

BEFORE
THE UNITED STATES OF AMERICA
DEPARTMENT OF HEALTH AND HUMAN SERVICES
FOOD AND DRUG ADMINISTRATION

COMMENTS OF THE
AMERICAN HERBAL PRODUCTS ASSOCIATION

ON THE
FOOD AND DRUG ADMINISTRATION'S

INTERIM FINAL RULE
on

PETITIONS TO REQUEST AN EXEMPTION FROM 100 PERCENT IDENTITY
TESTING OF DIETARY INGREDIENTS
under

CURRENT GOOD MANUFACTURING PRACTICE IN MANUFACTURING,
PACKAGING, LABELING AND HOLDING OPERATIONS FOR DIETARY
SUPPLEMENTS

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

Background

In the Federal Register on June 25, 2007, the Food and Drug Administration (FDA) issued a final rule, now codified at Title 21 of the Code of Federal Regulations, Part 111 (21 CFR 111), establishing current good manufacturing practice in manufacturing, packaging, labeling and holding operations for dietary supplements (the cGMP final rule). The cGMP final rule at § 111.75(a)(1) requires each manufacturer of dietary supplements to “conduct at least one appropriate test or examination to verify the identity of any component that is a dietary ingredient,” whether the dietary ingredient is purchased from a supplier or manufactured on its own, prior to use in the manufacturing process (100 percent identity testing).

In the same issue of the Federal Register, FDA issued an interim final rule to provide an exemption to 100 percent identity testing under certain circumstances (the interim final rule). The agency explained its decision to add this exemption as follows:

“...we recognize that it may be possible for a manufacturer to demonstrate, through various methods and processes in use over time for its particular operation, that a system of less than 100 percent identity testing would result in no material diminution of assurance of the identity of the dietary ingredient as compared to the assurance provided by 100 percent identity testing. To provide an opportunity for a manufacturer to make such a showing and reduce the frequency of identity testing of components that are dietary ingredients from 100 percent to some lower frequency, we decided to add to § 111.75(a)(1), an exemption from the requirement of 100 percent identity testing when a manufacturer petitions the agency for such an exemption to 100 percent identity testing under § 10.30 and the agency grants such exemption.” 72 FR 34959-34960.

The interim final rule modifies § 111.75(a)(1) and renumbers it as § 111.75(a)(1)(i) and adds § 11.75(a)(1)(ii). The modified § 111.75(a)(1) reads as follows, with the portion issued in the cGMP final rule in standard font and the portion added by the interim final rule in italic font:

§ 111.75(a) Before you use a component, you must:

(1)(i) Conduct at least one appropriate test or examination to verify the identity of any component that is a dietary ingredient, *unless you petition the agency under paragraph (a)(1)(ii) of this section and the agency exempts you from such testing;*

(ii) *You may submit a petition, under 21 CFR 10.30, to request an exemption from the testing requirements in paragraph (a)(1)(i) of this section. The petition must set forth the scientific rationale, and must be accompanied by the supporting data and information, for proposed alternative testing that will demonstrate that there is no material diminution of assurance, compared to the assurance provided by 100 percent identity testing, of the identity of the dietary ingredient before use when the dietary ingredient is obtained from one or more suppliers identified in the petition. If FDA grants the petition, you must conduct the tests and examinations for the dietary ingredient, otherwise required under § 111.75(a)(1)(i), under the terms specified by FDA when the petition is granted; [and]*

In discussing the procedure for submission of a petition to FDA under new § 111.75(a)(1)(ii), the agency clarifies that it is a manufacturer who may request an exemption from the requirements set forth in § 111.75(a)(1)(i); that any petition would be required to identify one or more supplier of the specific ingredient that is the subject of such petition; and that petitions will not be accepted until the compliance date that is applicable for the submitting manufacturer (i.e., June 25, 2008 for firms with 500 or more full-time equivalent employees; June 25, 2009 for those with fewer than 500, but 20 or more employees; and June 25, 2010 for those with fewer than 20 employees). The agency provides additional commentary on this process, including the following:

"...the level of continued testing at a rate less than 100 percent should provide the statistical confidence that the probability of receiving a dietary ingredient that does not meet the established specifications for identity is less than a small chosen percentage at a statistical confidence level, e.g., 95 percent. The petition must set forth proposed alternative testing for identity while an exemption is in effect. If FDA grants the petition, the manufacturer must conduct the tests and examinations for the dietary ingredient, otherwise required under § 111.75(a)(1)(i), under the terms specified by FDA when the petition is granted." 72 FR 34960.

"We would consider such a petition under § 10.30 (21 CFR 10.30), the citizen petition process. Generally, § 10.30 requires your petition to include:

- The action requested (i.e., a request for an exemption from the requirements of § 111.75(a)(1)(i));
- A statement of grounds;
- A section on environmental impact, including either a claim for categorical exclusion under § 25.30 (21 CFR 25.30) or 21 CFR 25.32 or an environmental assessment under 21 CFR 25.40;

- A statement certifying that, to the best of your knowledge and belief, your petition includes all information and views on which the petition relies, and that it includes representative data and information known to you which are unfavorable to the petition.” 72 FR 34960.

The interim final rule also adds a new recordkeeping requirement in § 111.95(b), related to any FDA response to a petition described above, as follows:

§ 111.95(b) Under this subpart E, you must make and keep the following records:

- (6) *Documentation of FDA’s response to a petition submitted under § 111.75(a)(1)(ii) providing for an exemption from the provisions of § 111.75(a)(1)(i).*

Also relevant to the issues addressed by the interim final rule is new § 111.75(h)(2), which describes the “tests and examinations that you use” to determine whether specifications are met, including specifications for identity of dietary ingredients. These “tests and examinations... must include at least one of the following:

- (i) Gross organoleptic analysis;
- (ii) Macroscopic analysis;
- (iii) Microscopic analysis;
- (iv) Chemical analysis; or
- (v) Other scientifically valid methods.”

AHPA members that manufacture dietary supplements, as well as members that manufacture and supply dietary ingredients, may be affected by the interim final rule. AHPA supports FDA’s decision to provide exemptions to 100 percent identity testing of dietary ingredients and believes that such exemptions may provide industry with more efficient alternative methods and processes that will assure the identity of dietary ingredients. AHPA also supports the interim final rule’s provision of pre-approval authority for FDA for each proposed alternative testing for identity. Nevertheless, AHPA does not agree with all elements of the interim final rule, and therefore submits the below comments.

Suppliers of dietary ingredients should be allowed to request exemptions to 100 percent identity testing under § 111.75(a)

As discussed above, the interim final rule creates a regulatory process whereby dietary supplement manufacturers, but not dietary ingredient suppliers, may request exemptions to 100 percent identity testing for dietary ingredients. AHPA believes that the interim final rule should also allow suppliers of dietary ingredients to make such requests for exemptions for one or more of their ingredients so that

a successful submitting ingredient supplier's customers who are dietary supplement manufacturers would be allowed, in lieu of 100 percent identity testing, to conduct the tests and examinations for the dietary ingredient under the terms specified by FDA when the petition is granted.

A petition submitted by a dietary supplement manufacturer under § 111.75(a)(1)(ii) must specifically address the following four elements: a dietary ingredient; alternative identity testing for the ingredient; a dietary supplement manufacturer that uses the ingredient; and one or more suppliers of the ingredient. In reviewing how the interim final rule addresses each of these elements it can be seen that there would be no flexibility in regard to the first three and some limited flexibility in regard to the fourth. For example:

1. Each petition must be for a specifically identified dietary ingredient;
2. Each petition must describe specific alternative identity testing that will consist of specified tests and examinations proposed to be conducted in lieu of 100 percent testing for the identified dietary ingredient;
3. Each petition would be applicable only to the specific dietary supplement manufacturer that submits the petition and that uses the identified dietary ingredient in one or more dietary supplements;
4. Each petition could specify one or more named suppliers of the identified dietary ingredient.

In requesting here that suppliers of dietary ingredients also be allowed to submit petitions for exemption to 100 percent identity testing under § 111.75(a), AHPA believes that the present limitations in the first two of these elements would continue to be appropriate, and must be maintained. AHPA is requesting, however, that flexibility be provided so that an ingredient supplier could submit such a petition under § 111.75(a) that would be applicable to any of their customers for the specified ingredient, so long as that customer utilizes the specific alternative testing and meets the other requirements under the terms specified when FDA grants a submitted supplier's petition. In other words, AHPA is suggesting the following approach to the same four elements when a petition for alternative identity testing is submitted by a dietary ingredient supplier:

1. Each petition must be for a specifically identified dietary ingredient [no change is suggested regarding this element];
2. Each petition must describe specific alternative identity testing that will consist of specified tests and examinations proposed to be conducted in lieu of 100 percent testing for the identified dietary ingredient [no change is suggested regarding this element];

3. Each petition would be applicable to any dietary supplement manufacturer that uses the identified dietary ingredient, when supplied by the submitting ingredient supplier and when that manufacturer (a) performs the specified tests and examinations that are to be conducted in lieu of 100 percent testing for the identified dietary ingredient prior to use as an ingredient in one or more dietary supplements; and (b), where applicable, retains any lot-specific identity data provided by the supplier [this is a significant change with regard to this element];
4. Each petition would be applicable only to the specific dietary ingredient supplier that submits the petition [this is a change in language with regard to this element, but of no great significance (it has the same effect, as applicability would be to the only named supplier, i.e., the submitting firm)].

AHPA believes that a petition for alternative identity testing under § 111.75(a) submitted by a dietary ingredient supplier will be at least as effective in ensuring that there is no material diminution of assurance, compared to the assurance provided by 100 percent identity testing, of the identity of the dietary ingredient before use. In fact, when considering botanical dietary ingredients, AHPA believes that such petitions submitted by suppliers can be significantly more effective in making such assurance.

As noted above, FDA expressed its recognition that “it may be possible for a manufacturer to demonstrate, through various methods and processes in use over time for its particular operation, that a system of less than 100 percent identity testing would result in no material diminution of assurance of the identity of the dietary ingredient as compared to the assurance provided by 100 percent identity testing.” In suggesting that ingredient suppliers should also be allowed to initiate petitions under § 111.75(a)(1)(ii), AHPA believes that it should also be recognized that it may be possible – or in the case of botanical ingredients, more likely – for the *supplier of a botanical ingredient* to demonstrate, through various methods and processes in use over time for *its* particular operation, that a system of less than 100 percent identity testing by its customers would result in no material diminution of assurance of the identity of the dietary ingredient as compared to the assurance provided by 100 percent identity testing by these same customers.

Particular relevance of supplier petitions for processed botanical dietary ingredients

AHPA notes that, although the above stated request to allow suppliers of dietary ingredients to submit petitions for exemptions to 100 percent identity testing for one or more of their ingredients is intended to be applicable to suppliers of all dietary ingredients, AHPA's primary interest is in the applicability of this request to suppliers of botanical dietary ingredients.

Dietary supplements are required under current federal labeling regulations to identify on their label each contained botanical dietary ingredient by its Latin binomial name and/or by its established common or usual name (21 CFR 101.4(h)(2)). In addition, and except for algae, the specific part of the plant for each botanical dietary ingredient must be on the label (21 CFR 101.4(h)(1)).

Botanical dietary ingredients are supplied to dietary supplement manufacturers in several forms. For purposes of this discussion, the following forms can be described, and these terms will have these given meanings throughout the balance of these comments:

- "Crude botanical ingredient," defined for the purposes of this discussion as a single botanical ingredient in the form of a raw agricultural commodity in which macroscopic morphological characteristics are still present;
- "Processed botanical ingredient," defined herein to include (a) a crude botanical ingredient that has been dried and reduced to powder; (b) an extract of one or more botanical ingredient(s); or (c) a blend of two or more botanical powder(s) or extract(s).¹

When a botanical dietary ingredient is in its crude form, it can be readily tested or examined using many of the tests and examinations that are described at § 111.75(h)(2), such as gross organoleptic, macroscopic, microscopic, and chemical analysis, and the use of such tests will usually allow confirmation of both the plant species and the plant part with a high degree of certainty.² When a botanical dietary ingredient is obtained in a powdered crude form, however, macroscopic analysis can no longer be used as a test or examination to identify it. Similarly, neither macroscopic analysis nor microscopic analysis are relevant for identifying botanical extracts.

¹ Other types of processing may also occur, such as aging, soaking, steaming, frying, etc.

² In some cases, absolute species confirmation may require examination of the intact plant during flowering.

Primary processors are properly positioned to ensure crude botanical identity

In order for any alternative to 100 percent identity testing of a processed botanical ingredient to ensure that it would not result in any material diminution of assurance of the identity of the botanical ingredient, it is critical for the company that buys the botanical ingredient in its crude form and subsequently transforms it into a processed botanical ingredient to perform thorough, accurate, and well-documented tests or examinations on the identity of the material while it is in its crude form. The results of these tests or examinations must then accompany the processed material throughout subsequent distribution. If identity is not established when the botanical ingredient is whole, it may not be possible to assure the identity of subsequent materials – that is, a processed botanical ingredient – at any later point. Therefore, botanical ingredient suppliers are the natural and logical companies to submit identity testing petitions under § 111.75(a)(1)(ii).

Proving crude botanical identity is not always practical for purchasers of processed botanicals, unless the source crude

As has been noted above, proper botanical identification often cannot be reliably performed on processed botanical ingredients because botanical identification often requires examination of the macroscopic morphology of the intact plant. Once material is powdered or extracted, it is possible to provide some evidence to support the crude botanical identification of the material, but proof of that identity may not be possible.^{3, 4} Thus, companies that receive processed botanicals must be ensured that identity is determined on the source crude botanicals.

Furthermore, the difficulty in establishing crude botanical identity is compounded in the case of materials sold as blends. It is not uncommon for a commercial material to consist of a blend of two or more botanical ingredients. For the purchaser to develop data merely to indicate – much less prove – that the correct crude botanicals were used in this blend can be extremely difficult and expensive.

³ For herb powders, reliable identification based on DNA technologies may be possible in the future; however, at the current time, this technology remains experimental and controversial. DNA identification is generally not possible for botanical extracts.

⁴ For a more complete discussion of the requirements to establish botanical identity, and what testing can be done at various stages of processing, refer to the 06/25/99 Draft Report of the FDA Food Advisory Committee Dietary Supplement Working Group on Ingredient Identity Testing [and] Records and Retention (accessible at <http://www.cfsan.fda.gov/~dms/facgmp.html>).

Purchasers of processed botanical ingredients must rely on information from the primary processor to confirm crude botanical identity, in combination with tests to verify the processed botanical identity

AHPA believes that purchasers of processed botanical ingredients often must – indeed, often can only – rely on crude botanical identity information provided by the primary processor, in combination with appropriate tests or examinations to confirm the identity of the processed botanical.

For example, when making an extract – depending on the solvents, temperatures, drying procedures, etc. used – the chemical fingerprint of the processed material will differ from that of the crude botanical. As a particular example, dried seeds of *Ziziphus jujuba* var. *spinosa* contain constituents called jujubosides, and chemical identity tests for this crude botanical often require confirming the presence of these markers. However, commercial hydro-ethanolic extracts of this seed often will not contain significant levels of jujubosides, because they are destroyed during the typical extraction procedure. Therefore, applying the crude botanical identity test for jujubosides will produce false negatives when used on these extracts (i.e. since the jujubosides were destroyed during processing, the test will incorrectly indicate that the extract was not made from seeds of *Ziziphus jujuba* var. *spinosa*).⁵

This problem is obviously exacerbated in the case of blends of botanical extracts, in which several extracts of several crude botanicals may be combined.

Therefore, to confirm the identity of a processed botanical ingredient, a different identity test is often required than for the crude botanical(s) that is/are the source(s) of the processed botanical ingredient. In the case of extracted or blended botanicals, such tests would be largely specific to the particular processing method used, and will therefore often need to be provided by the ingredient supplier. These processed botanical tests can serve to confirm that the purchasers receive the same processed ingredient from shipment to shipment, but as discussed above, they cannot necessarily confirm the identity of the crude botanical(s) from which the processed botanical ingredient was derived.

In addition to being more effective in assuring botanical identity, AHPA believes that allowing dietary ingredient suppliers to submit petitions for alternative identity testing under § 111.75(a) will be much more efficient – in terms of both industry

⁵ Similarly, it is possible for chemical tests on processed botanicals to give false positives, as in the test for ellagic acid in “pomegranate skin extract,” which can be easily fooled by using ellagic acid isolated from other sources.

and agency resources – than limiting this procedure only to dietary supplement manufacturers. As a general rule, dietary ingredient suppliers strive to sell their ingredients to as many dietary supplement manufacturers as possible. Taking as a simple example a scenario in which an ingredient supplier sells a specific dietary ingredient to only two such manufacturers, it is obvious that more work – and arguably twice as much work – will be required by industry if both of those manufacturers submit petitions for exemptions to 100 percent identity testing under § 111.75(a) than if a single such petition is submitted by the ingredient's supplier. It is equally obvious that FDA will be required to do more work – and again, arguably twice as much work – if it receives two such petitions for the exact same ingredient provided by the exact same supplier. This example can be expanded to consider scenarios in which a supplier has 10, or 30, or 100 or more customers for the same ingredient.

In suggesting here that FDA should accept petitions for exemptions from 100 percent identity testing from dietary ingredient suppliers as well as from dietary supplement manufacturers, and in observing that increased efficiency is inherent in such a revision to § 111.75(a)(1)(ii), AHPA does not intend to reduce in any way the expectation that petitions would only be granted by FDA when the described alternative identity testing would ensure that there is no material diminution of assurance, compared to the assurance provided by 100 percent identity testing, of the identity of the dietary ingredient. If FDA accepts this request to allow dietary ingredient suppliers to submit petitions for alternative identity testing under § 111.75(a)(1)(ii), it should be accompanied by the requirement for every dietary supplement manufacturer that wishes to use any alternative identity testing granted under a supplier's petition to conduct the alternative tests and examinations for the dietary ingredient under the terms specified by FDA when a supplier's petition is granted. AHPA would also expect, recommend, and support a requirement for every such dietary supplement manufacturer to obtain from the specific dietary ingredient supplier a record of FDA's response to the supplier's petition and to maintain this record under § 111.95(b).

Finally, as discussed in more detail below, AHPA believes that many of the elements desirable in a submitted petition consist of information which is confidential, proprietary, and/or a trade secret of the ingredient supplier. As such, dietary supplement manufacturers generally have no access to the information and it would be inappropriate for the supplier to provide the information to supplement manufacturers. By allowing petitions to be filed by suppliers, FDA will

be provided access to important information without compromising suppliers' confidentiality.

The minimum required information to accompany a petition for a botanical ingredient must be specific and thorough

AHPA is providing below three lists of the minimum supporting data and information that should be included in petitions under § 111.75(a)(1)(ii) for any proposed exemption to 100 percent identity testing for botanical ingredients. The first of these lists is relevant to submissions related to all forms of botanical ingredients – crude or processed. The second list is related only to petitions related to processed botanical ingredients. The third list can apply to either or both. A fourth list of additional optional elements that may be useful in a petition follows.

Each of these lists is relevant to petitions submitted by dietary supplement manufacturers for the botanical ingredients that they receive, and also to petitions submitted by suppliers of botanical ingredients, should FDA accept our above request to allow suppliers to submit such petitions. Although these lists are addressed specifically to botanical ingredients, some of the aspects addressed here may also be relevant to other dietary ingredients.

Some of the information listed below will be considered confidential, proprietary, and/or a trade secret by the botanical ingredient supplier. Items which might be so considered are marked with an asterisk. In the case of petitions submitted by a dietary supplement manufacturer, it will be necessary for FDA to provide a mechanism by which the botanical ingredient supplier can submit this information directly to FDA in a manner by which strict confidentiality will be preserved.

Minimum information related to crude botanical ingredient that should be included in both (a) petitions related to the crude botanical itself, and (b) petitions related to a processed botanical ingredient for which the whole botanical is a source:

- Description of the specific tests or examinations used by the submitting firm to confirm the identity of the crude botanical ingredient, including:
 - Description of any examinations related to the ingredient's botanical morphology (e.g., macroscopic; microscopic; etc.), along with:
 - Detailed description of any morphologic characteristics examined and/or identified;
 - Photographs, photomicrographs, and/or other images that illustrate the characteristics examined.

- Description of any chemical analysis test methods used to confirm the identity of the crude botanical ingredient (e.g., thin layer chromatography (TLC); high-performance liquid chromatography (HPLC); and/or others), including:
 - Detailed description of the specific method;
 - Exemplars of target chromatograms, spectra, or other graphical data.
- Description of lot control method for the incoming crude botanical ingredient.
- Description of representative sampling plan for lots of incoming crude botanical.
- *Description of how whole crude botanical raw material is sourced (directly from growers; purchase on the world market; etc.).

Minimum information related to the processed botanical ingredient that should be included in any petitions related to a processed botanical ingredient:

- All of the above, as it relates to the crude botanical ingredient(s) that is/are the source of the processed botanical; **plus the following:**
- *General description of the processing of the source crude botanical, that is, of the steps taken to produce the processed botanical ingredient.
- Description of the specific tests or examinations used to confirm the identity of the processed botanical ingredient, including:
 - Description of any examinations related to the ingredient's botanical morphology (e.g., microscopic; etc.), along with:
 - Detailed description of any morphologic characteristics examined and/or identified;
 - Photographs, photomicrographs, and/or other images that illustrate the characteristics examined.
 - Description of any chemical analysis test methods used to confirm the identity of the processed botanical ingredient (e.g., thin layer chromatography (TLC); high-performance liquid chromatography (HPLC); and/or others), including:
 - Detailed description of the specific method;
 - Exemplars of target chromatograms, spectra, or other graphical data.
- Description of lot or batch control method for the processed botanical ingredient.
- Description of the representative sampling plan for the processed botanical ingredient.

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- Description of procedures which ensure traceability to the specific lot(s) of associated crude botanical ingredients.
 - Description of packaging and labeling controls used by the supplier to prevent labeling mixups of the botanical ingredient.
 - Description of lot-specific crude botanical identity data, which is to be provided to dietary supplement manufacturers with each lot or batch of a finished processed botanical ingredient, and which the supplement manufacturer should be required to keep on file under § 111.95(b)(6) along with documentation of FDA's response to the ingredient's supplier's petition.
 - NOTE: This last point represents AHPA's view that some lot-specific crude botanical identity data be provided to and retained by the supplement manufacturer.

Additional minimum information that should be included in all petitions related to botanical dietary ingredients:

- Information on the training, experience, or other qualifications of the persons performing morphological exams and chemical testing.
- A discussion of the cGMP standards to which the named or submitting supplier adheres, and which must be relevant and sufficient to ensure the identity of the dietary ingredients marketed by the supplier that are subject of any petition.
 - NOTE: It is AHPA's view that compliance with any one of a number of well-designed GMP standards should be deemed sufficient, including but not limited to 21 CFR 111; Health Canada Natural Health Product GMP standards; European Traditional Medicines GMP standards; various national drug GMP standards; etc. Suppliers who are already in compliance with relevant and sufficient GMP standards should not be burdened with duplicative, redundant, or superfluous compliance standards, such as a requirement to comply with 21 CFR 111 in addition to their existing national drug or health product standards.
- A statement to acknowledge that the supplier of the botanical ingredient is subject to cGMP inspection, including records inspection, by FDA as necessary to ensure that adequate and suitable cGMP are in place at that facility as it pertains to ensuring the identity of ingredients that are the subject of petitions.
- Description of identity tests or examinations that the dietary supplement manufacturer who receives the ingredient should perform from time to time,

along with a recommended schedule for performing such tests or examinations.⁶

- AHPA suggests that the recommended schedule for the ingredient recipient's testing regimen in lieu of 100 percent identity testing declare that the recipient should not disclose to the supplier the specific lots on which identity testing is to be conducted.

Other (optional) elements of a petition might include:

- *Discussion of the reference(s) and/or data used to confirm that tests and examinations used to identify each ingredient are appropriate for the ingredient.
- The actual results of tests or examinations on at least one representative sample of the ingredient that is the subject of the petition.
- *Specific information as to growers, collection areas, etc. for the crude botanical.
- *Information on any voucher specimens maintained for the crude botanical ingredient.
 - NOTE: The utility of voucher specimens will depend upon the botanical and the nature of the supplier's sourcing practices. In some cases, voucher specimens may provide important and valuable additional assurance of identity; in other cases their use may be irrelevant, unnecessary, and burdensome.
- *Information on seed or propagative material sources of cultivated crude botanical.
- *Information about known potential adulterants, including whether the foreign material represents an economic or safety risk. If safety risks are present, the severity of the potential negative health consequences should be discussed.
- *Discussion of any processing steps which serve to further ensure proper identity.

⁶ For example, it might be appropriate for purchasers to first test 100% of the first 3-5 shipments of processed botanical purchased under the petition, followed by every third lot for the next 10 lots, followed by every 10th lot subsequent to that. AHPA believes that this type of reduced testing plan, when implemented in combination with the other elements of the petition, is perfectly adequate to ensure no material diminution of the assurance of identity, and that statistical analyses of data related to large numbers of incoming lots are unnecessary.

- For example, after a raw material lot or batch is approved for use in production, in many cases the first process step is to perform 100% inspection of the lot or batch to remove foreign organic (as well as inorganic) materials. This step can provide important assurance that the entire lot consists of the proper botanical, beyond what can be ensured through representative sampling.
- *Discussion of how processed ingredient identity test methods differ from the crude botanical identity test methods.

At the same time that AHPA is providing the above suggestions on the minimum required information and additional optional information for inclusion in a petition under § 111.75(a)(1)(ii), it is to be noted that each company will have a different set of concerns to address and different sourcing, manufacturing, and sales processes; therefore, the content of each petition will need to be customized for each situation. There can be no one-size-fits-all recipe.

FDA should accept petitions for exemptions to 100 percent ingredient testing in advance of the cGMP final rule's compliance dates

The interim final rule states that FDA "would consider a manufacturer's request for an exemption from the testing required by § 111.75(a)(1) of the CGMP final rule once the compliance date for that manufacturer (based on the various compliance dates based on size of the firm, as in the CGMP final rule) passes.... In the interim, manufacturers who may want to request such an exemption, could gather the data and information it needs to support a petition for exemption under § 111.75(a)(1)(ii)."

AHPA requests that FDA accelerate this described time line to allow a company that wishes to request exemptions from 100 percent identity testing for one or more dietary ingredients to do so sufficiently in advance of its relevant compliance dates so that exemptions are able to be utilized immediately upon the date of such compliance date.

Also, AHPA is requesting below that the interim final rule be revised to establish specific times after receipt of a petition for exemption from 100 percent identity testing by which FDA would be required to provide responses to the submitting firm. If that request is granted, AHPA further requests that FDA allow petitions under § 111.75(a) to be submitted under this rule by a date that will allow the agency's responses, within any such required response time, to be received by the submitting firm not later than its relevant compliance dates (or if petitions are

allowed by dietary ingredient suppliers, as requested above, by the relevant compliance date of its customers).

A citizen petition under § 10.30 is not the best regulatory mechanism to request an exemption from 100 percent identity testing

Title 21 of the Code of Federal Regulations addresses exemptions to certain of the regulations contained therein and presents various regulatory mechanisms to request and obtain such exemptions. AHPA believes that other of these regulatory mechanisms provide models for more efficient processes for requesting exemptions to 100 percent identity testing of dietary ingredients than submissions of citizen petitions under 21 CFR 10.30, and requests that FDA establish a different and more specific mechanism to receive requests for exemptions from the requirements of § 111.75(a)(1)(i).

AHPA notes that 21 CFR 170.39 describes the conditions under which a substance used in a food-contact article that migrates, or that may be expected to migrate, into food will be exempted from regulation as a food additive because it becomes a component of food at levels that are below the threshold of regulation. This rule describes, at § 170.39(c), the specific information that must be included in any request for FDA to exempt such use of a substance from regulation as a food additive and simply identifies, at § 170.39(d), the FDA office to which such a request should be submitted.

AHPA also notes that 21 CFR 171 deals with food additive petitions generally, and lays out a petition mechanism that is different from citizen petitions under § 10.30. Similar to the above example, this regulation also describes the specific information that must be included in any petition proposing the issuance of a regulation prescribing the conditions under which a food additive may be safely used and provides the address of the FDA office to which such a petition should be submitted.

On the other hand, FDA is requiring in the interim final rule that a request for exemption from 100 percent identity testing of a dietary ingredient must utilize the mechanism of a citizen petition under § 10.30. AHPA views this as a less efficient approach to request such an exemption, and believes that certain of the elements required to be included in a citizen petition are generally irrelevant to the issue at hand. For example, AHPA is not aware of any reason to require a company that submits a request for an exemption to 100 percent identity testing under § 111.75(a) to address the environmental impact of such alternative testing. In addition, AHPA believes that the lack of specific instructions as to the information

that must be submitted in a request for exemption from § 111.75(a)(1)(i), as is provided in the examples above, is likely to lead to a proliferation of flawed and incomplete citizen petitions, which would create a burden not only for the trade but also for FDA.

For all of the reasons stated here, AHPA strongly encourages FDA to consider other models that it has used in the past as better models for addressing exemption requests under § 111.75(a)(1)(ii) than citizen petitions under § 10.30. AHPA believes that a regulatory process that specifies exactly what must be submitted and to which FDA office, as is the case in the regulations at §§ 170.39 and 171, would provide significantly better guidance for submission of thorough and adequate requests for alternative identity testing, and would result in much more efficient use of both industry and agency resources.

If FDA insists, contrary to the AHPA's request here, that a request for alternative identity testing must be submitted as a citizen petition under § 10.30, AHPA strongly encourages FDA to clarify that environmental impacts should not be required in any such citizen petition. AHPA notes that 21 CFR 25.30 identifies classes of actions that are categorically excluded and, therefore, ordinarily do not require the preparation of an environmental assessment (EA) or environmental impact statement (EIS), and that § 25.30(j) specifically identifies the following as such "categorically excluded" class of action:

"Issuance of CGMP regulations, HACCP regulations, establishment standards, emergency permit control regulations, GLP regulations, and issuance or denial of permits, exemptions, variances, or stays under these regulations."

Any request for an exemption from 100 percent identity testing under § 111.75(a) is certainly related to an "exemption" under "CGMP regulations." It is clear from the language at § 25.30(j) that any such request for such an exemption would therefore be "categorically excluded" from this section. If FDA insists that citizens petitions under § 10.30 will be the only regulatory mechanism for requests for a subject exemption, FDA should state in no uncertain terms its belief that such petitions would be categorically exempt, and should advise all submitters to so state.

AHPA notes that in the preamble to the interim final rule FDA recommends that any information submitted in a petition under § 111.75(a)(1)(ii) that is considered to be confidential commercial or trade secret information should be identified as such and should be segregated from other information in a petition. The agency also acknowledges that information that is confidential or a trade secret is not available for public disclosure. This same treatment of confidential and trade

secret information should be extended to whatever alternative regulatory mechanism is established for submission of a request for exemption from 100 percent identity testing, should the agency grant the request made in this part of these comments. It should also be applied to any and all sources of confidential and trade secret information, whether received from a dietary supplement manufacturer or a supplier submitting a petition related to one or more dietary ingredients, or to a supplier that provides such information in support of a petition by a manufacturer.

FDA's assumption that statistical analysis is needed to support a request of exemption under § 111.75(a) is burdensome and unnecessary

In the preamble to the interim final rule FDA notes that some comments suggested that an alternative to 100 percent identity testing be allowed in the cGMP final rule, and noted specifically:

“...some comments recommended that the frequency of testing requirements, in general, be established using a statistically valid method and that the extent of testing be reduced taking into account the history of the supplier.” 72 FR 34960.

AHPA notes that it was not AHPA's comments that made such a recommendation, nor did the “joint industry submission” communicated to FDA on January 30, 2004, to which AHPA was a party, make such a suggestion. AHPA is concerned that the agency has misinterpreted comments that did suggest that “it is only necessary to test... for conformity with specifications based on a frequency established under a statistically valid method” to mean that there is no other means by which an option to 100 percent identity testing can ensure that an exemption to this 100 percent testing requirement can ensure that there will be no material diminution of assurance of identity. AHPA disagrees with any such supposition.

In discussing the costs associated with submitting a request to FDA for an exemption to 100 percent identity testing, the agency states that companies that submit such a request will “incur costs which, at a minimum will include: Employing a statistical expert to develop a verification testing plan that can prove the firm can adhere to the standard of ‘no material diminution of assurance.’” 72 FR 34963. This language implies that this will be a certain cost associated with any such request, and therefore further implies that statistical analysis will be a prerequisite to approval by FDA of any request for an exemption to § 111.75. Again, AHPA disagrees that such a prerequisite should be established.

Furthermore, in many cases it will be impossible for such a prerequisite to be established. Such a statistical analysis is possible only for companies which purchase a large numbers (at least dozens) of lots of the same material, i.e. generally large companies using common ingredients. For many companies and for many ingredients, new lots are not purchased frequently enough to develop the history necessary to admit of statistical analysis.

Finally, as described in great detail elsewhere in these comments, AHPA believes that the highest degree of assurance for identification of a botanical dietary ingredient is achieved when the supplier company that obtains the ingredient in its whole crude form – not its customers – reliably identifies 100% of its lots of crude botanical raw material and 100% of its lots of processed botanical product. This work on the part of these suppliers, in combination with other appropriate process controls as described below, is the best way to ensure identity and renders statistical analyses by the purchaser to be superfluous and irrelevant.

FDA must commit to specific timeframes for response to submissions under § 111.75(a)

AHPA is aware of citizen petitions that have languished at FDA for inordinate periods of time, regularly measured in years and too often measured in decades. AHPA requests that FDA set for itself specifically identified temporal obligations for responding to all submitted requests for exemptions to § 111.75(a)(1)(i), whether the agency insists on maintaining citizen petitions as the mechanism for such submissions or identifies another mechanism, as requested above. More specifically AHPA requests the following timelines be established after the agency's receipt of a request for exemption from 100 percent identity testing:

- Within 30 days, FDA should identify any such request that is deficient in any regulatory particular, and should return the request with a communication to inform the submitter that the request has not been filed, due to the specifically identified deficiency.
- Within 90 days, FDA should respond to any complete (not deficient) request by informing the submitting company that it has, or has not, granted the request. Communication at this time should identify the tests and examinations that must be conducted for the dietary ingredient and any and all additional terms that the agency is specifying in granting the request.

It is AHPA's view that the process for new dietary ingredient (NDI) notifications under 21 CFR 190.6 is at best functioning poorly, and should be more honestly described as dysfunctional. AHPA further believes that much of this dysfunction is

due to the fact that FDA is required to deal with even deficient NDI notifications. In suggesting that FDA assign to itself a 2-stage timeline for the regulatory process that is the subject of these comments – one related only to an evaluation of whether requests for exemptions to 100 percent identity testing are deficient – AHPA is hoping to avoid at the very outset the creation of another dietary supplement regulation with a notification requirement in which the agency would be required to address even incomplete submissions.

In requesting the second timeline by which time FDA should respond to requests for exemptions under this rule, AHPA is recognizing the pragmatic needs of industry. AHPA hopes that FDA will also recognize the pragmatic factor here and will commit to providing the necessary resources to ensure that the flexibility represented by the interim final rule's addition of § 111.75(a)(1)(ii) will provide an actual option for the trade.

AHPA further believes that by allowing and even encouraging petitions to be submitted by suppliers on behalf of their many customers, FDA will keep the number of petitions submitted to a manageable number, which will contribute to the agency's ability to address all petitions in a timely manner.

FDA guidance on this regulation should be prioritized

In the preamble to the interim final rule, FDA stated that it will issue guidance on the information and type of data it recommends be included in requests for exemptions from 100 percent identity testing, including what such requests should contain.

AHPA strongly encourages FDA to develop and publish such guidance as a priority, and at the earliest opportunity. AHPA also requests that the agency recognize that industry organizations, including AHPA, may develop and promulgate relevant guidance more promptly than the agency, and further requests and encourages FDA to incorporate such industry guidance in its own eventual guidance. In addition, AHPA believes that there could be value in convening one or more public meetings to address the many issues that should be discussed to create the most useful and well-informed guidance.

Conclusions

AHPA is expressing support through these comments for allowing the type of requests described by the interim final rule so that the final cGMP rule will provide flexibility in the essential step of assuring ingredient identity, at the same time that there is no material diminution of assurance of the identity of the dietary ingredient as compared to the assurance provided by 100 percent identity testing. AHPA believes that flexibility in this area is essential to ensure that the cGMP final rule does not create unnecessary and redundant burdens for dietary supplement manufacturers. AHPA also believes that this flexibility will allow identity testing options that will better incorporate information that is maintained by ingredient suppliers, who are often the most knowledgeable party in the supply chain as regards an ingredient's identity.

AHPA has also made substantive requests and suggestions for modifications to the interim final rule, including:

- That suppliers of dietary ingredient be allowed to submit petitions for exemptions to 100 percent identity testing;
- That the requested supplier petitions may have particular relevance to botanical dietary ingredients, especially when these are processed (i.e., in the form of powders, extracts, blends, etc.);
- That certain specific information be described as the minimum information that should be included in any request submitted under this part;
- That FDA should accept requests for exemptions to 100 percent identity testing in advance of the cGMP final rule's compliance dates;
- That FDA should consider mechanisms other than citizen petitions under § 10.30 for submitting such requests;
- That FDA should reconsider its expressed position that requests submitted under the interim final rule must necessarily rely on a statistical analysis;
- That FDA establish and declare reasonable timeframes for its response to requests submitted under this part; and
- That FDA should prioritize its issuance of guidance on the information and type of data it recommends be included in requests for exemptions from 100 percent identity testing.

AHPA has prepared a draft revision of the interim final rule that incorporates many of the requests and suggestions included in these comments, and has included that draft in an appendix attached hereto.

AHPA appreciates the opportunity to provide these comments. AHPA recognizes that the issues addressed here are complex, and AHPA staff and counsel will

make themselves available at any mutually convenient time to discuss any of the topics addressed herein.

Respectfully submitted,



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Addendum: Draft Revision to 21 CFR 111.75(a)(1)

The draft that follows incorporates many of the requests and suggestions included in the above comments. Added language is presented in underlined italic font and deletions or in ~~strikethrough~~ font.

§ 111.75(a) Before you use a component, you must:

(1)(i) Conduct at least one appropriate test or examination to verify the identity of any component that is a dietary ingredient, unless

(A) You petition the agency under paragraph (a)(1)(ii) of this section and the agency exempts you from such testing; or

(B) You obtain the ingredient from a supplier that has petitioned the agency under paragraph (a)(1)(ii) and has received a response from the agency that exempts recipients of the ingredient from such testing.

(ii) You or the supplier of a dietary ingredient may submit a petition, ~~under 21 CFR 10.30,~~ to request an exemption from the testing requirements in paragraph (a)(1)(i) of this section.

The petition must:

(A) Identify the dietary ingredient that is the subject of the petition, including, if the ingredient is a botanical or derived from a botanical, the Latin name (including the author) and the plant part.

(B) Identify the name and address of the submitting firm and the name and phone number of an individual contact.

(C) Set forth the scientific rationale, and must be accompanied by the supporting data and information, for proposed alternative testing that will demonstrate that there is no material diminution of assurance, compared to the assurance provided by 100 percent identity testing, of the identity of the dietary ingredient before use when the dietary ingredient is obtained from one or more suppliers identified in the petition.

(D) Include a statement certifying that, to the best of your knowledge and belief, your petition includes all information and views on which the petition relies, and that it includes representative data and information known to you which are unfavorable to the petition.

(E) Identify and segregate any information in the petition that you consider to be confidential commercial or trade secret information.

[(F) Other information as appropriate, for example, from the lists of minimum information that AHPA has suggested be included in a submission.]

(G) Be submitted to the Food and Drug Administration's Office of [fill as appropriate] (HFS-xxx), 5100 Paint Branch Pkwy., College Park, MD 20740.

(iii) If FDA grants the a petition submitted under paragraph (a)(1)(ii) of this section, you must conduct the tests and examinations for the dietary ingredient, otherwise required under § 111.75(a)(1)(i), under the terms specified by FDA when the petition is granted; [and]