of small businesses.

⁴⁵ 72 FR 34752, at 34938.

the regulated trade but are at least partly caused by a lack of clarity, confusing organization, and internal contradictions contained in the rule as currently written. AHPA therefore believes a thorough review of the rule is in order.

In addition to problems in the rule cited elsewhere in these comments, AHPA offers the following examples of areas where the rule should be rewritten for clarity or practicality. These are only examples; AHPA would be willing to provide a more extensive list if FDA would find it useful.

- (a) The rule calls for an excessive number of written justifications for points that are either obvious, superfluous, or redundant. For example, § 111.70(c)(1) requires that manufacturers provide “adequate documentation of your basis for why meeting the in-process specifications, in combination with meeting component specifications, will help ensure that the specifications are met for the identity, purity, strength, and composition of the dietary supplements and for limits on those types of contamination that may adulterate or may lead to adulteration of the finished batch of the dietary supplement.” However, this justification should not be necessary in every circumstance (e.g., if every lot of finished product is tested for such specifications). Similarly, § 111.75(c)(3) mandates written justifications that should not be required in all circumstances (e.g., if all established specifications are tested in the finished product).

- (b) The precise intent of certain provisions of the rule is not clear, even to manufacturers with experienced quality control staff. For example, § 111.75(d)(1) provides, “You may exempt one or more product specifications from verification requirements in paragraph (c)(1) of this section if you determine and document that the specifications you select under paragraph (c)(1) of this section for determination of compliance with specifications are not able to verify that the production and process control system is producing a dietary supplement that meets the exempted product specification and there is no scientifically valid method for testing or examining such exempted product specification at the finished batch stage.” AHPA requests that sentences such as this be rewritten in a manner that is unambiguous and readily understood.

(c) Certain elements of the rule are overly prescriptive or too limited. For example, § 111.77(a) requires that if a component or product fails to meet established specifications, quality control personnel must either reject the material or approve an appropriate treatment, in-process adjustment, or reprocessing to ensure the quality of the finished product. However, it is not uncommon that a component which deviates from specifications may still be used without requiring such additional steps and without compromising quality. For example, quality control may determine that an ingredient that fails to meet a particle size specification can still be used without any change to the manufacturing process and without affecting product quality.

In addition, this provision's list of remedial options is too limited. For example, if an ingredient lot is subpotent, quality control may still approve its use so long as the amount of the ingredient in product batches is correspondingly increased; this is an adjustment, but it is not an "in process" adjustment. Similarly, if a component fails to meet its specifications then quality control may determine that the established specifications are too strict and should be revised; the rule as currently written does not contemplate this option.

As another example, § 111.260(l)(1)(ii) requires component test records to be included in the batch production record, but as a general rule this is both impractical and unnecessary. Dietary supplement manufacturers have systems for receiving, quarantining, sampling, testing, and approving or rejecting each lot of components; these systems and related documents are separate from those for manufacturing, sampling, testing, and approving or rejecting each finished product batch. Since each lot of component will likely be used in many different batches of product, it would be onerous and pointless to include copies of the component records in every batch record where the component is used. And since the components are approved or rejected before production of a finished product batch even begins, there is no need for quality control to re-review the component-related documents in order to approve or reject the finished batch.

DATA ON COST OR ECONOMIC IMPACT – AHPA has no original data but notes that FDA provided estimated costs when the final rule was issued.⁴⁶

PROPOSED SOLUTION – As follows:

FDA should consider a complete review and rewrite of 21 CFR Part 111 with input from the regulated trade, not to expand the burdens it imposes on industry but simply to ensure the requirements are both appropriate and clearly stated, and that the rule provides sufficient flexibility to be practical. A review of the rule with a better focus on transparency and collaboration could result in revisions that might lead both to better compliance and saved jobs in small businesses.

RELEVANCE TO DOCKET NO. FDA-2017-N-5094 AND/OR EO 13771 AND/OR EO 13777 –

One of the questions posed by FDA in the September 8 CFSAN Notice is, “Could the goal of the regulation be achieved by less costly means that would provide the same level of public health protection?” AHPA considers the proposed solution presented above to address this question, and strongly believes that an in-depth review and appropriate amendment of 21 CFR Part 111 would present a less costly means to meet the regulation’s goal with equal or even improved public health protection.

V. Issues related to Produce Safety rule (21 CFR Part 112)

The following issue is specifically addressed to details in 21 CFR Part 112 and to related rules in 21 CFR Part 117.

Adjust definitions and scope of 21 CFR Part 112 for Produce Safety, and related definitions in Part 117 for food manufacturing, to conform to Congressional intent

FDA CENTER REGULATING THE PRODUCT – CFSAN

CITATION TO CFR – 21 CFR §§ 112.1, 112.2, 112.3, 117.3

OMB CONTROL NUMBER – Not applicable.

⁴⁶ Ibid.

BRIEF DESCRIPTION OF CONCERN – As follows:

In promulgating regulations under the Food Safety Modernization Act (FSMA), FDA adopted a formal definition of “produce” and an interpretation of “processed food” which, taken together, will unnecessarily impose the burdens of Part 112 on a large proportion of farmers, and will furthermore transform many farmers into food manufacturers subject to the heavy expenses of compliance with food Good Manufacturing Practice (GMP) regulations.

AHPA believes these actions by FDA are fundamentally wrongheaded and go far beyond the Congressional intent of FSMA.

To begin with, in passing FSMA, Congress directed FDA to develop regulations to ensure the safety of “produce” consumed by the American public. The term “produce” is ordinarily understood to encompass those fruits and vegetables (and arguably also nuts, sprouts, mushrooms, and culinary herbs such as parsley or basil) that are commonly consumed in fresh, unprocessed form.⁴⁷

In promulgating the implementing regulations for FSMA, however, FDA goes much farther than this. FDA has defined “produce” to encompass every crop meeting the botanical definition of a “fruit” (i.e., the reproductive structure of a plant that develops from a flower) or “vegetable” (i.e., any part of a plant or fungus other than the fruit) with the sole exception of food grains.

FDA also promulgated in 21 CFR § 112.1(b)(1) a list of examples of produce covered by the rule⁴⁸ and in § 112.2(a)(1) a defined list of produce excluded from the rule; FDA describes this list as an “exhaustive” list of produce that is rarely consumed raw, but in fact it fails to include many food crops that are rarely

⁴⁷ The Merriam-Webster Dictionary defines the noun “produce” to mean “agricultural products and especially fresh fruits and vegetables as distinguished from grain and other staple crops.”

⁴⁸ AHPA notes this list is not comprehensive but is merely a list of examples, because the rule states that the produce covered by the rule “includes” the items in the list, and FDA has previously stated in 78 FR 3694 that it would use “includes” to mean “includes, but is not limited to” in regulations.

consumed raw (e.g., yuca (cassava) root; taro root; yams; tepary beans; mashua tubers; ginkgo nuts; etc.).⁴⁹

The net effect of these provisions leaves a wide variety of crops that are not commonly understood as “produce” and which are always or almost always cooked or otherwise processed prior to consumption, nevertheless subject to the burdens of Part 112 “Produce Safety” compliance. This includes a huge range of crops used to make the flavors, colors, excipients, process aids, and dietary ingredients used in food, including dietary supplements (collectively hereinafter referred to as “non-fresh-produce botanicals”). For example, unless the farmer qualifies for an exemption (and maintains the associated documentation required therefor), FDA has imposed the extensive costs and burdens of Part 112 on the cotton used to make microcrystalline cellulose; the acacia used to make gum arabic; the alfalfa used to make green food color; the oak chips used to make food flavorings; and the hops used to make beer. This makes no sense.

AHPA believes this goes far beyond the intent of Congress in passing FSMA; that FDA has neither the authority nor the resources to enforce Part 112 compliance on such a wide range of farm operations; that, as discussed elsewhere in these comments, even the maintenance of the documents required to obtain FDA-sanctioned exemption from Part 112 (e.g., the “annual written assurances” required in 21 CFR § 112.2(b)(3)) represents a significant and largely pointless burden; and, most importantly, that Part 112 “Produce Safety” compliance *is not necessary to protect the public health* for crops that are not, in fact, “produce” *that is consumed in fresh, unprocessed form*, especially in view of the new food manufacturing safety requirements imposed under 21 CFR Part 117.

⁴⁹ AHPA notes that there appears to be little discernible logic or science behind the inclusion of any given food crop on the § 112.1(b)(1) list of produce covered by the rule vs. the § 112.2(a)(1) list of produce excluded from the rule. To take just one example, “yams” (which contain toxins and are almost never eaten raw) are covered by the rule, while “sweet potatoes” (which are not toxic and may occasionally be eaten raw) are excluded from the rule. Similarly, “taro” (which is toxic and is never eaten raw), “plantains” (which, while not toxic, are unpleasant, somewhat bitter, and difficult to digest when raw), and “cowpea beans” (which are no more likely to be eaten raw than the various beans exempted in § 112.2(a)(1)) are all covered by the rule, for reasons that remain mysterious.

AHPA therefore strongly recommends that the scope of Part 112 should be significantly narrowed to focus specifically on those crops that are, in fact, likely to be consumed by the public in fresh, unprocessed form and for which stringent food safety regulations at the farm level are therefore truly justified to protect the public health.

Additional concerns arise in grappling with the distinction between “raw agricultural commodities” (RACs) and “processed food,” where FDA has drawn the line in a manner that significantly expands the scope of what is considered “processed food,” redefining as “processed food” thousands of items that previously were considered “raw agricultural commodities.” This will transform many farm operations into “food manufacturers” that are subject to facility registration⁵⁰ and good manufacturing practices for food.⁵¹ FDA’s current policy with respect to “processed food” is fundamentally inconsistent with facts on the ground and in adopting this position, FDA has acted without the authority of Congress.

21 USC § 321(gg) defines “processed food” to mean “any food other than a raw agricultural commodity and includes any raw agricultural commodity that has been subjected to processing, such as canning, cooking, freezing, dehydration, or milling.” 21 USC § 321(r) defines “raw agricultural commodity” to mean “any food in its raw or natural state, including all fruits that are washed, colored, or otherwise treated in their unpeeled natural form prior to marketing.”

To apply these statutory terms in practice, it has been necessary to consider various nuances to accommodate the realities of the food supply chain. For example, while “dehydration” is listed as an activity that creates a processed food, FDA has long interpreted this provision to apply only when the dehydration creates a new or distinct commodity (for example, drying grapes into raisins). In contrast, where the dehydration is a normal part of preparing the crop for trade as food (e.g., drying of hay or grains), FDA considers that the resulting material

⁵⁰ 21 CFR Part 1 Subpart H.

⁵¹ For example, 21 CFR Part 117 and/or 21 CFR Part 111.

remains a “raw agricultural commodity” rather than a “processed food.” AHPA agrees with this interpretation.

However, in promulgating the implementing regulations for FSMA, FDA has defined “manufacturing/processing” very broadly and “farm” very narrowly.⁵² As a result, numerous activities that farms normally use to prepare a food crop for trade as a RAC are now activities that transform the crop into a “processed food” and are therefore subject to food facility registration and food GMPs.

For example, FDA considers⁵³ cutting, chopping, and slicing to be “manufacturing/processing” activities that are outside the scope of the farm definition and therefore subject to food facility registration and regulations. AHPA does not disagree that, with respect to crops *that are used as fresh produce* as that term is commonly understood (for example, apples, lettuce, or carrots), these activities do transform the RAC into a processed food. However, for crops that are not typically used as fresh produce (i.e., “non-fresh-produce botanicals” - see comments above; these include, for example, crops used to make food flavors, colors, excipients, dietary ingredients, etc.), these activities are often a farm activity normally used to prepare the crop for sale *as a raw agricultural commodity*. Non-fresh-produce botanicals are normally traded in dehydrated form and packed in sacks, and as a practical matter these botanicals often require some kind of size reduction in order to facilitate dehydration, handling, and packing. For example, large roots and many barks are typically cut into smaller pieces to facilitate drying, packing, and handling. In these circumstances, the cutting, chopping or slicing is not “adding value” to the commodity or “transforming” the commodity into a new commodity; they are steps taken as a practical matter in order to prepare the crop for sale as a RAC.

As a further example, FDA considers heating (except brief external heating to kill pests) and freezing (for any purpose) to be “manufacturing/processing” activities

⁵² See 21 CFR § 112.3 and 21 CFR § 117.3.

⁵³ FDA’s current thinking on these matters can be found in the draft guidance “Classification of Activities as Harvesting, Packing, Holding, or Manufacturing/Processing for Farms and Facilities: Guidance for Industry,” August 2016.

that are outside the scope of the farm definition. Again, AHPA does not disagree that heating or freezing of *crops used as fresh produce* transforms the RAC into a processed food; for example, AHPA agrees that cooked tomatoes and frozen peas are processed foods rather than RACs. However, for non-fresh-produce botanicals, it is quite common that heating or freezing is a normal farm activity used to prepare the crop for sale as a RAC. For example, the harvested crop may be heated or temporarily frozen in order to kill pests, to kill the plant tissue and stop further development, or to initiate enzymatic fermentation. Furthermore, heating such as boiling or steaming may be necessary to soften the material in order to facilitate size reduction for packing (e.g., for bark and similarly tough materials). Again, these steps *when applied to crops that are not fresh produce crops* do not create a separate commodity but merely prepare the crop for sale *in its normal form as a RAC*.

AHPA therefore strongly contends that FDA must acknowledge the distinction between produce crops and non-fresh-produce crops, and must permit a much wider range of activities to remain within the farm definition when performed on non-fresh-produce crops. In the absence of these adjustments, these rules as currently written will cause massive and unnecessary disruption to farm operations, significantly increasing costs to food processors and consumers, with no concomitant benefit in public health protection.

DATA ON COST OR ECONOMIC IMPACT – AHPA has no such data.

PROPOSED SOLUTION – As follows:

The scope of 21 CFR Part 112 should be significantly narrowed to focus specifically on those crops that are, in fact, likely to be consumed by the public in fresh, unprocessed form and for which stringent food safety regulations at the farm level are therefore truly justified to protect the public health. In addition, FDA needs to acknowledge the distinction between produce crops and non-fresh-produce crops, and for practicality must permit a much wider range of activities to remain within the farm definition when performed on non-fresh-produce crops. In the absence of these adjustments, these rules as currently written will cause massive and unnecessary disruption to farm operations, significantly increasing

costs to food processors and consumers, with no concomitant benefit in public health protection.

RELEVANCE TO DOCKET No. FDA-2017-N-5094 AND/OR EO 13771 AND/OR EO 13777 –

In the September 8 CFSAN Notice FDA provides descriptions of the types of regulations that each RRTF is required to attempt to identify, including regulations that “are ... ineffective” or “impose costs that exceed benefits.” For the reasons stated above, AHPA believes the regulation cited here as currently written are extremely ineffective and will impose unnecessary and quite costly burdens on many affected businesses. AHPA further believes these issues can be readily corrected by accepting AHPA recommended revision, with no diminution whatsoever to public health protection.

VI. Issues related to labeling of food (inc. conventional food and dietary supplements)

The following issues are specifically addressed to certain FDA regulations that affect labeling of conventional food products and that may also, to the degree that certain food labeling rules also apply to dietary supplement labeling, affect labeling of dietary supplements.

Greater clarity and transparency is needed in FDA’s guidance documents on scientific evaluation for health claims and qualified health claims

FDA CENTER REGULATING THE PRODUCT – CFSAN

CITATION TO CFR AND STATUTORY CITATION – 21 U.S.C. § 343(r)(3); 21 CFR § 101.14(c); elsewhere as applicable

OMB CONTROL NUMBER – Not applicable.

BRIEF DESCRIPTION OF CONCERN – As follows:

In January 2009 FDA issued “Guidance for Industry: Evidence-Based Review System for the Scientific Evaluation on Health Claims-Final,” hereinafter referred to as the Health Claims Guidance, that describes a systematic science-based evaluation system the Agency intends to use to evaluate Significant Scientific Agreement (SSA) health claims and qualified health claims. In the Health Claims

Guidance, the Agency addresses specific topics to inform industry about FDA's interpretation of the SSA standard for authorizing health claims. Despite FDA's intention to provide guidance to health claim petitioners on how the Agency will "determin[e] whether there is SSA to support an authorized health claim, or credible evidence to support a qualified health claim," the Health Claims Guidance does not reflect current best practices in systematic review framework and provides inadequate information to the industry to understand how the Agency will conduct systematic science-based evaluations of the strength of the evidence in an objective manner. AHPA notes that FDA's "Guidance for Industry: Interim Procedures for Qualified Health Claims in the Labeling of Conventional Human Food and Human Dietary Supplements," published in 2003, also lacks transparency and does not provide sufficient clarity on the objective standard used by the Agency to determine qualified claims language.

DATA ON COST OR ECONOMIC IMPACT – AHPA has no such data.

PROPOSED SOLUTION – As follows:

AHPA requests FDA to provide sufficient information for the industry to clearly understand how the Agency evaluates and assesses scientific evidence and arrives at an objective conclusion about SSA health claims and qualified health claims. AHPA also requests FDA to adjust the Agency's evaluation process to improve scientific accuracy.

More specifically:

- **Reduce bias to improve scientific rigor:** In the Health Claims Guidance, FDA states that the Agency will only consider "publicly available data and written information pertaining to the relationship between a substance and disease." For a systematic review to be rigorous, AHPA requests that unpublished data to be also considered as long as the information is pertinent for the evaluation of health claims. According to the U.S. Department of Health and Human Services' Agency for Healthcare Research and Quality's "Methods Guide for Effective and Comparative Effectiveness Reviews" (2014), a comprehensive literature search in a systematic review process includes both published studies as well as "grey literature" defined as, "that which is produced on all levels of government, academics, business and industry in print and electronic

formats, but which is not controlled by commercial publishers.” Examples of “grey literature” include unpublished trial data. This is recommended to identify and overcome any bias introduced by selecting only published studies and for an objective assessment of reporting bias for each study. Similarly, in its “Guidance Document for Preparing a Submission for Food Health Claims” (2009), Health Canada allows applicants to submit unpublished and in-press articles in the petition in addition to published studies. Additionally, in its most recent “Scientific and Technical Guidance for the Preparation and Presentation of a Health Claim Application” (2016), the European Food Safety Authority requests that all pertinent scientific data, both published and unpublished, be submitted for review. FDA should adopt similar procedures. This revision would allow FDA to draw a conclusion based on a comprehensive review of scientific evidence with reduced reporting bias and random error.

- Transparency in assessing methodological quality of studies and strength of studies: In the Health Claims Guidance, FDA lists a number of factors for consideration when assessing the methodological quality of studies, such as study design, data collection, the quality of statistical analysis, the type of outcome measured, and the study population characteristics. However, the Agency does not provide an objective way to appraise quality of each study using a rating system. A transparent and robust appraisal system and standard scale can help industry to estimate whether a study would receive a high, moderate, or low quality rating. In its “Guidance Document for Preparing a Submission for Food Health Claims” (2009), Health Canada provides an objective way for petitioners to conduct quality appraisal of both intervention and observational studies. By using the tool, petitioners can easily understand what is expected from the regulatory agency; such transparency helps eliminate questions of bias or subjectivity in the assessment. FDA should adopt a similar approach.

- Transparency in assessing totality of scientific evidence: According to FDA’s Health Claims Guidance, “the SSA standard is intended to be a strong standard that provides a high level of confidence in the validity of the substance/disease relationship... [that] is not likely to be reversed by new and

evolving science.” AHPA requests FDA to provide an objective system to be used by qualified experts in evaluating the totality of scientific evidence and to provide a definition of “a high level of confidence.” FDA’s explanation should inform the industry on the scientific evidence threshold required for a SSA health claim, and should ensure that a consistent approach is applied from one health claim review to another.

- Transparency in specifying qualified health claim language: AHPA also requests FDA to provide a transparent and objective system used to evaluate scientific evidence to specify language for qualified health claims. The Health Claims Guidance does not provide clarity on how FDA comes to a decision on scientific ranking associated with qualified claims language using an objective tool. This is also not clearly addressed in FDA’s “Guidance for Industry: Interim Procedures for Qualified Health Claims in the Labeling of Conventional Human Food and Human Dietary Supplements” (2003), except that the Agency plans to establish criteria at some point. In July 2003, the Agency published “Guidance for Industry and FDA: Interim Evidence-based Ranking System for Scientific Data,” in which the Agency has chosen to model its system on Institute for Clinical Systems Improvement’s system published in 2000. Since then, a number of expert groups have published scientific evidence rating systems such as the Grading of Recommendations, Assessment, Development and Evaluation (GRADE) approach, the Consolidated Standards of Reporting Trials (CONSORT) statements, and the Strengthening the Report of Observational Studies in Epidemiology (STROBE) initiative. AHPA requests FDA to update its guidance documents by providing a clear guidance to the industry on how the Agency intends to objectively rank scientific evidence that translates into a qualified health claim language, and encourages FDA to adopt procedures modeled on the more recent recommendations from these expert groups.

RELEVANCE TO DOCKET No. FDA-2017-N-5094 AND/OR EO 13771 AND/OR EO 13777 –

One of the questions posed by FDA in the September 8 CFSAN Notice is, “Could the goal of the regulation be achieved by less costly means that would provide the same level of public health protection?” AHPA believes the proposed solutions would reduce costs for both FDA and the regulated trade, by providing clear and

transparent roadmaps for evaluation and assessment of scientific evidence to arrive at objective conclusions regarding the validity of SSA health claims and qualified health claims. In addition, the inclusion of the totality of the scientific evidence – rather than merely publicly available data – will enhance public health by improving the accuracy of the information provided to consumers in the form of such claims.

The revised rule for nutrition labeling for dietary fiber should be reviewed and revised to reduce the burden of citizen petitions and to “grandfather” ingredients recognized by international health authorities

FDA CENTER REGULATING THE PRODUCT – CFSAN

CITATION TO CFR – 21 CFR §§ 10.30 and 101.9

OMB CONTROL NUMBER – Not applicable.

BRIEF DESCRIPTION OF CONCERN – As follows:

On May 27, 2016, FDA published the final rule amending the Nutrition Facts and Supplement Facts label regulations at 21 CFR §§ 101.9 and 101.36. The amended rule defines the term “dietary fiber” for the first time for the purposes of nutrition labeling, as “non-digestible soluble and insoluble carbohydrates (with three or more monomeric units), and lignin that are intrinsic and intact in plants; isolated or synthetic non-digestible carbohydrates (with three or more monomeric units) determined by FDA to have physiological effects that are beneficial to human health.” FDA has determined to use the citizen petition process (21 CFR § 10.30) for manufacturers to submit a petition to request an amendment to the definition of dietary fiber.

In addition, under the revised rule FDA does not recognize isolated or synthetic non-digestible carbohydrates identified by foreign government agencies: In the final rule amending the Nutrition Facts and Supplement Facts label regulations, FDA declines to accept a list of isolated or synthetic non-digestible carbohydrates for which the European Food Safety Authority (EFSA) has authorized health claims based on beneficial physiological effects. AHPA believes EFSA has adequate evidence of benefit for the fibers in its list and FDA should not adopt a list that is more restrictive than the EFSA list.

DATA ON COST OR ECONOMIC IMPACT – AHPA has no such data.

PROPOSED SOLUTION – As follows:

AHPA requests FDA adjust the list of approved dietary fibers to include additional non-digestible carbohydrates that the European Commission currently authorizes for health claims, so that these additional ingredients may be used as sources of dietary fiber in U.S. marketed foods without manufacturers having to send citizen petition. In the final rule amending the Nutrition Facts and Supplement Facts label regulations, FDA determined that only beta-glucan soluble fiber, psyllium husk, cellulose, guar gum, pectin, locust bean gum and hydroxypropylmethylcellulose meet the new “dietary fiber” definition because these added dietary fiber sources have beneficial physiological effects such as improving bowel function and lowering blood total and/or LDL cholesterol levels. Similarly in the European Union, added non-digestible carbohydrates must show beneficial physiological effects for the European Commission to authorize health claims for these fibers. Since FDA and European Commission both share the same definition of “dietary fiber,” and since EFSA is equally as competent to evaluate health benefits as FDA, the lists used in both markets should be harmonized. AHPA therefore requests the Agency to include all fibers for which the European Commission has authorized health claims, in the list of dietary fibers in 21 CFR § 101.9(c)(6)(i).

RELEVANCE TO DOCKET NO. FDA-2017-N-5094 AND/OR EO 13771 AND/OR EO 13777 –

In the September 8 CFSAN Notice FDA provides descriptions of the types of regulations that each RRTF is required to attempt to identify, including regulations that “are ... ineffective” or “impose costs that exceed benefits.” For the reasons stated above, AHPA believes FDA’s currently described approach to addressing labeling of dietary fiber in food and supplement products is both ineffective and imposes unnecessary costs on food and supplement marketers that provide products that include dietary fiber. AHPA further believes these issues can be readily corrected by accepting AHPA’s recommended revisions.

Greater clarity and transparency is needed in FDA's guidance documents on scientific evaluation for evidence on beneficial effects of non-digestible carbohydrates

FDA CENTER REGULATING THE PRODUCT – CFSAN

CITATION TO CFR – 21 CFR §§ 10.30 and 101.9

OMB CONTROL NUMBER – Not applicable.

BRIEF DESCRIPTION OF CONCERN – As follows:

In November 2016 FDA issued “Scientific Evaluation of the Evidence on the Beneficial Physiological Effects of Isolated or Synthetic Non-digestible Carbohydrates Submitted as a Citizen Petition (21 CFR § 10.30): Guidance for Industry,” hereinafter referred to as the Dietary Fiber Guidance. This guidance explains the scientific review approach the Agency plans to use for evaluating scientific evidence to determine whether an isolated or synthetic non-digestible carbohydrate that is added to food has a physiological effect that is beneficial to humans. Despite FDA's intention to provide information to those submitting evidence to the Agency to determine if the added non-digestible carbohydrate meets the new definition of “dietary fiber,” the Dietary Fiber Guidance provides inadequate information to the industry to understand the strength of the evidence required and how the Agency will evaluate the evidence in an objective manner.

DATA ON COST OR ECONOMIC IMPACT – AHPA has no such data.

PROPOSED SOLUTION – As follows:

AHPA requests FDA to provide sufficient information for the industry to clearly understand how the Agency evaluates and assesses scientific evidence and arrives at an objective conclusion about the beneficial physiological effects of isolated or synthetic non-digestible carbohydrates. AHPA also requests FDA to adjust the Agency's evaluation process to improve scientific accuracy.

- More specifically: *Reducing bias to improve scientific rigor*: In the Dietary Fiber Guidance, FDA states that the agency will only consider “publicly available data and written information.” For the scientific review to be rigorous, AHPA requests that unpublished data to be also considered as long as the information is relevant for the evaluation of beneficial physiological effects of added non-digestible carbohydrates. According to the U.S. Department of

Health and Human Services' Agency for Healthcare Research and Quality's "Methods Guide for Effective and Comparative Effectiveness Reviews" (2014), a comprehensive literature search in a systematic review process includes both published studies as well as "grey literature" defined as, "that which is produced on all levels of government, academics, business and industry in print and electronic formats, but which is not controlled by commercial publishers." Examples of "grey literature" include unpublished trial data. This is recommended to identify and overcome any bias introduced by selecting only published studies and for an objective assessment of reporting bias for each study. Similarly, in its "Guidance Document for Preparing a Submission for Food Health Claims" (2009), Health Canada allows applicants to submit unpublished and in-press articles in the petition in addition to published studies. Additionally, in its most recent "Scientific and Technical Guidance for the Preparation and Presentation of a Health Claim Application" (2016), EFSA requests that all pertinent scientific data, both published and unpublished, be submitted for review. FDA should adopt similar procedures. This revision would allow FDA to draw a conclusion based on a comprehensive review of scientific evidence with reduced reporting bias and random error.

- Clearly define the level of evidence required to demonstrate beneficial physiological effect: AHPA requests FDA to provide an objective system for use in evaluating the totality of scientific evidence to make a determination on whether or not an isolated or synthetic non-digestible carbohydrate has a beneficial physiological effect. The Dietary Fiber Guidance does not provide adequate guidance on the level of scientific evidence required. FDA's explanation would inform the industry to better understand the amount of scientific evidence required for an ingredient to be considered as having a beneficial physiological effect.

RELEVANCE TO DOCKET No. FDA-2017-N-5094 AND/OR EO 13771 AND/OR EO 13777 –

One of the questions posed by FDA in the September 8 CFSAN Notice is, "Could the goal of the regulation be achieved by less costly means that would provide the same level of public health protection?" AHPA considers the proposed solutions presented above to address this question, and to represent alternative means of ensuring thorough public health protection.

Clarity and consistency are needed in FDA's description of how protein is calculated for nutrition labeling

FDA CENTER REGULATING THE PRODUCT – CFSAN

CITATION TO CFR – 21 CFR § 101.9

OMB CONTROL NUMBER – Not applicable.

BRIEF DESCRIPTION OF CONCERN – As follows:

21 CFR § 101.9(c)(7) provides that a food label must declare the number of grams of protein in a serving, and that protein content *may* (emphasis added) be calculated on the basis of the factor 6.25 times the nitrogen content of the food as determined by the appropriate AOAC method of analysis except when the official procedure for a specific food requires another factor.

The optional nature of this provision can lead to use of various practices in calculating protein for the labeling of foods (e.g., breakfast cereal, meal replacement products, dietary supplements, etc.) that contain protein combined with non-protein sources of nitrogen such as free amino acids and non-proteinogenic nitrogen compounds (L-carnitine, creatine, D-phenylalanine, adenosine, niacinamide, etc.). Companies may calculate the declared protein content either: (1) exactly as described in the rule, and thus measuring the total nitrogen content – including nitrogen from non-proteinogenic sources – and multiplying by the appropriate factor; or (2) may instead determine the amount of nitrogen, calculate an “apparent” total protein content, and subtract the known quantities of non-protein nitrogen compounds (e.g., free proteinogenic amino acids; non-proteinogenic amino acids; other nitrogen-containing compounds such as nucleotides, vitamins, or alkaloids when present in appreciable quantities) to arrive at the declared protein content; or (3) the protein content may be determined by measuring the total amino acid content and subtracting the free amino acid content (this method is often preferable for complex matrices and foods containing a wide variety of nitrogen sources). Depending on which of these three calculations is used, the level of protein determined to be present in a food and declared in its labeling may vary in quantity, even though each of these means of calculation apparently comply with the rule.

AHPA believes it is not desirable to have the protein content of foods labeled using widely divergent approaches by different companies. To address this concern, AHPA and the Council for Responsible Nutrition (CRN) in 2014 developed guidelines for industry recommending that the declared content of protein in grams should represent only actual protein (i.e., free proteinogenic amino acids, free non-proteinogenic amino acids, and other non-proteinogenic nitrogen compounds should be excluded).⁵⁴

Even though 21 CFR § 101.9(c)(7) as written allows different calculations of the level of protein in a food as noted above, FDA apparently agrees with the approach recommended by AHPA and CRN as evidenced by the following published statement:

“FDA requires that dietary supplements be labeled in a manner that is truthful and not misleading. With regard to the labeling of protein content, FDA’s expectation for proper nutrition labeling is that firms will evaluate the protein content from actual protein sources—not other nitrogen-containing ingredients such as individual amino acids—and label the products consistent with the results of such evaluations,” said FDA press officer Jennifer Dooren.

Dooren added that FDA regulations for dietary supplements specifically require that “protein shall not be declared on labels of products that, other than ingredients added solely for technological reasons, contain only individual amino acids.”⁵⁵

AHPA believes consumers deserve accurate, reliable, and consistent information about the protein content of the foods they consume. AHPA furthermore believes that industry members deserve a level playing field on which to compete; companies who choose to use stricter, more accurate criteria for declaring protein content should not be placed at a disadvantage to companies that use looser, less accurate criteria. AHPA therefore requests that FDA should revise the protein labeling regulations to ensure consistency and accuracy.

⁵⁴ The AHPA guidelines can be accessed at http://www.ahpa.org/Portals/0/PDFs/Policies/Guidance-Policies/AHPA_Labeling_Protein_FoodDietarySupplements.pdf?ver=2016-04-26-135912-380.

⁵⁵ Morrell A. March 12, 2015. Lawsuits Say Protein Powders Lack Protein, Ripping Off Athletes. Forbes.com: <https://www.forbes.com/sites/alexmorrell/2015/03/12/lawsuits-say-protein-powders-lack-protein-ripping-off-athletes/#4c25813e7729>; accessed November 8, 2017.

DATA ON COST OR ECONOMIC IMPACT – AHPA has no such data.

PROPOSED SOLUTION – As follows:

AHPA submitted extensive comments on August 1, 2014 to FDA’s proposed rule titled, “Food Labeling: Revision of the Nutrition and Supplement Facts Labels” (Docket No. FDA-2012-N-1210). AHPA included in those comments specific recommendations to update and clarify FDA’s regulatory provisions for protein labeling in the context of the Agency’s proposed 2014 revisions to the nutrition labeling rule, including recommended revisions to 21 CFR §§ 101.9(c)(7), 101.9(g)(10), 101.36(b)(2)(i), and 101.36(b)(2)(111)(B). AHPA hereby restates each of these recommended regulatory revisions and incorporates by reference to the present comments an excerpt from the above-cited August 1, 2014 comments consisting of that portion of those comments that address protein labeling and the contained AHPA recommendations for protein labeling regulations, and will submit that excerpt, identified as Addendum 3, to the present Docket simultaneous to submission of these comments.

RELEVANCE TO DOCKET No. FDA-2017-N-5094 AND/OR EO 13771 AND/OR EO 13777 –

One of the questions posed by FDA in the September 8 CFSAN Notice is, “Could the goal of the regulation be achieved by less costly means that would provide the same level of public health protection?” AHPA considers the proposed solution presented above to address this question, and believes it would present a less costly means to meet the regulation’s goal with equal or even improved public health protection.

Certain claims that a conventional food product affects the structure or function of the body should not be considered to be drug claims

FDA CENTER REGULATING THE PRODUCT – CFSAN

STATUTORY CITATIONS – 21 U.S.C. § 321(g)(1)(C) and § 343(r)

OMB CONTROL NUMBER – Not applicable.

BRIEF DESCRIPTION OF CONCERN – As follows:

On its website, FDA notes that structure/function claims may be made for foods as follows:

Structure/function claims for conventional foods focus on effects derived from nutritive value, while structure/function claims for dietary supplements may focus on non-nutritive as well as nutritive effects. FDA is likely to interpret the dividing line between structure/function claims and disease claims in a similar manner for conventional foods as for dietary supplements.

FDA does *not* require conventional food manufacturers to notify FDA about their structure/function claims, and disclaimers are not required for claims on conventional foods.⁵⁶

AHPA finds the first paragraph's analysis to be outdated and, in view of current science, unjustifiably restrictive. Dietary science continues to discover new and additional ways by which foods promote health that are not strictly tied to the "nutritive value" of the food; for example, the benefits of dietary fiber are now well recognized, although dietary fiber is not a nutrient essential for human survival, growth, or reproduction.

Therefore, while AHPA agrees that structure/function claims are allowed for conventional foods, AHPA does not believe such claims should be limited to "effects derived from nutritive value."

For example, probiotics are a class of foods that has been in the market place for many years. Many probiotics are self-affirmed as GRAS for use in foods and many of these are notified to FDA under 21 CFR 170.203. Probiotics should be recognized by FDA as a category of foods and food ingredients that may make structure/function claims (e.g., for digestive health) under the policy set forth above. Similarly, botanical ingredients used as conventional food or in conventional food, e.g., cherries, should also be recognized as a category of foods and food ingredients that may make such claims (e.g., based on the benefits of anthocyanins). Both, of course, may not make disease claims.

DATA ON COST OR ECONOMIC IMPACT – AHPA has no such data.

⁵⁶ <https://www.fda.gov/Food/LabelingNutrition/ucm2006881.htm>; accessed February 3, 2018.

PROPOSED SOLUTION – As follows:

FDA's policy with respect to structure/function claims for conventional foods should be clarified and expanded to avoid restricting these claims to those based on "nutritive value."

RELEVANCE TO DOCKET No. FDA-2017-N-5094 AND/OR EO 13771 AND/OR EO 13777 –

One of the questions posed by FDA in the September 8 CFSAN Notice is, "Could the goal of the regulation be achieved by less costly means that would provide the same level of public health protection?" AHPA considers the proposed solution presented above to address this question, and believes it would present a less costly means to meet the regulation's goal with equal public health protection.

Except for nutrients that have an established RDI or DRV, the use of ingredient and constituent names should be allowed to be highlighted on food labels without declaring the quantity in the same place

FDA CENTER REGULATING THE PRODUCT – CFSAN

CITATION TO CFR – 21 CFR §§ 101.13 and 101.54

OMB CONTROL NUMBER – Not applicable.

BRIEF DESCRIPTION OF CONCERN – As follows:

Under the present regulations for nutrient content claims, a claim that a particular substance is contained in a food must be accompanied by the amount of the substance in the food. This is set forth in the Food Labeling Guide as follows:⁵⁷

N21. Is there any way that a manufacturer can let consumers know that a product contains nutrients without DVs, such as omega-3 fatty acids?

Answer: A manufacturer may make a statement about a nutrient for which there is no established daily value as long as the claim specifies only the amount of the nutrient per serving and does not implicitly characterize the level of the nutrient in the product. Such a claim might be "x grams of omega3 fatty acids." Such claims must be outside the Nutrition Facts label. 21 CFR 101.13(i)(3).

⁵⁷

<https://www.fda.gov/food/guidanceregulation/guidancedocumentsregulatoryinformation/ucm2006828.htm>, accessed 01/29/18.

N22. May a label make statements using the words “contains” and “provides” (e.g., “Contains x grams of omega3 fatty acids”) for nutrients without DVs?

Answer: To use the words “contains” or “provides” for nutrients without DVs, the specific amount of the nutrient must be stated. The statements “Contains x grams of omega-3 fatty acids per serving” or “Provides x g of omega-3 fatty acids” are permitted.

However, “Contains omega-3 fatty acids” or “Provides omega-3 fatty acids” (without the specific amount statement) would not be permitted. Such claims would be synonyms for a “good source” claim which is not permitted for nutrients that do not have established DVs. 21 CFR 101.54(c)

This interpretation of FDA’s nutrient content claim regulations is unnecessarily restrictive with respect to how substances may be highlighted on a food label. A less restrictive but equally informative way to achieve the FDA goal that the amount of the substance be declared would be to also allow the amount of the substance to appear in the ingredient declaration or the Supplement Facts label of the food. Thus, the statement “Contains omega-3 fatty acids” would be allowed to appear on the label of the food (outside the Nutrition Facts or Supplement Facts label) so long as the amount of omega-3 fatty acids appears in the ingredient declaration or Supplement Facts. This change could be made in the Food Labeling Guide as it is a reasonable interpretation of the present nutrient content claims regulations.

DATA ON COST OR ECONOMIC IMPACT – AHPA has no such data.

PROPOSED SOLUTION – As follows:

Revise the Food Labeling Guide to provide that, except for nutrients that have an established RDI or DRV, the presence of ingredients or constituents is allowed to be highlighted on food labels outside the Nutrition Facts or Supplement Facts label, so long as the amount of the ingredient or constituent appears in the ingredient declaration or in the Supplement Facts label of the food.

RELEVANCE TO DOCKET No. FDA-2017-N-5094 AND/OR EO 13771 AND/OR EO 13777 –

One of the questions posed by FDA in the September 8 CFSAN Notice is, “Could the goal of the regulation be achieved by less costly means that would provide the

same level of public health protection?” AHPA considers the proposed solution presented above to address this question, and believes it would present a reasonable alternative to meet the regulation’s goal with equal public health protection.

The current rule for foreign language labeling should be amended

FDA CENTER REGULATING THE PRODUCT – CFSAN

CITATION TO CFR – 21 CFR § 101.15

OMB CONTROL NUMBER – Not applicable.

BRIEF DESCRIPTION OF CONCERN – As follows:

A food in packaged form is required at 21 CFR § 101.3 to bear on its principal display panel a statement of the identity of the commodity. The statement of identity is required to be “in terms of: (1) The name now or hereafter specified in or required by any applicable Federal law or regulation; or, in the absence thereof, (2) The common or usual name of the food; or, in the absence thereof, (3) An appropriately descriptive term, or when the nature of the food is obvious, a fanciful name commonly used by the public for such food.”⁵⁸

Under current regulation as codified at 21 CFR § 101.15(c)(2), if a food label contains “any representation in a foreign language” then, with certain specified exceptions (e.g., for single-serving packages for restaurant use), “all words, statements, and other information required by or under authority of the act to appear on the label shall appear thereon in the foreign language.”⁵⁹ This means that such a food label that contains, for example, Italian or Spanish words interpreted as “representation(s)” of the food would be required to include, for example, in the required Nutrition Facts panel the Italian or Spanish word, respectively, for each declared nutrient (for example, declarations in terms such as: “Calories / Calorías,” “Total Fat / Grasa Total,” “Cholesterol / Colesterol,” etc.).

⁵⁸ 21 CFR § 101.3(b).

⁵⁹ 21 CFR § 101.15(c)(2).

AHPA has been informed of instances in which FDA has taken the position that the use of ethnic product names on dietary supplements products triggers this bilingual label requirement. In particular, in connection with the nutrition labeling exemptions provided in 21 CFR § 101.9(j)(18), it is not uncommon for FDA to reject the firm's required annual notification if the labels include any ethnic words in the product name but do not present all required information in both languages.⁶⁰

AHPA believes this interpretation by FDA to be *ad hoc*, arbitrary, and fundamentally wrongheaded, for a number of reasons.

- Ethnic names are often precisely the names most familiar to the consumer. For example, Americans are far more likely to recognize *Euterpe oleracea* fruit when called by its ethnic name “açai” rather than its English name “cabbage palm.” Similarly, for typical consumers of dietary supplements and specialty produce “dong quai” is more familiar than “Chinese angelica”; “shiitake” is more familiar than “Japanese forest mushroom”; and “habañero” is at least as recognizable as “bonnet pepper.”
- In many other cases, there is not even an English equivalent to the ethnic name: chayote, yerba santa, and copaiba are known exclusively by their ethnic names.
- FDA has no history of objecting to use of ethnic names in other contexts. For example, while it may be that many of the Italian words that describe commonly available pasta shapes could now be considered to be English, and are found in English language dictionaries (e.g., farfalle; linguini; penne; rigatoni; spaghetti; etc.), there are numerous other pasta shapes available for sale in the U.S. that are described on product labels with their Italian language names and which have not come to be commonly used in English. Such pasta shapes include, for example: anelli; campanelle; casarecce; fideo; gigli; rocchetti; and tripolini. Each of these is marketed in the U.S. and AHPA was

⁶⁰ AHPA notes that the firms affected by the rejection of these notifications are almost exclusively small businesses, for whom the burden of redesigning and reprinting labels, or hiring legal counsel to argue with FDA, are particularly onerous.

able to find each available for sale at online retail sites during preparation of these comments. But neither of two online dictionaries commonly used as references by FDA in recent rulemaking⁶¹ include definitions for any of the pasta shape examples listed here. If FDA is consistent in the application of 21 CFR § 101.15(c)(2) at its most literal, these products should provide bilingual nutrition labeling, in English and Italian. But none of those identified here by AHPA appear to bear such labeling, nor does AHPA believe that the public would be served if FDA did enforce this rule to require bilingual nutrition labeling.⁶²

- Insofar as FDA has raised these bilingual labeling requirements in connection with use of pinyin names, AHPA notes that pinyin is not, in fact a language, but is instead a transliteration of the Chinese language. No person fluent in Chinese reads or writes in pinyin; rather, they use Chinese logogram characters.
- Finally, AHPA notes that under 21 CFR § 101.4(h), each botanical ingredient is required to be listed using its Latin name, except that the Latin is not required when it is available in *Herbs of Commerce* for the common or usual name listed on the label. Therefore, even if a consumer finds an ethnic product name confusing, the consumer will be able to accurately determine the actual contents of the product by way of the Supplement Facts and/or ingredient statement.

AHPA believes FDA must enforce the regulations consistently across all product types; there is no justification for dietary supplement products to be subjected to a different bilingual labeling standard than what FDA requires for conventional foods such as pasta or cured meats. Furthermore, AHPA can discern no public health benefit to be gained from requiring bilingual labeling merely due to the use of

⁶¹ The American Heritage Online Dictionary, available at <http://ahdictionary.com>; and Merriam-Webster Dictionary, available at <http://www.merriam-webster.com>; both accessed November 30, 2017.

⁶² The example of pasta shapes is simply representative of food labels that use a foreign language to represent the food. There are certainly other examples, such as various meat products (pancetta, guanciale, speck, etc.) and many other ethnic foods now demanded by American consumers.

ethnic product names, when the precise nature of the ingredients in the product is always clearly and unambiguously stated on the Information Panel of the label.

DATA ON COST OR ECONOMIC IMPACT – AHPA has no such data.

PROPOSED SOLUTION – As follows:

In light of the above comments AHPA recommends that FDA make the following simple amendment to 21 CFR § 101.15(c)(2):

“If the label contains any representation in a foreign language **except in the name of the food**, all words, statements, and other information required by or under authority of the act to appear on the label shall appear thereon in the foreign language: *Provided, however,* That individual serving size packages of foods containing no more than 1½ avoirdupois ounces or no more than 1½ fluid ounces served with meals in restaurants, institutions, and passenger carriers and not intended for sale at retail are exempt from the requirements of this paragraph (c)(2), ~~if the only representation in the foreign language(s) is the name of the food.~~”

AHPA acknowledges that even though the amendment proposed here is a simple change, the resources required by FDA to initiate notice and comment rulemaking to amend any regulation are not insignificant. A clear communication from the agency of its intention to exercise enforcement discretion in this matter might achieve the same end.

RELEVANCE TO DOCKET NO. FDA-2017-N-5094 AND/OR EO 13771 AND/OR EO 13777 –

In the September 8 CFSAN Notice FDA provides descriptions of the types of regulations that each RRTF is required to attempt to identify, including regulations that “are ... ineffective” or “impose costs that exceed benefits.” For the reasons stated above, AHPA believes the regulation as currently selectively interpreted by FDA to require bilingual nutrition labeling when a dietary supplement product is labeled with ethnic words in the product name is both ineffective and imposes unnecessary costs on certain dietary supplement manufacturers. AHPA further believes these issues can be readily corrected by accepting AHPA’s recommended revision to the regulation, or by creating a clear policy of enforcement discretion applicable to all food products that use ethnic words in the product name. AHPA also notes that one of the questions posed by FDA in the

September 8 CFSAN Notice is, “Could the goal of the regulation be achieved by less costly means that would provide the same level of public health protection?” AHPA considers the proposed solution presented above to address this question, and to represent an alternative means of thorough public health protection at a reduced cost.

Coconut should not be identified as a major food allergen in FDA’s guidance on FALCPA

FDA CENTER REGULATING THE PRODUCT – CFSAN

STATUTORY CITATION – 21 U.S.C § 321(qq)

OMB CONTROL NUMBER – Not applicable.

BRIEF DESCRIPTION OF CONCERN – As follows:

The Food Allergen Labeling and Consumer Protection Act (FALCPA), passed into law in 2004, requires any food ingredient (other than a raw agricultural commodity) that is a “major food allergen” to be identified by its common or usual name on the label of any food (including dietary supplement) that contains the major food allergen. The term “major food allergen” is defined, in relevant part to this comment, to mean any of the following:

21 U.S.C. 321(qq)

(1) Milk, egg, fish (e.g., bass, flounder, or cod), Crustacean shellfish (e.g., crab, lobster, or shrimp), tree nuts (e.g., almonds, pecans, or walnuts), wheat, peanuts, and soybeans.

(2) A food ingredient that contains protein derived from a food specified in paragraph (1)...

On November 2, 2006 FDA announced the availability of a revised guidance document entitled “Guidance for Industry: Questions and Answers Regarding Food Allergens, including the Food Allergen Labeling and Consumer Protection Act of 2004 (Edition 4).”⁶³ AHPA notes that this guidance (hereinafter the FDA FALCPA Guidance) is posted on FDA’s website as of the date of

⁶³ 71 FR 64542.

preparation of these comments as the Agency's current guidance on this subject.⁶⁴

FDA includes in the FDA FALCPA Guidance a list of ingredients it identifies as "tree nuts" for purposes of 21 U.S.C. 321 § 201(qq), and thus requiring FALCPA-compliant labeling; this list includes coconut (*Cocos nucifera*).

AHPA notes, however, that the edible fruit of this species is not a major food allergen. Some allergic responses, including occasional serious reactions such as anaphylaxis, have been reported in association with consumption of many common foods, including, for example, banana⁶⁵; spinach⁶⁶; and tomato.⁶⁷ Similarly, allergic reactions have been reported in association with consumption of coconut fruit, but only occasionally.

But the Congressional intent in adopting FALCPA was not to apply this law to every food ingredient for which case reports of allergic reactions can be found. The "findings" section of this law states that "eight major foods or food groups—milk, eggs, fish, Crustacean shellfish, tree nuts, peanuts, wheat, and soybeans—account for 90 percent of food allergies." These are exactly the same foods (or food groups) identified in FALCPA's definition of the "major food allergens" to which the law applies.

⁶⁴ Accessed November 25, 2017 at <https://www.fda.gov/Food/GuidanceRegulation/GuidanceDocumentsRegulatoryInformation/Allergens/cm059116.htm>.

⁶⁵ O'Keefe AW and Ben-Shoshan M. 2014. A 4-month-old baby boy presenting with anaphylaxis to a banana: a case report. *J Med Case Reports* 2014 8:62. doi:10.1186/1752-1947-8-62; also: Tokuyama K et al. March 1997. Banana allergy in infants. *Allergy* 52:350-351; also: Linaweaver WE, Saks GL and Heiner DC. 1976. Anaphylactic shock following banana ingestion. *Am J Dis Child* 130:207-209.

⁶⁶ Ferrer M et al. Nov-Dec 2011. Food allergy to spinach in an infant. *Allergol Immunopathol (Madr)* 39(6):378-379; also: Sellatary P, Nasser S and Ewan P. Sep 2015. The incidence and features of systemic reactions to skin prick tests. *Ann Allergy Asthma Immunol* 115(3):229-233.

⁶⁷ Dölle S et al. July 2011. Tomato allergy: impact of genotype and environmental factors on the biological response. *J Sci Food Ag* 91(12):2234-2240.

It should be assumed then that the Congress intended to apply this law to those foods accounting for the 90 percent of food allergies referred to in the findings, and not to every food for which there is an occasional report of an allergic reaction. Extending this to “tree nuts” as a food group identified in FALCPA, AHPA believes FDA should provide guidance that directs attention not to every nut that grows on any tree but instead to those tree nuts for which there is actually a record that substantiates, or at least suggests, that the specific nut is, in fact, a major food allergen. Any such analysis would conclude that coconut, even though it grows on a tree and is referred to as a nut⁶⁸, is not a major food allergen.⁶⁹

DATA ON COST OR ECONOMIC IMPACT – AHPA has not produced specific data on the costs borne by food and supplement manufacturers due to the erroneous listing of coconut in the FDA FALCPA Guidance. It is likely that the cost associated with reviewing and redesigning labels as needed to comply with the food allergen labeling requirements is modest (though nonetheless an unnecessary cost when applied to coconut ingredients in foods). But AHPA members have communicated that the primary cost they bear in this matter is the additional expense of the cleaning operations required for all food manufacturing equipment that comes in contact with coconut prior to using the same equipment to manufacture another food; the lost productivity of that equipment during this extensive cleaning; and the segregated storage and other “allergen” controls required as a result of coconut’s erroneous designation by FDA as a “major food allergen.”

PROPOSED SOLUTION – As follows:

FDA should amend the FDA FALCPA Guidance to remove coconut (*Cocos nucifera*) from the list of “tree nuts” identified as a major food allergen.

⁶⁸ There are several other foods that include the word “nut” within their name – such as nutmeg and butternut squash – that do not indicate that the food is actually a nut.

⁶⁹ AHPA believes there are other “nuts” included in the list of “tree nuts” in the FDA FALCPA Guidance that are also not major food allergens, and in at least one case – lichee nut (*Litchi chinensis*) – is not in fact a nut but is instead a fruit. AHPA strongly encourages FDA to review this entire list of articles identified a “tree nuts.”

RELEVANCE TO DOCKET No. FDA-2017-N-5094 AND/OR EO 13771 AND/OR EO 13777 –

One of the questions posed by FDA in the September 8 CFSAN Notice is, “Could the goal of the regulation be achieved by less costly means that would provide the same level of public health protection?” AHPA considers the proposed solution presented above to address this question, and to represent an alternative means of thorough public health protection at a greatly reduced cost.

VII. Issues related to labeling of dietary supplements

The following issues are specifically addressed to certain FDA regulations that affect labeling of dietary supplements.

The requirement for multiple DSHEA disclaimers is redundant

FDA CENTER REGULATING THE PRODUCT – CFSAN

CITATION TO CFR – 21 CFR § 101.93(d)

OMB CONTROL NUMBER – Not applicable.

BRIEF DESCRIPTION OF CONCERN – As follows:

21 CFR 101.93(d) requires as follows with regard to the disclaimer required to accompany structure/function claims:

(d) Placement. The disclaimer shall be placed adjacent to the statement with no intervening material or linked to the statement with a symbol (e.g., an asterisk) at the end of each such statement that refers to the same symbol placed adjacent to the disclaimer specified in paragraphs (c)(1) or (c)(2) of this section. On product labels and in labeling (e.g., pamphlets, catalogs), the disclaimer shall appear on each panel or page where there such is a statement. The disclaimer shall be set off in a box where it is not adjacent to the statement in question.

This regulation is unnecessarily restrictive and should be changed to require the disclaimer to be placed once on the label of a dietary supplement making such a claim and once on any labeling for the dietary supplement. The current regulation at this level of detail makes it difficult for marketers to make structure/function claims on multiple panels of labels because of space limitations. The same is true with respect to labeling.

DATA ON COST OR ECONOMIC IMPACT – AHPA has no such data.

PROPOSED SOLUTION – As follows:

Revise 21 CFR § 101.93(d) to provide that the disclaimer is required to be placed only once on the label of a dietary supplement making multiple structure/function claims, even if the claims appear on more than one panel of the label, and only once on any labeling where the claims appear.

RELEVANCE TO DOCKET No. FDA-2017-N-5094 AND/OR EO 13771 AND/OR EO 13777 –

One of the questions posed by FDA in the September 8 CFSAN Notice is, “Could the goal of the regulation be achieved by less costly means that would provide the same level of public health protection?” AHPA considers the proposed solution presented above to address this question, and believes it would present a less costly means to meet the regulation’s goal with equal public health protection.

FDA should remove implied disease claims from 21 CFR § 101.93

FDA CENTER REGULATING THE PRODUCT – CFSAN

CITATION TO CFR – 21 CFR § 101.93

OMB CONTROL NUMBER – Not applicable.

BRIEF DESCRIPTION OF CONCERN – As follows:

21 CFR § 101.93 – “Certain types of statements for dietary supplements” – is written to restrict implied disease claims for dietary supplements. Including implied or implicit disease claims in dietary supplement labels and labeling as disease claims in this regulation has stifled the ability of marketers to truthfully make statements and describe “the role of a nutrient or dietary ingredient intended to affect the structure or function in humans,” characterize “the documented mechanism by which a nutrient or dietary ingredient acts to maintain such structure or function,” or describe “general well-being from consumption of a nutrient or dietary ingredient” (21 U.S.C. 334(r)(6)(A)) as permitted by the Dietary Supplement, Health and Education Act of 1994.

This regulatory restriction against implied or implicit disease claims for dietary supplements is especially restrictive and unnecessary given the explicit requirement of 21 U.S.C. 334(r)(6)(C) that “the statement contains, prominently

displayed and in boldface type, the following: 'This statement has not been evaluated by the Food and Drug Administration. This product is not intended to diagnose, treat, cure, or prevent any disease.' Moreover, this provision mandates that "A statement under this subparagraph may not claim to diagnose, mitigate, treat, cure, or prevent a specific disease or class of diseases."⁷⁰

This provision also unnecessarily restricts and inhibits the First Amendment commercial free speech rights of the dietary supplement industry.

DATA ON COST OR ECONOMIC IMPACT – AHPA has no such data.

PROPOSED SOLUTION – As follows:

FDA should revise 21 CFR § 101.93 as follows:

(g)(2) FDA will find that a statement about a product claims to diagnose, mitigate, treat, cure, or prevent disease (other than a classical nutrient deficiency disease) under 21 U.S.C. 343(r)(6) if it meets one or more of the criteria listed below. These criteria are not intended to classify as disease claims statements that refer to the ability of a product to maintain healthy structure or function, ~~unless the statement implies disease prevention or treatment.~~ In determining whether a statement is a disease claim under these criteria, FDA will consider the context in which the claim is presented. A statement claims to diagnose, mitigate, treat, cure, or prevent disease if it claims, explicitly or implicitly, that the product: [continue to end with no other revisions.]

RELEVANCE TO DOCKET No. FDA-2017-N-5094 AND/OR EO 13771 AND/OR EO 13777 –

As noted in the September 8 CFSAN Notice, EO 13777 established a federal policy "to alleviate unnecessary regulatory burdens" on the American people. In addition, the September 8 CFSAN Notice provides descriptions of the types of regulations that each RRTF is required to attempt to identify for this purpose, as stated in EO 13777, including regulations that are "unnecessary." It is AHPA's view that FDA's practice of restricting implied disease claims is at its very core an unnecessary regulatory burden on American consumers of dietary supplements for the reasons described in this comment.

⁷⁰ 21 U.S.C. 334(r)(6).

Allow citations of scientific references on websites

FDA CENTER REGULATING THE PRODUCT – CFSAN

CITATION TO CFR – 21 CFR § 101.93(g)(2)(iv)(C)

OMB CONTROL NUMBER – Not applicable.

BRIEF DESCRIPTION OF CONCERN – As follows:

21 CFR 101.93(g)(2)(iv)(C) provides that citations to published literature in labeling can be construed as a disease claim:

(C) Citation of a publication or reference, if the citation refers to a disease use, and if, in the context of the labeling as a whole, the citation implies treatment or prevention of a disease, e.g., through placement on the immediate product label or packaging, inappropriate prominence, or lack of relationship to the product's express claims;

This section has been used by FDA to prohibit the use of citations to published literature and the use of published literature on the websites of companies marketing dietary supplements, especially literature that discusses the diagnosis, treatment, cure, or prevention of a disease. Warning Letters issued in late 2017 detail FDA's objections to such practices.

This regulation and the Warning Letters disrespect that part of the Dietary Supplement Health and Education Act that expressly permits the use of published literature. DSHEA provides:

21 USC 343B. (a) IN GENERAL.- A publication, including an article, a chapter in a book, or an official abstract of a peer-reviewed scientific publication that appears in an article and was prepared by the author or the editors of the publication, which is reprinted in its entirety, shall not be defined as labeling when used in connection with the sale of a dietary supplement to consumers when it –

- (1) is not false or misleading;
- (2) does not promote a particular manufacturer or brand of a dietary supplement;
- (3) is displayed or presented, or is displayed or presented with other such items on the same subject matter, so as to present a balanced view of the available scientific information on a dietary supplement;
- (4) if displayed in an establishment, is physically separate from the dietary supplements; and

(5) does not have appended to it any information by sticker or any other method.

Freedom to communicate scientifically accurate information is a backbone of DSHEA and certain of the “findings” underlying DSHEA provide ample evidence of this:

...
(5) preventive health measures, including education, good nutrition, and appropriate use of safe nutritional supplements will limit the incidence of chronic diseases, and reduce long-term health care expenditures;

...
(7) there is a growing need for emphasis on the dissemination of information linking nutrition and long-term good health;
(8) consumers should be empowered to make choices about preventive health care programs based on data from scientific studies of health benefits related to particular dietary supplements;

...
(13) although the Federal Government should take swift action against products that are unsafe or adulterated, the Federal Government should not take any actions to impose unreasonable regulatory barriers limiting or slowing the flow of safe products and accurate information to consumers;

Thus it is clear Congress intended the American public to be provided unfettered access to a wide variety of scientific literature. There is no logical justification for interfering with dissemination of third-party literature presented in electronic form as opposed to physically printed form, or for prohibiting firms from using citations to direct the attention of the public to the relevant literature.

Finally, there is no evidence Congress intended to exclude disease-oriented studies from use as third-party literature, and AHPA notes that such studies are often relevant to dietary supplement claims. For example, a scientific study on the use of an ingredient in the treatment of a disease (i.e., a claim that dietary supplements are not allowed to make) may contain information relevant to the mechanism of action of the ingredient; and this latter information may be important for understanding and substantiating the use of the ingredient in health maintenance (i.e., claims that are permitted for dietary supplements).

FDA should respect the Congressional intent of DSHEA and stop warning companies regarding the use of publications meeting the definition set out in the law, and warning companies regarding the use of citations to published literature.

Free and open communication of publications is especially important with regard to companies making such information available to practitioners on limited-access websites. Practitioners are knowledgeable intermediaries who often present sophisticated questions about a product, and scientific literature is often the best source of answers to their questions. These company-practitioner communications should also be respected. In this regard, companies should be free on such sites to respond to practitioner questions regarding the use of their products. This is not to say that companies can make claims for their products outside their established labeling, but that companies ought to be able to respond with truthful and not misleading information regarding the use of their products so long as such responses make clear that the products are labeled and intended only as dietary supplements and are not recommended or suggested for use in the diagnosis, treatment, cure, or prevention of a disease.

DATA ON COST OR ECONOMIC IMPACT – AHPA has no such data.

PROPOSED SOLUTION – As follows:

AHPA is proposing here that paragraph (C) of 21 CFR § 101.93(g)(2)(iv) (i.e., 21 CFR § 101.93(g)(2)(iv)(C)) be deleted.

Furthermore, FDA's policies with respect to Warning Letters should be revised to conform to the intent of Congress. Dietary supplement companies should be permitted to cite scientific studies in labeling, including literature relating to use of an ingredient or product in treatment of disease, so long as in the context of the labeling as a whole it is clear that the product is intended only as a dietary supplement and is not recommended or suggested for use in the diagnosis, treatment, cure, or prevention of a disease.

RELEVANCE TO DOCKET No. FDA-2017-N-5094 AND/OR EO 13771 AND/OR EO 13777 –

One of the questions posed by FDA in the September 8 CFSAN Notice is, "Could the goal of the regulation be achieved by less costly means that would provide the

same level of public health protection?” AHPA considers the proposed solution presented above to address this question, and strongly believes that it would present a less costly means to meet the regulation’s goal with equal or even improved and better informed public health protection.

FDA should reduce or remove requirements for multiple structure/function claim filings

FDA CENTER REGULATING THE PRODUCT – CFSAN

CITATION TO CFR – 21 CFR § 101.93

OMB CONTROL NUMBER – Not applicable.

BRIEF DESCRIPTION OF CONCERN – As follows:

In the regulations regarding structure/function claims (21 CFR § 101.93), FDA describes how to notify FDA regarding the claim:

(a)(1) No later than 30 days after the first marketing of a dietary supplement that bears one of the statements listed in section 403(r)(6) or the Federal Food, Drug, and Cosmetic Act, the manufacturer, packer, or distributor of the dietary supplement shall notify the Office of Nutritional Products, Labeling and Dietary Supplements (HFS-810), Center for Food Safety and Applied Nutrition, Food and Drug Administration, 5001 Campus Dr., College Park, MD 20740, that it has included such a statement on the label or in the labeling of its product. An original and two copies of this notification shall be submitted.

(2) The notification shall include the following:

(i) The name and address of the manufacturer, packer, or distributor of the dietary supplement that bears the statement;

(ii) The text of the statement that is being made;

(iii) The name of the dietary ingredient or supplement that is the subject of the statement, if not provided in the text of the statement; and

(iv) The name of the dietary supplement (including brand name), if not provided in response to paragraph (a)(2)(iii) on whose label, or in whose labeling, the statement appears.

(3) The notice shall be signed by a responsible individual or the person who can certify the accuracy of the information presented and contained in the notice. The individual shall certify that the information contained in the notice is complete and accurate, and that the notifying firm has substantiation that the statement is truthful and not misleading.

FDA has now launched an electronic portal for making these same claim notifications at <https://www.access.fda.gov/oa/logonFlow.htm?execution=e1s1>. This portal does not accept multiple notifications in the same submission.

In the past, FDA has accepted letter notifications for a claim that will be made on multiple products, e.g., “calcium builds strong bones,” for the following products containing calcium, then listing numerous products. Similarly, companies manufacturing their own and other brands in the past filed a claim and listed all the brands and names of the products that would make the claim. The new electronic portal should be modified to accommodate the filing of claims for multiple products.

DATA ON COST OR ECONOMIC IMPACT – AHPA has no such data.

PROPOSED SOLUTION – As follows:

FDA’s electronic portal for making dietary supplement structure/function claim notifications should be modified to accommodate the filing of claims for multiple products.

RELEVANCE TO DOCKET No. FDA-2017-N-5094 AND/OR EO 13771 AND/OR EO 13777 –

One of the questions posed by FDA in the September 8 CFSAN Notice is, “Could the goal of the regulation be achieved by less costly means that would provide the same level of public health protection?” AHPA considers the proposed solution presented above to address this question, and believes that it would present a less costly means to meet the regulation’s goal with equal or even improved public health protection.

VIII. Issues related to new dietary ingredients

The following issues are specifically addressed to FDA's current regulation on submission of a notification to FDA in the matter of a new dietary ingredient.

Several simple amendments to 21 CFR § 190.6 would provide greater clarity for submission of NDI notifications

FDA CENTER REGULATING THE PRODUCT – CFSAN

CITATION TO CFR – 21 CFR § 190.6

OMB CONTROL NUMBER – Not applicable.

BRIEF DESCRIPTION OF CONCERN – As follows:

AHPA notes that 21 CFR § 190.6, the specific regulation in which FDA articulates the requirements for premarket notification of a new dietary ingredient (NDI), does not include some details that are relevant to submission of an NDI notification.

Specifically, 21 CFR § 190.6(b) identifies requirements for information that must be included in an NDI notification to be limited to the following:

- (1) The name and complete address of the manufacturer or distributor of the dietary supplement that contains a new dietary ingredient, or of the new dietary ingredient;
- (2) The name of the new dietary ingredient that is the subject of the premarket notification, including the Latin binomial name (including the author) of any herb or other botanical;
- (3) A description of the dietary supplement or dietary supplements that contain the new dietary ingredient including: (i) The level of the new dietary ingredient in the dietary supplement; and (ii) The conditions of use recommended or suggested in the labeling of the dietary supplement, or if no conditions of use are recommended or suggested in the labeling of the dietary supplement, the ordinary conditions of use of the supplement;
- (4) The history of use or other evidence of safety establishing that the dietary ingredient, when used under the conditions recommended or suggested in the labeling of the dietary supplement, will reasonably be expected to be safe, including any citation to published articles or other evidence that is the basis on which the distributor or manufacturer of the dietary supplement that contains the new dietary ingredient has concluded that the new dietary supplement will reasonably be expected to be safe. Any reference to published information offered in support of the notification shall be accompanied by reprints or photostatic copies of such references. If any part of the material submitted is in a foreign language, it shall be accompanied by an accurate and complete English translation; and

- (5) The signature of the person designated by the manufacturer or distributor of the dietary supplement that contains a new dietary ingredient.

There are no other requirements identified in 21 CFR § 190.6 for any additional specific information to be included in an NDI notification. Notably absent from the information required by 21 CFR § 190.6 to be submitted with an NDI notification is a description of the NDI itself, and, when the NDI is an herb or other botanical, identification of the part of the plant from which the ingredient is derived.

Yet FDA, in reviewing NDI notifications, has developed a policy of expressing significant concerns to notifications that do not include a sufficiently precise description of the NDI or that do not identify the relevant part of the plant for botanically-derived ingredients – even when a notification provides all of the information currently required to be included in an NDI notification under 21 CFR § 190.6.

On the issue of identification of a plant part for botanical ingredients, there is a notable contrast between the absence of a requirement for this information in 21 CFR § 190.6(b) in relation to NDI notifications and the statutory language at 21 U.S.C § 343(s)(2) that establishes that a dietary supplement that contains as an ingredient an “herb or other botanical,” as identified in 21 U.S.C. § 321(ff)(1)(C), is misbranded if the label of the product “fails to identify any part of the plant from which the ingredient is derived.”⁷¹

DATA ON COST OR ECONOMIC IMPACT – AHPA has no such data.

⁷¹ To further complicate this issue, 21 U.S.C. § 343(s)(2) only places this labeling requirement on “herbs or other botanicals” as described in 21 U.S.C. 321(ff)(1)(C)), and does not specify that the part of the plant of the source ingredient of a “concentrate, metabolite, constituent, extract, or combination” of an herb or other botanical, as described in 21 U.S.C. 321(ff)(1)(F), must be disclosed. It is AHPA’s view, however, that an article of commerce that is an herbal or other botanical, whether in an unprocessed form or as a concentrate, metabolite, constituent, or extract, cannot be completely and accurately identified without specifying the part or parts of the plant that constitute the article, or that serve as the starting material for the manufacture of the article.

PROPOSED SOLUTION – As follows:

AHPA recommends that FDA propose revisions to 21 CFR § 190.6(b) through notice and comment rulemaking to square the regulation with the Agency's expectation of performance by industry when submitting an NDI notification, and to therefore establish a clear requirement for such notifications to include an accurate and sufficiently complete identification of any NDI that is the subject of the notification, including, for botanical ingredients, the relevant part of the subject plant.

In addition to the two current specific gaps in 21 CFR § 190.6(b) discussed above, AHPA believes additional revisions should be made to this regulation, both to provide greater clarity and to make the regulation more consistent with the NDI provisions of the FDCA.

More specifically, AHPA recommends that 21 CFR § 190.6(b) be amended by adding the following additional requirements for submitting an NDI notification:

- (1) The name and complete address of the manufacturer or distributor **of the new dietary ingredient or of dietary supplement(s) that contains a new dietary ingredient**, that is submitting the notification.
- (2) The name of the new dietary ingredient that is the subject of the premarket notification, including the Latin binomial name (including the author) of any herb or other botanical;
- (3) **The part of the plant from which the ingredient is derived if the ingredient is an herb or other botanical; a concentrate, metabolite, constituent of an herb or other botanical; or a combination of herbs or botanicals;**
- (4) **A description of the new dietary ingredient;**⁷²
- (5) A **specific** description of the **a** dietary supplement **or a general description of a range of dietary supplements** that contains **or will contain** the NDI, including:

⁷² On April 27, 2013 AHPA submitted follow-up comments to Docket No. FDA-2011-D-0376 (FDA's initial (2011) draft guidance on NDI notifications) specific to guidance needed on identification of an NDI (Follow-up comments of the American Herbal Products Association on Draft Guidance for Industry; Dietary supplements: New dietary ingredient notifications and related issues – Specific to Guidance needed on identification of a new dietary ingredient). The information presented by AHPA in these follow-up comments presented specific suggestions on the types of information that is needed to accurately and adequately describe dietary ingredients of many varying types, and so may be a useful reference in any rulemaking undertaken to make the recommended revision to 21 CFR § 190.6.

- a. the level of the NDI in the dietary supplement(s), and
 - b. the conditions of use recommended or suggested in the labeling of the dietary supplement(s) **containing the NDI**, or if no conditions of use are recommended or suggested in the supplement's labeling, the ordinary conditions of use of the supplement(s).
- (6) The history of use or other evidence of safety, **including any citation to published articles**, establishing that the dietary ingredient, when used under the conditions recommended in the labeling of the dietary supplement, will reasonably be expected to be safe **which is the basis on which the manufacturer or distributor has concluded that a NDI will reasonably be expected to be safe in one or more dietary supplements**.
- (7) The signature of a person designated by the manufacturer or distributor **of the new dietary ingredient or the dietary supplement that contains a new dietary ingredient** to sign the notification on its behalf.

RELEVANCE TO DOCKET No. FDA-2017-N-5094 AND/OR EO 13771 AND/OR EO 13777 –

In the September 8 CFSAN Notice FDA provides descriptions of the types of regulations that each RRTF is required to attempt to identify, including regulations that “are ... ineffective.” It is clear to AHPA that 21 CFR § 190.6 is ineffective since the rule does not completely and accurately describe the information that FDA expects to receive in an NDI notification. AHPA further believes this issue can be readily corrected by accepting AHPA recommended amendment to this regulation.

FDA should allow review of NDI submissions to be halted

FDA CENTER REGULATING THE PRODUCT – CFSAN

CITATION TO CFR – 21 CFR § 190.6

OMB CONTROL NUMBER – Not applicable.

BRIEF DESCRIPTION OF CONCERN – As follows:

21 CFR § 190.6 sets forth the procedure for making a new dietary ingredient notification to FDA. This regulation should be interpreted to allow a submitter to ask FDA to cease review of a submission. This has been the FDA practice regarding GRAS notifications for over nineteen years. In so doing, the notification itself remains on file at FDA and may be released under the Freedom of Information Act with confidential proprietary and trade secret information

redacted. This practice should be adopted for new dietary ingredient notifications as well.

DATA ON COST OR ECONOMIC IMPACT – AHPA has no such data.

PROPOSED SOLUTION – As follows:

21 CFR § 190.6 should be interpreted to allow a submitter to ask FDA to cease review of a submission.

RELEVANCE TO DOCKET No. FDA-2017-N-5094 AND/OR EO 13771 AND/OR EO 13777 –

One of the questions posed by FDA in the September 8 CFSAN Notice is, “Could the goal of the regulation be achieved by less costly means that would provide the same level of public health protection?” AHPA considers the proposed solution presented above to address this question, and believes that it would present a less costly means to meet the regulation’s goal with equal or even improved public health protection.

FDA should withdraw or significantly revise the 2016 revised NDI guidance

FDA CENTER REGULATING THE PRODUCT – CFSAN

CITATION TO CFR – 21 CFR § 190.6

OMB CONTROL NUMBER – Not applicable.

BRIEF DESCRIPTION OF CONCERN – As follows:

The Dietary Supplement Health and Education Act of 1994 (DSHEA) codified 21 U.S.C. § 350(b), which sets forth the definition of and legal requirements for new dietary ingredients (NDIs). The corresponding regulation implementing this requirement is 21 CFR § 190.6. In 2011, as a result of requirements established in FSMA, FDA published a draft guidance (the 2011 draft NDI guidance) discussing its interpretation of 21 U.S.C. § 350(b); this draft guidance was so egregiously inconsistent with the actual requirements of the law that, at the urging of Congress, FDA agreed to issue a revised draft rather than follow the normal course of moving to final guidance.

In 2016 FDA published a new draft guidance (the 2016 revised draft NDI guidance) which is once again wholly inconsistent with the statutory provisions.

The 2016 revised draft essentially seeks to regulate dietary ingredients on a model similar to drugs and food additives, which directly contravenes the express intent of Congress in passing DSHEA. Congress explicitly rejected these regulatory models for dietary ingredients and supplements and explicitly directed FDA to regulate dietary ingredients and supplements as foods which enjoy a presumption of safety.

AHPA submitted comments to FDA on December 12, 2016 explaining in detail its strong objections to the 2016 revised draft NDI guidance (Docket No. FDA-2011-D-0376), and hereby incorporates by reference those comments to the present comments, and will submit those 2016 comments to the present Docket simultaneous to submission of these comments, identified as Addendum 4.

AHPA further believes that the Agency's current use of the 2016 revised draft NDI guidance as a reference in responding to submitted NDI notifications is confusing. The 2016 revised draft plainly states "Draft-Not for Implementation" and "This guidance is being distributed for comment purposes only," yet it is referred to in official correspondence responding to NDI notifications.

As a matter of urgency, therefore, the existence of the 2016 revised draft NDI guidance is highly misleading to the regulated industry and its negative impacts are already being felt on dietary ingredient and supplement manufacturers. Therefore, in view of its severe inconsistency with the statute, it should be immediately either significantly revised or completely withdrawn.

DATA ON COST OR ECONOMIC IMPACT – AHPA has no such data.

PROPOSED SOLUTION – As follows:

Immediately withdraw or significantly revise the current draft NDI guidance and immediately discontinue referring to the contents of that draft in responding to NDI notifications.

RELEVANCE TO DOCKET No. FDA-2017-N-5094 AND/OR EO 13771 AND/OR EO 13777 –

In the September 8 CFSAN Notice FDA provides descriptions of the types of regulations that each RRTF is required to attempt to identify, including regulations

that “are ... ineffective” or “impose costs that exceed benefits.” For the reasons stated above and in AHPA’s previous comments to FDA two separate drafts of guidance on NDI notifications, AHPA strongly believes the revised (2016) draft, if finalized without significant additional revision, would be both ineffective in providing meaningful guidance to industry to comply with the laws NDI provisions and would impose unnecessary costs on dietary ingredient and dietary supplement companies that seek to bring NDIs to market. AHPA further believes that the Agency’s current use of the 2016 draft as a reference in responding to submitted NDI notifications is already imposing such unnecessary costs.

IX. Issues related to enforcement of pesticide regulations

The following issue is specifically addressed to FDA’s enforcement of pesticide regulations for conventional foods, dietary ingredients, and dietary supplements.

FDA should work with EPA to rationalize pesticide regulations and enforcement

FDA CENTER REGULATING THE PRODUCT – CFSAN

CITATION TO CFR – 21 CFR Part 117; 21 CFR Part 111; 40 CFR Part 180

OMB CONTROL NUMBER – Not applicable.

BRIEF DESCRIPTION OF CONCERN – As follows:

The Federal Insecticide, Fungicide, and Rodenticide Act (FIFRA) as amended in 1972 requires that tolerances for the permissible levels of pesticides be approved on a crop-by-crop basis, and provides that in the absence of an established tolerance for a particular pesticide on a particular crop, any detectable level of the pesticide on that crop is unacceptable. This is commonly referred to as a “zero tolerance” policy.

This policy has always posed challenges to the food industry since it is quite expensive for chemical manufacturers to develop the necessary data to obtain approval for use of their products on a crop-by-crop basis. As a result, there are often few or no pesticides approved for use on many minor food crops.

Furthermore, in the decades since this regulatory regime was enacted, the world has changed in ways that make it increasingly difficult for food companies to comply with this zero tolerance requirement:

- Analytical technologies have improved dramatically, so that pesticides can now be detected at levels thousands of times lower than what was possible when FIFRA was enacted in the 1970s.
- Pesticide contamination has become increasingly ubiquitous. Even where pesticides are not directly applied to crops, it is not uncommon to find detectable levels due to contamination from the soil, water, or air.
- The food supply has become dramatically internationalized, and farmers in foreign countries often have a legitimate and scientifically valid need to use different pesticides from those approved in the U.S. For example, different pests occur in different parts of the world and these require different pesticides. This is compounded by the fact that using a rotating panel of pesticides is often environmentally preferable in order to avoid the development of pesticide resistance.
- GMP regulations for food manufacturing now require food companies to actively control for the presence of pesticides as a potential hazard in the foods they sell.

As a result of these factors, food companies are finding it increasingly difficult or even impossible to find botanical ingredients that meet the stringent requirements of the “zero tolerance” policy and AHPA has been informed that this policy has led to increasing supply shortages. These supply shortages impact not only the ingredient vendor itself, but also the farmers (many of whom are located in the U.S.) whose crops are being rejected; the downstream companies (many of which are manufacturing companies) who cannot obtain the ingredients they need; and eventually the American consumers who find their desired products missing from the store shelves.

AHPA notes that in many if not most cases, the levels of pesticides in question are so low that they do not in fact pose an actual risk to human health. AHPA furthermore notes that, when properly used in accordance with the relevant laws

and regulations of the pertinent foreign jurisdiction, pesticides used in foreign jurisdictions do not necessarily pose a risk to environmental health even if they are not approved for use in the U.S.

AHPA therefore believes it urgently necessary to rationalize EPA and FDA policies surrounding pesticide enforcement to avoid significant and growing disruption to the food industry and the unnecessary waste of food that presents no actual significant risk to public or environmental health. AHPA believes that the Congressional intent of 1972 was inextricably tied up with the facts on the ground at that time (e.g., the relatively crude analytical technologies available with their commensurately higher thresholds of detection, and the domestic sourcing of most foods), and that the current literal reading of the statute cannot be enforced in perpetuity.

DATA ON COST OR ECONOMIC IMPACT – AHPA has no such data.

PROPOSED SOLUTION – As follows:

AHPA submitted comments to EPA on May 15, 2017 describing how EPA and FDA could work together to modernize and rationalize pesticide regulations and enforcement; a copy of these comments to EPA, identified as Addendum 5, will be submitted to the present Docket simultaneous to submission of these comments.

In these comments to EPA, AHPA recommended (and restates here), in relevant part to FDA's enforcement authority, the following:

- Rather than regulating trace levels of pesticides in foods and food ingredients as adulterants under EPA's "zero tolerance" policy, these traces should be controlled as contaminants regulated by FDA through enforcement of current good manufacturing practice for food (21 CFR Part 117) and supplements (21 CFR Part 111).

- FDA should set appropriate action levels for these contaminants as it has done for other types of pesticides. In general, an action level of 0.1 ppm⁷³ would be protective of public health and consistent with documented levels of unavoidable, inadvertent pesticide contamination. Lower action levels may be appropriate for substances of unusually high toxicity or whose toxicity is unknown.

In addition, since the time AHPA's comments to EPA were submitted, NSF International conducted an assessment utilizing the publicly available health effects criteria derived by authoritative agencies internationally to develop chemical-specific, risk-based maximum allowable levels that can be applied to all pesticide residues in dietary supplements, regardless of the food commodity on which they are found; a description of these limits and the strategy by which they were derived, identified as Addendum 6, will be submitted to the present Docket simultaneous to submission of these comments, as this document may be useful to establishing a sound and realistic regulatory policy to address trace levels of pesticides.

RELEVANCE TO DOCKET No. FDA-2017-N-5094 AND/OR EO 13771 AND/OR EO 13777 –

In the September 8 CFSAN Notice FDA provides descriptions of the types of regulations that each RRTF is required to attempt to identify, including regulations that “are ... ineffective” or “impose costs that exceed benefits.” AHPA strongly believes that enforcement of current pesticide regulations with no attention to the contemporary real-world factors is both ineffective and imposes unnecessary costs on the entire food industry, and ultimately on consumers.

⁷³ This is the general action level established in Canada's regulations; see “Pesticides and MRLs in Canada,” USDA Foreign Agricultural Service, 2015.

Closing

AHPA greatly appreciates the opportunity to present comments on this matter. AHPA staff and counsel will make themselves available at any mutually convenient time to further address any of the topics addressed herein. Please feel free to contact us if clarification or additional discussion is needed on the issues raised in these comments.

Respectfully submitted,



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Addenda submitted to the Docket:

- Addendum 1: AHPA Citizen Petition, dated October 17, 2013.
 - Addendum 2: FDA Response to AHPA's October 17, 2013 Citizen Petition, dated July 23, 2014.
 - Addendum 3: Excerpt from AHPA Comments to Docket No. FDA-2012-N-1210, dated August 1, 2014.
 - Addendum 4: AHPA Comments re: FDA's 2016 Revised Draft NDI Guidance (Docket No. FDA-2011-D-0376), dated December 12, 2016.
 - Addendum 5: AHPA Comments re: EPA's Request for Comments on Evaluation of Existing Regulations (Docket No. EPA-HQ-OA-2017-0190), dated May 15, 2017.
 - Addendum 6: NSF International: Chemical-Specific Maximum Allowable Levels for Pesticide Residues in Dietary Supplements, dated December 19, 2017.
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