USP Statement on Validation of DNA Test Methods for Regulating the Quality of Herbal Supplements

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The United States Pharmacopeial Convention Urges Scientific Validation of DNA Test Methods for Regulating the Quality of Herbal Supplements

(Rockville, MD – April 16, 2015) – *In response to an agreement announced between the New York State Attorney General (NYAG) and GNC Holdings, Inc. (GNC) the United States Pharmacopeial Convention (USP), an independent, science based, standards setting organization and publishers of the United States Pharmacopeia-National Formulary (USP-NF), an official compendia of quality standards for dietary supplements sold in the U.S., issued the following statement:*

Statement by Gabriel Giancaspro, PhD – Vice President –Foods, Dietary Supplement and Herbal Medicines United States Pharmacopeial Convention (USP)

"As a science-based standards-setting organization, the United States Pharmacopeial Convention (USP) has a keen interest in adopting emerging technologies to ensure the test methods and quality standards included in the *United States Pharmacopeia-National Formulary (USP-NF)* are current and reflect the state of the industry. DNA testing including DNA Barcoding, is just one example of a technology that has been recently added to the *USP-NF*.

As of December 2014, DNA-based identification methods are included in the official USP chapter <563> Identification of Articles of Botanical Origin. However, this method is not yet referenced in a *USP-NF* monograph (quality standard) for a specific ingredient or product. That is because USP quality standards are specific for each ingredient, product and dosage form and the standards we develop include only those test methods that have been scientifically validated and shown to be fit for purpose.

With the appropriate validation, USP may incorporate DNA tests into specific product quality standards, but even then it is envisioned not as stand-alone procedure, but as a complement to existing chromatographic, spectroscopic, and botanical morphological (microscopic/macroscopic) analytical procedures.

DNA testing poses some unique benefits. Its sensitivity and specificity helps in accurate identification of the botanical species as well as adulterants and contaminants – especially in material where the macro-botanical characteristics are no longer present, such as powdered or ground material. However, this same sensitivity can lead to false results and that calls for careful interpretation of the data.

Also, identity is just one of many attributes that are used to determine the overall quality of a given material. Quality of plant materials is determined by identity, purity and the content of bioactive constituents. DNA based tests should not be used as the only way to determine botanical content.

There are also materials for which DNA testing is not recommended. DNA-based methods are not suitable for materials, such as botanical extracts, that were subjected to processes that denature, degrade and destroy DNA.

USP has public quality standards for all of the ingredients identified by the NY Attorney General's office in their cease and desist letters, including standards for the raw plant material, the plant

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extract and/or the botanical supplement of: Saw palmetto, Echinacea, Garlic, Ginkgo Biloba, Ginseng and St. John's Wort. Currently, none of the standards for these products include DNA testing for identity.

For nearly 200 years, USP has helped protect public health by providing a forum where the views of a diverse array of stakeholders are fully exchanged and the resulting quality standards not only reflect those views, but are also based on the best available science."

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The U.S. Pharmacopeial Convention (USP) is a global health organization that improves lives through public standards and related programs that help ensure the quality, safety, and benefit of medicines and foods. USP's standards are used worldwide. For more information about USP, visit http://www.usp.org .

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Establishing the Identity and Quality of Botanical Dietary Ingredients – The Potential Role of DNA-based Methods Amongst Others

Dietary Supplements e-Newsletter

Establishing the Identity and Quality of Botanical Dietary Ingredients – The Potential Role of DNA-based Methods Amongst Others

The New York Attorney General letter of February 2, 2015 to major retail stores to "cease and desist" supply of several store brand botanical dietary supplements (http://www.nytimes.com/interactive/2015/02/02/health/herbal_supplement_letters.html) brought renewed attention to a familiar discussion on how to ensure the identity and quality of such products. As of this article, no information has been publicly shared by the Attorney General or the targeted manufacturers about the scientific validity and fitness for the purpose of the methods they used for assessing the identity and quality of the dietary supplements in question. This article briefly reviews the regulatory requirements in the context of analytical methods used for identification of botanical ingredients. This article also advocates for the use of public standards that may help manufacturers comply with regulatory requirements.

Regulatory Requirements

Effective 2010, all dietary supplement manufacturers are required to implement the current Good Manufacturing Practices (cGMPs) which include conducting at least one appropriate test or examination to verify the identity of the dietary ingredient, before a dietary ingredient is used (21 CFR 111.75). In addition, the regulations require that specifications be established for product components to ensure the purity, strength and composition of dietary supplements manufactured using these components; and that limits be established on those types of contaminants that may adulterate or may lead to the adulteration of finished batches of the dietary supplements to ensure the quality of the dietary supplement (21 CFR 111.70). With regard to the analytical methods to be used for these tests; the regulation requires that manufacturers verify that the laboratory examination and testing methodologies are appropriate for their intended use, and to identify and use appropriate scientifically validated method(s) for each established specification for which testing or examination is required (21 CFR 111.320). The preamble to the cGMPs final rule indicates that typical validation characteristics include accuracy, precision, specificity, detection limit, quantitation limit, linearity, range, and robustness and that a scientifically valid method is accurate, precise, and specific for its intended purpose (http://www.fda.gov/ohrms/dockets/98fr/cf0441.pdf; page 400). The manufacturer´s responsibility to meet these requirements can be accomplished either through their own private specifications (and thereby taking the onus of proving that the methods are valid and fit for purpose) or through voluntary use of public standards. The preamble to the cGMPs also noted that "We [FDA] explicitly stated that you may use validated methods that can be found in official references, such as AOAC International, USP, and others…. compendial standards may be appropriate reference materials for use in conducting tests or examinations (http://www.fda.gov/ohrms/dockets/98fr/cf0441.pdf; page 402 and 563)". Under current U.S. law, a dietary supplement may be deemed to be misbranded if a dietary supplement manufacturer claims conformance with specifications in a USP-NF

monograph–a detailed guide that establishes quality (identity, purity, potency, etc.)–and fails to so conform.

DNA-based Methods for the Botanical Identification

DNA-based methods can be used in the identification of articles of botanical origin, if used in conjunction with chemical or botanical (morphological / microscopy) methods. DNA barcoding is a sequence-based identification method that uses short sequences of specific DNA loci for identification of plant species. Briefly, the method involves amplification of regions of botanical DNA that are variable between species. Due to amplification of copies of DNA, it is a sensitive method, provided the plant materials being analyzed have not been subjected to processes (such as solvent extraction) which could affect the quality of genomic DNA. DNA-based methods can distinguish closely related or morphologically similar species in cases where morphological taxonomic characteristic identification features have been lost due to processing e.g., by drying, cutting or comminuting. While sensitivity and accuracy of detection is a major attribute of DNA-based methods, there are limitations to the use of these methods, which include:

1. DNA can be damaged during processing (extraction, heat, and other manufacturing processes) to a point that is no longer extractable, thus giving false negatives. For this method to work, the extracts should be prepared in a manner that conserves the integrity of the DNA. However the vast majority of plant extracts are prepared to maximize the content of secondary metabolites, and under such conditions, keeping DNA intact or sufficiently recoverable is difficult.
2. Due to its sensitivity, the DNA-based method can give positive results due to impurities, contaminants or adulterants present in the test material at extremely low levels. For example, USP botanical monographs permit Not More Than 2% foreign organic matter. Depending on the sampling procedure, it is conceivable that DNA from the foreign material could be erroneously amplified and presented as a positive reaction. As such, the DNA-based method cannot distinguish deliberate adulteration from the identity of an ingredient, unless complemented with other orthogonal tests. For these reasons, the presence or absence of DNA in a botanical extract should not be used by itself or alone as the only test to confirm the identity of an ingredient in the form of a plant extract.
3. The presence of DNA does not guarantee that the plant was grown under appropriate Good Agricultural Practices, from the right location, collected at the right time, or processed under the right conditions to deliver the botanical substances responsible for the purported health benefit.
4. DNA from excipient botanical fillers may dominate the DNA patterns, masking the presence of the plants of interest.
5. DNA presence does not give a quantitative result; as such it is impossible to determine whether the plant material is present in the amounts claimed.
6. Non-biological adulterants (including synthetic drugs) cannot be detected by DNA-based methods.

USP Resources

As a science-based standard-setting organization, USP has a keen interest in adopting emerging technologies in its standards development process. While DNA testing became an official technology recognized by USP in December 2014, it is envisioned as a method to be applied mostly to test plant materials that have not been subjected to extraction procedures and complementary to other chemical tests. Currently, the method is not referenced in any dietary supplement monograph in USP-NF. USP resources and

experience in the context of the DNA-based methods for the identification of botanical ingredients are as follows:

1. USP dietary supplement **monograph standards** are available for all the ingredients and some of the dosage forms identified by the Attorney General´s office; including standards for the raw plant materials, plant extracts and/or the botanical supplement dosage form (Saw Palmetto, Echinacea, Garlic, Ginkgo, Ginseng, and St. John´ Wort). These USP monographs contain analytical procedures based on orthogonal chemical methods for establishing the identity and quality of the ingredient. For example, the USP standards for Powdered Ginkgo Extract includes the following:
    - Identification by two different methods (HPTLC and HPLC): Comparison of chromatographic patterns of the sample with that of the reference standard; the ratio and relative abundance of the flavonol glycosides.
    - Composition: Contents of flavonol glycosides (22% - 27%); terpene lactones (5.4% - 12.0%); bilobalide (2.6% - 5.8%).
    - Limits for contaminants: Pesticide residues; elemental impurities; microbial load
    - Specific tests: Limits for rutin and quercetin; Limits for Ginkgolic acid; Limit of residual solvents.
2. USP revised **General Chapter** <563> Identification of Articles of Botanical Origin by including a new section on DNA-based methods as a complement to chemical-based/chromatographic methods and the microscopic and macroscopic methods (Pharmacopeial Forum 39(5); available freely at www.usppf.com (access requires registration); see pages 12-13 of the proposed revision). The method involves marker selection, DNA extraction, PCR primers and amplification, DNA sequencing and comparison with reference materials
3. A **Stimuli Article** on DNA-based methods was published in the Pharmacopeial Forum 39(5) (available free at www.usppf.com; access requires registration). The article provides a summary of DNA-based methods for botanical authentication and adulterant detection and discusses the pros and cons of each method for compendial application.
4. USP held a **workshop** on October 23–24, 2014, that was co-sponsored by the United States Department of Agriculture (USDA). The workshop brought stakeholders together to discuss the strengths, limitations, and applications of DNA-based identification methods and to collect feedback on the technology and its utility as a tool for botanical identification and quality control. For additional information see the following: http://www.usp.org/sites/default/files/usp_pdf/EN/dietarySupp/newsletter/dna-workshop.pdf. The key messages from the workshop were as follows:
    - Use orthogonal chemical methods to complement the DNA-based methods for establishing the identity and quality of the ingredient.
    - Qualitative and quantitative considerations, genotype/chemotype correlations, and inclusion/exclusion panels are important in interpreting the results.
    - DNA-based methods could be used to comply with regulatory requirements for identification of botanical articles if the requirements under section §111.320 (laboratory methods for testing and examination) are met.

Concluding Remarks

The issue concerning the testing of botanical dietary supplements could be easily resolved if manufacturers followed public quality standards such as those available from

USP-NF, the European Pharamcopeia, or any other compendial standards. The cGMPs regulations permit manufacturers to set their own private specifications for dietary ingredients. Compliance with cGMPs means that the dietary ingredient used in the product meet the quality specifications privately established by dietary supplement manufacturers, which can only be verified through an FDA inspection. Unless the manufacturers adopt public standards as their specifications, there is no way for consumers to know whether private specifications are sufficient to ensure the identity and quality of the dietary ingredients. Non-compliance with FDA regulations requiring the establishment of quality specifications including identity can be avoided when dietary supplement manufacturers use compendial standards.

The recent developments related to the use of DNA-based methods for identification of botanical ingredients/extracts is indicative of the need for transparency of the analytical methods used for assessing the identity and quality of dietary ingredients. FDA regulations require that suitable validation and verification studies be performed to establish whether the selected test method is fit for the purpose. Unless demonstrated otherwise, information is not currently available to support that DNA-based methods are scientifically valid and fit as the sole method to be used for botanical identification. Given the dialogue concerning the availability of methods that are suitable for intended purposes, public quality standards provide a uniform point of reference for regulators and manufacturers, and promote consumer confidence.

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Dietary supplements quality analysis tools from the United States Pharmacopeia

Perspective

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Dietary supplements quality analysis tools from the United States Pharmacopeia

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The United States Food and Drug Administration (FDA) issued the dietary supplement (DS) current good manufacturing practice (GMP) regulations in compliance with the mandate from the Dietary Supplements Health and Education Act (DSHEA), with the intention of protecting public health by ensuring the quality of DS. The GMP regulations require manufacturers to establish their own quality specifications for identity, purity, strength, composition, and absence of contaminants. Numerous FDA-conducted GMP inspections found that the private specifications set by these manufacturers are often insufficient to ensure adequate quality of dietary ingredients and DS. Wider use of the public standards developed by the United States Pharmacopeial Convention (USP), in conjunction with GMP compliance, can help ensure quality and consistency of DS as they do for medicines. Public health protection could be enhanced by strengthening the GMP provisions to require conformance with relevant *United States Pharmacopeia–National Formulary* (*USP–NF*) standards, or in the absence of *USP* standards, other public compendial standards. Another serious concern is the presence of synthetic drugs and drug analogues in products marketed as DS. Use of the new *USP* General Chapter *Adulteration of Dietary Supplements with Drugs and Drug Analogs* <2251> may reduce the exposure of consumers to dangerous drugs disguised as DS. Copyright © 2016 John Wiley & Sons, Ltd.

Keywords: Dietary Supplements; DSHEA; Good Manufacturing Practices; USP–NF; Adulteration; PDE5

Dietary Supplements Health and Education Act (DSHEA), good manufacturing practice (GMP), and unresolved issues with quality of dietary supplements (DS)

In the United States, DSHEA (Public Law 103-417, October 25, 1994) provides a regulatory framework for manufacturing and marketing DS that are intended to supplement the diet and contain dietary ingredients (vitamin, mineral, herb or other botanical, amino acid, or a concentrate, metabolite, constituent, or extract, or combination of any of these ingredients). DSHEA enabled consumer access to supplementation with the idea of promoting and maintaining health, and at the same time, it enabled the industry in the USA to grow from an initial base of about $4 billion in 1994 to an estimated $35 billion in 2015.[1] Under DSHEA, DS manufacturers are responsible for establishing the safety and quality of a product, but they are not required to share that information with the Food and Drug Administration (FDA) before the product enters the market, unless it contains a new dietary ingredient (NDI), i.e., introduced to the market after October 15, 1994. Manufacturers are required to file a 75-day pre-market notification to the FDA for any NDIs, with the information based on which the manufacturers reached the conclusion of reasonable expectation of safety. The FDA has the authority to remove a product from the marketplace if it presents 'significant or unreasonable risk of illness or injury'. However, the FDA is charged with the responsibility of proving that the product presents such a risk to public health, which is a resource-intensive activity. It took a concerted effort pooling resources from multiple agencies to initiate legal action with the Department of Justice leading the charge.[2] It remains to be seen if similar actions will be regularly in place to monitor compliance. Because the FDA has limited resources to ascertain harm, products of dubious quality can stay in the market without consequence. Moreover, by taking advantage of DSHEA's minimum requirements of pre-marketing oversight, prescription drugs and their analogues, masqueraded as DS, have been illegally introduced.[3] In addition, deficiencies in the current surveillance system have been reported.[4–6]

To address quality issues, DSHEA gave the FDA authority to prescribe and implement current GMPs for DS. Thirteen years after the passing of DSHEA, GMP became a rule in the Code of Federal Regulations (CFR) in 21 CFR Part 111 [Current Good Manufacturing Practice in Manufacturing, Packaging, Labeling, or Holding Operations for Dietary Supplements].[7] Regarding the quality of DS, GMPs require manufacturers to establish their own specifications for dietary ingredients, other components, in-process materials, and finished dietary supplements. Implementation of GMP requirements through manufacturer's private specifications has led to a lack of uniformity across the industry.[8] Two products from different manufacturers may both carry an identical label, yet be formulated to very different quality specifications. GMP regulations also allow end-product testing by just one of the established specifications to serve as a proxy for all quality attributes of the finished DS (21 CFR 111.75). Therefore, manufacturers may choose different tests to evaluate the quality of DS, even if they contain the same ingredient or are labelled with the same generic name. With regard to the analytical methods used as part of these specifications, GMP regulations require manufacturers to verify that the laboratory

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examination and testing methodologies are appropriate for their intended use, and to identify and use appropriate scientifically valid method(s) for each established specification for which testing or examination is required (21 CFR 111.320), but the rule does not require a complete formal validation for the analytical procedures.

Even with these limited requirements, there were numerous non-compliance observations noted by the FDA during GMP inspections, where the analytical methods employed were either non-specific or not fit for purpose.[9] As an example of the inadequacy of analytical procedures within private manufacturer specifications, the FDA has noted in one of the warning letters that colour, particle size, pH, and comparison of the certificate of analysis supplied by the ingredient manufacturer with the specifications are not suitable tests for identity, because these tests neither uniquely identify an ingredient nor discriminate it from other ingredients.[10,11] Regulatory investigators also may have a hard time in determining what test should be used in cases of suspected adulteration, given the wide variety of dietary ingredients. Recent regulatory investigations, which used a DNA-based method as the sole basis for determining adulteration of several botanical DS products, including ginkgo, St John's Wort, valerian, echinacea, and garlic are an example of this.[12] While sensitivity of detection is a major attribute of DNA-based methods, there are limitations to the use of these methods. False negatives may be reported as a result of the DNA being damaged during processing of the botanical ingredients (extraction, heat, and other manufacturing processes) or due to clearance of the DNA resulting from purification steps intended to enrich the content of constituents with bioactivity. In these cases, DNA may be no longer recoverable, even when the bioactive constituents are present in the formulation at the intended level. A negative test result may also be due to interferences from the matrix, which may complicate the recovery of a sufficient amount of DNA.[13] On the other hand, false positive identification is also possible due to organic matter naturally occurring in the plant material at low but allowable levels (no more than 2%). Due to their high sensitivity, DNA-based methods may be fooled by the deliberate addition of minute amounts of material rich in DNA from the plant stated on the label, even when the constituents desired for bioactivity are absent from the formulation. It is for these reasons that, although DNA techniques are powerful tools for authentication of plant materials at the early stages of processing, unless complemented with other orthogonal techniques, the presence or absence of DNA in more processed botanicals (i.e., extracts or finished dietary supplements) should not be used as the sole basis to evaluate quality in processed botanicals.

The second serious concern arises from several reports of adulteration of products marketed as dietary supplements with synthetic drugs and drug analogues. The addition of these synthetic substances (such as recent DMAA or BMPEA)[14–16] is illegal since they do not meet the legal definition of a DS under the Food & Drugs Control Administration (FDCA), are not declared on the product label, and present a significant threat to consumer health, considering that these products are consumed without medical supervision, may contain toxic constituents or substances whose safety has never been examined, and whose interaction with medications may be unpredictable or lethal. The significant public health problem posed by products that are marketed as DS but contain undeclared substances was recognized as a major concern in a letter from the FDA Commissioner, Dr Margaret Hamburg.[3] These synthetic substances could be prescription drugs, their unapproved analogues, or other compounds, such as novel synthetic steroids, that do not qualify as dietary ingredients. Use of these substances can pose considerable dangers to consumers who may take these products without knowing that the ingredients are present, since these undeclared ingredients may be associated with serious side effects or may interact with other products consumers may be taking. Dr Hamburg's letter noted that the FDA received numerous reports of serious adverse events associated with consumer use of these tainted products including strokes, acute liver injury, kidney failure, pulmonary embolisms (artery blockage in the lung), and even death. Adulteration of finished DS products in the following categories has been recognized as a major concern in the letter from Dr Hamburg:

- **Sexual enhancement:** Also referred to as the Erectile Dysfunction category, this encompasses a functionally coherent group of adulterants, including several approved drugs (e.g. sildenafil), their numerous approved and unapproved analogues, synthetic intermediates, and derivatives.[16,17] Their functionality is manifested by selective inhibition of phosphodiesterase type 5 enzyme (PDE5), which hydrolyzes cyclic guanosine 3,5-monophosphate (GMP).
- **Weight loss:** This category comprises a functionally and chemically diverse collection of compounds that include stimulants, laxatives, diuretics, anorexiants, and psychoactive drugs.[18] Although stimulants constitute an important segment of weight loss adulterants, the oral anorexiant sibutramine dominates this category, frequently in combination with phenolphthalein, a banned laxative.
- **Sports performance enhancement:** Professional and amateur athletes are targeted with designer anabolic steroids and stimulants, many of which are banned by the World Anti-Doping Agency (WADA).[19] Functional and structural diversity, synthetic proclivity of the adulterators, and the generally small amounts of the infringing substances required to elicit a therapeutic effect make this category especially challenging to address. These DS are customarily formulated in protein- and fat-rich matrices, thereby further complicating detection.

The nature of intentional adulteration is inherently not predictable and variable, since the adulterators are not guided, let alone bound, by GMP controls.

USP dietary supplement standards

For nearly 200 years, the United States Pharmacopeial Convention (USP), an independent, non-profit, scientific-based organization, has worked with volunteer experts from a wide cross-section of stakeholders to develop and continuously revise and update science-based quality standards for medicines, including their test methods and other tools that help protect public health. Standardization of botanicals and minerals dates back to the first edition of the USP in 1820, when physicians concerned with the quality of medicinal products developed a formulary, which later became an official compendium.[20] Vitamins were admitted into the USP during the early 1900s. Since 1992, after the passing of the Nutritional Labeling and Education Act, the USP has developed the same kind of science-based quality standards for nutritional and DS following an open and transparent public consultation process, whereby input from manufacturers, regulators, suppliers, and any other interested party is considered and evaluated by volunteer experts organized in Expert Committees. The USP prioritizes DS standards development based on considerations that include the extent of use,

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evidence of benefit, interest from a governmental body, and safety risk associated with its use. The USP admission evaluation process involves consideration of safety information from multiple sources, including adverse event reports from FDA MedWatch.[21,22] This assessment is conducted for the sole purpose of determining whether or not to develop a compendial monograph that is admitted in the *United States Pharmacopeia–National Formulary* (USP–NF) and is not intended as a determination of the intrinsic safety or efficacy of the DS ingredient or product under review. While estimates vary, the number of DS products in the market are estimated to be over 55 000, with a majority of the market value covered by about 100 ingredients (e.g. fish oil, calcium, glucosamine/chondroitin, CoQ10, and ginkgo), and major product categories (e.g. multivitamins, sports nutrition, and probiotics).[1,23,24] The current revision of the USP–NF includes almost 500 monographs for DS ingredients and finished DS that cover most of the commonly used DS in commerce. USP–NF standards are used in about 140 countries worldwide, and are often referred as the basis for the specifications agreed in contractual agreements between buyers and sellers in international trade. Within the USA, the FDCA and its subsequent amendments recognize the USP and NF as 'official compendia of the United States'.[25] Federal regulations governing drugs require mandatory compliance with the USP–NF. However, compliance with the official compendia is only optional for DS.

Under DSHEA, a DS may be deemed 'misbranded' if the manufacturer claims conformance with specifications of an official compendium (USP–NF) and fails to comply. Because the enforceability of compliance with USP standards is conditional to the claim, DS manufacturers typically avoid claiming USP quality on labels in order to avoid the risk of being deemed misbranding because of an eventual lack of compliance. Despite the good intentions to include compendial standards in the law as a resource for manufacturers, by incorporating them under the misbranding provisions rather than as a minimum requirement for quality, DSHEA has effectively created a disincentive for manufacturers to claim compendial standards on their labels in detriment of transparency for the consumers.

Given the complexity of the DS matrices, attributes of an analytical method in USP monographs that are fit for the intended purpose depend on the nature of the analyte (ingredient or a product), as well as the analytical objectives (qualitative, quantitative, or others). Accordingly, methods for identification, composition, or strength, and limits for contamination require the consideration of the types of DS or dietary ingredients (e.g. botanicals or non-botanicals), and whether the DS is administered in solid oral dosage forms, solutions, or suspensions. For example, in addition to quality standards for the dietary ingredients – the raw material (Ginkgo leaves) and the extract (Powdered Ginkgo Extract), the USP-NF also provides standards for the final dosage forms, such as Ginkgo Capsules and Ginkgo Tablets.[26] In addition, the USP–NF provides guidelines and general chapters applicable to DS related to methods and limits for pesticide residues, elemental contaminants (such as arsenic, lead, mercury, and cadmium), residual solvents, microbial contamination, and detection of irradiated botanical ingredients. Compendial identification tests for dietary ingredients include use of macroscopic/microscopic, chemical, spectroscopic and chromatographic methods. Since the objective of an identification test method is to be able to discriminate between related species and/or potential adulterants or substitutes, which are likely to be present, the specific tests for a botanical ingredient usually include a combination of two or three procedures.

Suitability of an analytical method depends on the matrix of the analyte as well as the objectives of the analysis. While an intact botanical plant material or its powdered form may be identified by macroscopic or microscopic features, the identifying features are lost when such material is extracted or processed. In these cases, chromatographic procedures, such as high-performance thin-layer chromatography (HPTLC) or high-performance liquid chromatography (HPLC), are used for qualitative and quantitative assessment of identity, composition, and detection of adulterants. Continuing with the example of ginkgo, adulteration is known to occur with less expensive flavonol aglycones to achieve the market desired 24% flavonol glycoside content or by using other parts of the plant (root bark) to achieve the standard of 6% of ginkgo terpene lactones.[27,28] USP standards for Powdered Ginkgo Extract include the following orthogonal test methods and acceptance criteria that define the essential quality attributes and help detect adulteration[26]:

- Identification by two complementary methods (HPTLC and HPLC). These qualitative methods compare chromatographic patterns of the sample with that of the reference standard, and define the acceptance criteria in terms of the ratio and relative abundance of flavonol glycosides and ginkgo terpene lactones (Figures , 1a–1c).
- Composition: These quantitative methods specify the acceptance criteria for the content of flavonol glycosides (22–27%), and the terpene lactones (5.4–12.0%), with specific content of ginkgolides A, B, and C and bilobalide that are unique to ginkgo (Figures 1c and 1d).
- Limits for contaminants: pesticide residues (USP General Chapter <561>); elemental impurities (USP General Chapter <561>); microbial load (USP General Chapters <2021> and <2022>).
- Specific tests: These tests specify limits for the content of rutin (not more than 4%) and quercetin (not more than 0.5%) which may be added in adulterated products; limits for the ginkgolic acid[29] at not more than 5 μg/g (Figure 1e); and limit of residual solvents (USP General Chapter <565>).

While these science-based methods and acceptance criteria from USP–NF public standards are available to define the quality of ginkgo and to prevent adulteration, incidence of ginkgo adulteration may occur when these are ignored.[30] The most common form of ginkgo adulteration is spiking with pure flavonoids (rutin and quercetin), hydrolyzed extracts or extracts from other flavonoid-rich material such as Japanese sophora (*Styphnolobium japonicum*)[31] in order to comply with the compendial requirement for not less than 22% of flavonol glycosides. The limits for the content of rutin (not more than 4%) and quercetin (not more than 0.5%) was introduced in the compendia to detect these adulterated products.[26] Further, the compendial requirement for terpene lactones (not less than 5.4%) can prevent ginkgo adulteration with botanicals containing flavonol glycosides but lack the unique terpene lactones.

USP–NF standards for ginkgo illustrate the approach to use orthogonal methods to define the identity and quality of a botanical ingredient since any one test method cannot be a surrogate for each of the diverse quality attributes. DNA testing is arising as another useful orthogonal analytical procedure to ensure plant authentication and became an official USP method in General Chapter <563> *Identification of the Articles of Botanical Origin* in December 2014. DNA methods are not yet referenced in any DS monograph in USP–NF, though when the validation data is available, USP may incorporate DNA tests into specific monographs, but even then

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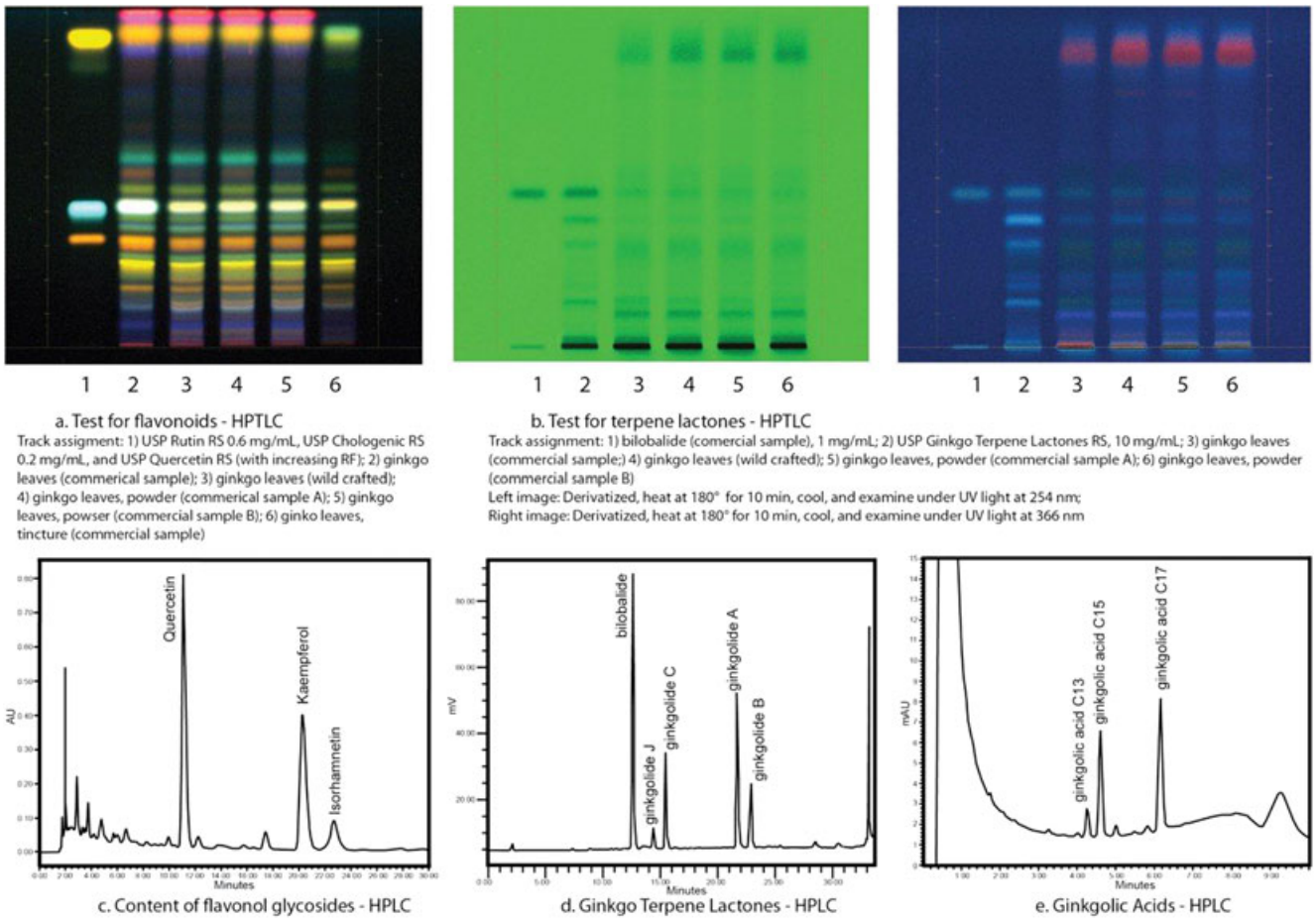

Figure 1. Tests of Monograph Standards: Ginkgo. Examples of the testing standards used with *USP* monographs[26]

the test is not expected to be utilized as a standalone procedure, but as a complement to chromatographic, spectroscopic, and botanical (microscopic or macroscopic) procedures.[32]

The Office of Dietary Supplements at National Institutes of Health runs Analytical Methods and Reference Materials Program[33] which funds AOAC International to develop analytical methods for select DS. The USP participates in the AOAC method development process as a stakeholder. Some of the resulting analytical methods developed through public funding could be adopted into the USP. The Office of Dietary Supplements also supports development of National Institute of Standards and Technology reference materials. These methods and reference materials complement the USP DS quality standards (analytical methods, acceptance criteria and reference standards).

Potential solutions to lack of uniformity in product quality

For generic and over-the-counter (OTC) drugs, minimum quality is ensured by mandatory compliance with the minimum requirements set in the official compendia. Adherence to public standards set by USP for DS in the same way that works so well for generics and OTCs would alleviate the problem of quality disparity; if all products comply with the minimum standard required in the compendia, then the public will know that two products labelled Echinacea Tablets share at least the minimum standards for quality.

The FDA has recognized the value of USP–NF-validated analytical methods in the preamble of the GMP as it noted: 'We [FDA] explicitly stated that you may use validated methods that can be found in official references, such as AOAC International [an analytical methods development organization], USP, and others' and that 'compendial standards may be appropriate reference materials for use in conducting tests or examinations'.[34] Unfortunately, validation of analytical methods is not required, nor is the use of validated method such as those in *USP* or AOAC. Here again, the USP can help to alleviate the problem should industry follow General Chapter <1225> *Validation of Compendial Methods,* which defines the parameters to be used to determine fitness for purpose.[35]

Given the dialogue concerning the availability of methods that are suitable for intended purposes, public quality standards provide a uniform point of reference for regulators and manufacturers, and promote consumer confidence. If DS manufacturers and government regulators adopt USP–NF public standards, they acquire a transparent means to help ensure the quality of DS products through the supply chain, and allow consumers to have confidence in the quality of the products on the market.

Currently, manufacturers may self-determine the quality of their products indicating compliance with USP public standards by listing the monograph title of the article along with the letters U-S-P on the product label. Participation in the USP's voluntary third-party

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verification program is another way to demonstrate the quality of DS. USP DS verification services include (1) an on-site facility audit for compliance with FDA GMPs and USP's more rigorous GMPs in General Chapter <2750> *Manufacturing Practices for Dietary Supplements*; (2) a thorough review of manufacturing and quality control product documentation; (3) comprehensive laboratory testing for conformance to dietary supplement standards found in the USP–NF; (4) continuous change control monitoring; and (5) off-the-shelf surveillance testing of randomly selected samples of products to confirm that USP-verified products continue to meet the USP's stringent standards. It is primarily the combination of the GMP audit and the product documentation review that forms the basis of product quality and (batch-to-batch) consistency. This approach confirms the principle that quality needs to be built into the product, not tested into the product.[36]

USP tools to detect intentional adulteration of dietary supplements

In order to address the serious concerns arising from the adulteration of products marketed as DS with synthetic drugs and drug analogues, a case could be made for public standards and reference materials for targeted common adulterants considering the repeat offences in specific product categories. In 2013, the USP convened an Expert Panel to investigate and recommend analytical methodologies capable of detection of pharmaceutically adulterated DS. In May 2015, the work of the Expert Panel led to a proposed new guidance document in the form of General Chapter <2251> *Adulteration of Dietary Supplements with Drugs and Drug Analogs*.[37] Presently, the chapter targets supplements adulterated with PDE5 inhibitors; subsequent revisions will include methodologies specific to analysis of adulterated weight loss and sports performance enhancement products. The proposed chapter suggests multiple analytical methods, including HPLC with photodiode array and mass-spectrometric (MS) detection, HPTLC with visual, UV, and MS detection, ambient ionization mass spectrometry, NMR spectroscopy (both low- and high-field), and a bioluminescent phosphodiesterase inhibition method. It is advisable to use several screening techniques to maximize the potential for adulteration detection, because no single methodology is universally applicable. Supplementary material includes MS and UV absorbance data, relative retention time values for common adulterants, and chemical structures. Relevant *USP–NF* Reference Standards for adulterant screening are included; however, considering the rate of propagation of structural analogues and proliferation of newly developed 'designer' molecules, establishing and maintaining an all-inclusive catalog of reference materials would be challenging and impractical. USP public standards, including the monographs and General Chapter <2251>, are intended to provide the analytical tools that are necessary for detecting DS adulteration thereby enabling diligent manufacturers and regulators to assess the quality of their DS ingredients and products all through the supply chain. Availability of these tools is not sufficient to prevent unscrupulous criminal supply of adulterated DS in the US market, Therefore, the USP is developing a Dietary Supplements Adulteration Database of the incidences of DS adulteration to provide an easily searchable public database of the risks of adulteration and the available detection methods, similar to how the USP's Food Fraud Database has analyzed the economically motivated adulteration of food ingredients.[38,39] The DS adulteration database is also intended to highlight the gaps and needs for public standards to counteract adulteration. The analytical challenges in the detection of unintentional or deliberate adulterants are varied. USP–NF monographs utilize targeted analytical methods to assess quality of an ingredient or dosage form in terms of its identification, composition or strength, performance attributes, and limits of contaminants. Multiple tests are typically used to impart orthogonal assessments of the unique quality attributes of the test substance, and to increase confidence in the analysis. Compendial standards for ginkgo, ginseng, bilberry, and chondroitin sulfate, for example, include tests for common adulterants. However, detection of unlabeled adulterants demands the use of non-targeted methods.

Targeted techniques are warranted when the analytes are known or can be reasonably anticipated. An example of a targeted approach is the monitoring a chromatographic run at a particular wavelength (or mass-to-charge ratios), and quantifying the analyte that appears within a pre-defined retention-time window. Targeted analysis is conceptually straightforward, because it relies on pre-existing knowledge of the analyte and allows optimization of test methodology for its reliable detection. Targeted screening may be sometimes informed by functional categories as in case of PDE-5 inhibitor analogues that are adulterants in products marketed as sexual enhancement DS. Bioassay based screening methods may be used to detect these class of compounds.

In contrast, non-targeted methods are necessary because the nature of the analyte may be difficult to predict, and variable amounts of multiple adulterants, belonging to several functional categories, are commonplace. Non-targeted screening trades precise knowledge of the analyte identity, along with specificity and accuracy, for a wider detection scope. Examples of non-targeted chromatographic screening include acquisition of photodiode array data and full mass-spectral scanning following a chromatographic separation. Adulteration paradigms favor utilization of detection techniques in a non-targeted mode, thereby facilitating detection of a suspect adulterant even in the absence of a matching reference compound.

Conclusion

The lack of uniformity of product quality and adulteration of DS should be a concern for manufacturers, regulators and consumers alike. The provision of GMPs to allow manufacturers to set their own private standards contributes to a lack of transparency that makes it difficult for different parties to agree on what quality means for a given product. Therefore, the current GMP requirements provide limited assurance that the dietary ingredients and DS are of adequate and consistent quality across different manufacturers. The presence of products spiked with synthetic drugs marketed as DS demands the use of innovative tools to protect public health; USP has responded to the challenge by developing General Chapter <2251>. Stronger adoption of science-based public quality standards by the industry or in the regulations would provide a solution to these issues. Compliance with USP–NF standards help ensure the consistency and quality of medicines in the USA and could do the same for DS. Public health is best served when public standards for quality are required as a minimum, as it is the case with drugs in the USA. We believe that the universal adoption of the USP–NF science-based public standards would serve regulators (e.g. the FDA), manufacturers and consumers by improving the consistency and quality of DS marketed in the USA. This may be accomplished by strengthening GMP provisions to

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require conformance with standards established by USP–NF or other compendia when a monograph title is used as the name of an ingredient or product.

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USP Gummy Dietary Supplements Roundtable Discussion

USP Gummy Dietary Supplements Roundtable Discussion
Thursday, March 3, 2016
USP–U.S., Rockville

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Executive Secretariat Representative: Marie Temple

Notes–Draft

** The notes of this meeting are provided as an informal resource. They are not meant to provide a transcript of the roundtable proceedings, do not reflect any determinations or policy on the part of USP, FDA, or other participants, and should not be used as an interpretation of USP compendial standards.*

Attendees
See separate attendee list (distributed at the meeting)

Much of the recent growth in the dietary supplement (DS) industry can be attributed to dietary supplements marketed as chewable gel products known as a "gummy" or "gummies." USP convened stakeholders from industry and regulatory agencies to assist in the development of standards for finished gummy DS. The following is a summary of stakeholder feedback.

1. Raw Materials and Manufacturing

a. Raw Materials and Manufacturing Process

Typical Raw Materials Used in Gummy Manufacturing

- Gelling agents: Gelatin, pectin, agar, starch, gum
- Sweeteners: Sugar, glucose syrup, syrup from other sources, sorbitol, maltitol, inulin
- Colors, Flavors
- Organic acids
- Agents to reduce water activity
- Agents to ensure the gummy does not dry out too fast

Compendial Grade Materials

- Compendial and *Food Chemicals Codex* (*FCC*) grade raw materials are difficult to obtain.

Manufacturing Process

- Starch deposit
- Other types of molding (e.g., plastic or silicon)

Types of Gummies

- Gummies containing gelling agents such as gelatin or pectin
- Agar based gummies
- Starch molded gummies with gelatin are the major gummy type in the U.S. market. USP may not need to develop standards for other types of gummies.

Gelatin Types

- Manufacturer's decision based on the nature of the formulation and the desired organoleptic characteristics
- Porcine
- Fish
- Bovine: Bovine spongiform encephalopathy (BSE) is not a concern.
    - Supplier provides a BSE bovine somatotropin statement.
    - Gelatin is not sourced from cattle older than 30 months.
- Purity of sources is important.

b. Compendial Monographs and General Chapters

Usefulness of USP Monographs

- Commonly used raw materials are "commodity materials" (not compendial grade) provided by a number of suppliers. Harmonization of specifications from different suppliers would be helpful. USP may have a role in this regard.
- Too many specifications could inhibit innovation. Commercial commodity grade or food grade materials are adequate.
- Compendial monographs are useful.
- DS manufacturers verify the Certificate of Analysis (CoA) provided by the supplier.
- U.S. DSs are foods and should meet food standards, not drug standards.

Water

- Water meeting USP Purified Water monograph specifications is not needed because the manufacturing process involves thermal exposure.
- For cost-efficiency, potable water may be used in the manufacture of gummies.
- Manufacturers using General Chapter <2750> *Manufacturing Practices for Dietary Supplements* may infer that purified water should be used, but potable water is adequate for conventional food forms. Purification does not add value.
- Water content could be variable depending on the season and source.
- High quality municipal water that is not considered hard would be adequate (hard water affects pectin). The manufacturer should qualify municipal water by reviewing city water reports and testing the water periodically at the point of use.
- Trace minerals in water could impact product stability, but raw materials would have a larger impact on stability than water.

Dock-to-Stock Time

Manufacturers should manage the receipt of materials efficiently. The dock-to-stock time and turnaround time for bulk tankers to unload raw materials are critical. Rapid testing methods are desirable in this regard.

Pectin

Pectin used in gummy manufacturing does not meet the USP Pectin monograph specifications because it includes buffers. A compendial method for buffered pectin would be useful.

c. Weight Variation–Content Uniformity

Weight Variation

- Piece weight variation is expected because the product cures for a long time.
- The weight variation range depends on the equipment and the variability of the process.
- Piece-to-piece weight variation can be the target weight ± 1% to ±10% depending on the gelling agent manufacturing process.

- With a starch molding process, piece weight variation is measured post-depositing prior to curing, coating, or sanding. If tests are conducted after sugar sanding, it can be difficult to identify the source of weight variation. Weight variation may not measure a problem with content uniformity.
- A suggestion was made for industry to confidentially supply their piece weight variations to USP to help guide specifications for the range +/- in the development of the monograph and related revisions to General Chapter <2091> *Weight Variation of Dietary Supplements*. USP sought information on the weight variation from manufacturers in order to set informed data-based specifications for the compendial articles.

Controlling Gummy Uniformity

- Piece weight on depositing is the key parameter. The gummy should contain a certain concentration of dietary ingredients based on a formula.
- Uniformity control depends on the risk associated with the dietary ingredients. Weight variation should be tighter for fat soluble vitamins. The risk is lower for water soluble vitamins.
- The impact of piece weight variation on shelf life is important. The maximum and minimum content should be met over the life of the product.
- Content uniformity is not an in-process control.

Content Uniformity Testing

- Based on the formulation and ingredients
- Not an issue with water soluble vitamins
- Used to monitor the robustness of the process, particularly during product development
- Conducted to capture variation
- Content uniformity is not a problem for dosage forms containing calcium, but is very important for products containing micronutrients such as vitamin B12.
- Content uniformity is established on the first three lots for qualification of the manufacturing process. Manufacturer disposition decisions are not based on content uniformity.

d. Overage Challenges in Formulations

- The need for an overage depends on the process and how and when ingredients are added. Overages are set as a part of the qualification of the manufacturing process.
- Low pH and high water activity impacts the overages. Ingredients such as calcium pantothenate and folic acid need higher overages.
- Overages based on shelf life studies have been practiced in the industry in the U.S. and throughout the world.
- An overage depends on the shelf life; the overage is smaller if the shelf life is shorter.
- Ambient studies tell manufacturers how much they can decrease the overage in a product.
- Public safety is a key consideration when determining overages.
- Specific overage amounts are confidential. USP should seek this information through direct, confidential interactions with manufacturers.
- USP is in the process of publishing a *Stimuli* article in *Pharmacopeial Forum* that deals with factors to consider for setting adequate overages of vitamins and minerals in dietary supplements.

2. Quality Parameters in Product Specification

a. Quality Parameters

- Label claim (100% label claim for shelf life)
- Physical specifications: Weight variation per gummy piece, flavor, color
- pH (formulation specific, no specific limits)
- Water activity (formulation specific, no specific limits)
- Titratable acidity
- Loss on drying (LOD)
- Moisture (Karl Fisher [KF])
- Brix test
- Microbial testing (include limits)
- Gluten test, depending on the formulation
- General Chapter <2232> *Elemental Contaminants in Dietary Supplements*

b. Performance Testing

- Need to simulate chewing process.
- Need *in vitro* to *in vivo* correlation to show bioavailability.
- Develop a test to determine how coatings erode in finished dosage form.
- Dissolution testing is not a value-added test for DS gummies.
    - Consumers use DSs to supplement the diet over a long period of time. The digestion process takes 18 to 24 hours.
    - The USP dissolution test may not be appropriate for gummies. A gummy swells in water and may not dissolve in a reasonable amount of time.
- A disintegration test may be more meaningful because the formulation system of a gummy will disintegrate.
- The majority of gummy manufacturers consider performance testing unnecessary. Meeting the strength requirements could be enough for product quality control.
- Some of the gummies are complex and have encapsulated active ingredients. For these products, meaningful performance testing is needed.
- Drug controls are not appropriate for gummy DS types.
- When testing gummies, water and a hydrochloric acid solution, or dimethyl sulfoxide (DMSO) for ingredient extraction, can be used.

c. Stability and Shelf Life

- Monitor appearance and flavor changes.
- Stability is a function of temperature and humidity.
- Follow International Council for Harmonization of Technical Requirements for Pharmaceuticals for Human Use (ICH) guidelines.
- Conduct microbial and pH testing.
- Monitor hardness of water.
- Manufacturers have monitored customer complaints and gummy product labels state that the product will change color over time.
- The shelf life of a gummy is usually approximately 2 years.
- A gummy product fails when it loses its snack-like quality.

3. Testing Procedures–Gummies, Ingredients, and Contaminants

The USP–India laboratory is working on validated testing procedures for gummy multivitamins, oil soluble vitamins, water soluble vitamins, and minerals. USP is seeking modern methods for the analysis of vitamins in gummies.

a. Sample Preparation

- Some laboratories use an analytical approach for the extraction of fat soluble vitamins from gummies, which is applicable for a food matrix.
- Melting gummy samples in hot water is used for sample preparation.

- Slicing the gummy into small pieces to increase the surface area was found helpful for sample preparation, and one manufacturer suggested using a garlic press.
- Liquid nitrogen freezing followed by grinding produces a homogenous blend of gummy samples.

Challenges

- When melted, the solution can be viscous and difficult to transfer into a measured flask.
- Water soluble vitamins are easier to recover. A solvent such as DMSO and/or hexane is needed to dissolve fat-soluble vitamins.
- The sample solution contains multiple components which cause interference during the separation process.
- Scientific method validation is needed.
- Typical method variability (10% to 20%) for gummies is to be expected.

b. Testing Methods

- Instrumental methods for vitamins: high-performance liquid chromatography (HPLC), ultra-performance liquid chromatography (UPLC), liquid chromatography-mass spectrometry (LC-MS)
- Inductively coupled plasma-optical emission spectroscopy (OES) or mass spectrometry (MS) for trace elements and minerals
- Validated in-house methods
- Microbial quantitation methods: Specificity depends on microorganisms and how well stock cultures are maintained.
- Moisture controls: Water activity (Aw), Karl Fisher, or LOD (USP may need to develop a general chapter for water activity measurement)
- Total dietary fiber: AOAC method (very complicated, involves several enzymatic digestions)
- Method variability: within 2% to 3%
- Method should cover the overage.
- USP limits should be specific for a gummy formulation, not generic limits.

4. Labeling, Shipping, and Handling

a. Compendial Nomenclature

The USP Dietary Supplements and Herbal Medicines Nomenclature Joint Subcommittee will propose the following title: “Chewable Gels,” also known as “Gummies.”

- A Definition of the gummy dosage form would be added to General Chapter <1151> *Pharmaceutical Dosage Forms* and the text will indicate that the title applies to DSs only.
- The U.S. Food and Drug Administration is concerned that the term “Gummies” poses a safety concern because it can be confused with candy. Food connotations in pharmaceuticals should be avoided. When this technology crosses over into drug manufacturing, then “Chewable Gel” could be used for drug product titles.
- The Nomenclature and Labeling Expert Committee (NL EC) will consider the proposed title at its March 2016 meeting. The NL EC may form a working group with representatives from the dietary supplements Expert Committees to discuss the issue and determine the best solution.

Industry Perspectives

- Two participants suggested either “Soft Chewable Tablet” or “Chewable Tablet” nomenclature. Most advocated use of the term “Gummy” and were not in favor of other options.

- A gummy is a different matrix than a chewable tablet.
- Changing the nomenclature will not change the safety profile and it may not change the potential for misuse. There were few adverse event reports (AERs) associated with gummies and no serious AERs associated with gummies compared to other dosage forms.
- Safety issues pertaining to overconsumption of gummies depend on the gummy ingredients.
- The regulatory difference between a food and a DS could partially depend on the serving size. For example, the serving size of a confection may be 42 grams while a 2-piece serving size of a DS may be less than 10 grams.
- U.S. food regulations do not define a gummy. In Europe, such products are called “gum drops.”

b. Safety/Child-resistant Caps

- Industry usually uses child-resistant (CR) caps for any dosage form targeted for use in children. This requirement does not need to be included in a monograph.
- Use of a CR cap depends on the daily dose and the gummy contents.

c. Specific Challenges in Packaging, Storage, and Handling

- Stability during transportation: Heat and humidity exposure should be limited.
- Light exposure: Most gummies are packaged in clear polyethylene terephthalate (PET) bottles, which protect the product throughout its shelf life.
- Shipping temperature: Depends on the type of gel.
- Foil bags: There has been some interest in other packaging formats such as foil bags and blister packs.

5. Wrap-up and Next Steps

USP staff will send meeting notes to Roundtable participants and provide updates to the relevant Expert Committees.

Guideline for Assigning Titles to USP Dietary Supplement Monographs

STIMULI TO THE REVISION PROCESS

Stimuli articles do not necessarily reflect the policies
of the USPC or the USP Council of Experts

GUIDELINE FOR ASSIGNING TITLES TO USP DIETARY SUPPLEMENT MONOGRAPHS

USP Dietary Supplement and Herbal Medicines Nomenclature Joint Subcommittee, USP Staff[a,b]

ABSTRACT The first publication of the *Pharmacopoeia of the United States* in 1820 included quality monographs of articles that would today be considered dietary supplements, for example, vitamins, minerals, and certain botanicals. Titles for such monographs were crafted to be brief and distinct, and in many instances a single word sufficed if that word was expressive and unambiguous. The 1820 volume discussed a guide for developing botanical monograph titles and indicated that USP would adapt a nomenclature that was simple, with the intent that the monograph title would be brief and explicit, expressing the medical meaning and nothing else. This *Stimuli* article presents a new guideline for formulating titles of dietary supplement monographs. The intent of this article is to initiate a discussion on this new proposed guideline, to solicit public comments, and to invite the participation of interested parties in USP's efforts to develop a nomenclature guideline for dietary supplement monographs. The goal of this effort is to eventually bring existing monograph titles into alignment with a uniform naming convention.

INTRODUCTION

The first publication of the *United States Pharmacopeia* (*USP*) in 1820 included quality monographs of articles that today are referred to as dietary supplements (DSs), including vitamins, minerals, and certain botanicals. Monographs for some of these articles have been included in the compendium since the 1820 edition. In 1993, in response to the Nutrition Labeling and Education Act (NLEA) of 1990, a separate compendium section titled *Nutritional Supplements* was created to contain monographs for vitamins and mineral combinations. DS monographs were started in 1995 in response to the Dietary Supplement Health and Education Act of 1994 (DSHEA) and included some monographs for botanicals that were originally placed in the *National Formulary* (*NF*). The *Nutritional Supplements* section was active through the publication of *USP 26–NF 21* in 2003. In 2004, a new section, *Dietary Supplements*, was introduced into *USP 27–NF 22* to replace the *Nutritional Supplements* section and included monographs for ingredients and dosage forms of DSs as defined by DSHEA. Monographs for botanical DSs originally in the *NF* were also moved to this new DS section. This new DS section is currently published in the *USP–NF*, which combines all of the dietary supplement monographs from the two compendia.

It should be noted, however, that other botanical articles in the *USP–NF* are not necessarily DSs because they are classified as drugs, excipients, or medical devices. For example, *Aloe*, *Elm*, *Ipecac*, *Psyllium*, and *Senna* remain in the *USP* section of the *USP–NF*. There is a *USP* monograph for *Gutta Percha*, which is used as a medical device material, e.g., for endodontic (root canal) treatment. *Belladonna*, *Digitalis*, *Opium*, *Podophyllum*, and *Rauwolfia serpentina* are monograph examples currently included in the *USP* as prescription drugs or sources of prescription drugs. Other articles, such as flavors, fragrances, and other excipients, were placed in the *NF*.

Crafting monograph titles for vitamins and minerals has always been more straightforward than it is for botanicals, as the former are mostly comprised of single ingredients with titles largely formulated in a manner similar to those for drugs. A guide for developing botanical monograph titles was discussed in the first *USP* (published as the *Pharmacopeia of the United States*) in 1820 to adopt a nomenclature to "…be conformable to the present language of science, divested of as much of its prolixity as can be done consistently with clearness and distinctness." The intent was for the monograph title to "…expresses the medicine, and nothing else; …needed to be short and explicit, and does not require to be mutilated in practical use, as long names will inevitably be" (*1*). Thus, a monograph title was to be brief and distinct; a single word sufficed if that word was expressive and unambiguous. Plant parts were not included in monograph titles except where multiple monographs were developed for different plant parts of the same species, in which case the plant part was included to distinguish the monographs from each other by title. The USP staff followed this format when formulating monograph titles until the enactment of DSHEA in 1994.

DSHEA defines a DS as: "(1) a product (other than tobacco) intended to supplement the diet that bears or contains one or more of the following dietary ingredients: (A) a vitamin; (B) a mineral; (C) a herb or other botanical; (D) an amino acid; (E) a dietary substance for use by man to supplement the diet by increasing the total dietary intake; or (F) a concentrate, metabolite, constituent, extract, or combination of any ingredient described in clause (A), (B), (C), (D), or (E)."[1] DSHEA also mandates that the label of a DS must bear a statement of identity that, as stated in the Code of Federal Regulations Title 21 (21 CFR) section 101.4 (h), includes the common or usual names of botanical dietary ingredients (including fungi and algae) and these names must be consistent with the names standardized in *Herbs of Commerce* (*2*).

In accordance with DSHEA, USP adopted common names of botanicals utilized in North American commerce as monograph titles (*3*). In some cases, two or more species of plants may have the same standardized common name (SCN) in *Herbs of Commerce* but they can be distinguished from each other in the monograph title—if necessary to meet the requirements of the monograph—by including another common name (OCN) provided in *Herbs of Commerce* (*2*). For example, "Labrador tea" is the SCN for both *Ledum groenlandicum* [currently accepted name: *Ledum palustre* subsp. *groenlandicum* (Oeder) Hultén] and *Ledum palustre* subsp. *decumbens*, but to have a separate DS monograph for each species, the OCNs "Bog Labrador Tea" and "Marsh Labrador Tea," respectively, could be included in the monograph titles.

The Latin binomial or a recognized common name used in commerce is required in the DS monograph title for plants that are not listed in the *Herbs of Commerce* and thus not assigned an SCN in *Herbs of Commerce*, e.g., *Pelargonium sidoides*, or Banaba for *Lagerstroemia speciosa*; or if the SCN applies to more than one species, no OCNs are provided to distinguish those species, and a distinction is necessary for the purposes of the monograph. There are some cases where the SCN provided in *Herbs of Commerce* is not necessarily the most common name in commerce (*2*), e.g., *Euterpe oleracea* has the SCN "Cabbage Palm" but is now better known as "Açaí Palm". *Siraitia grosvenorii* has the SCN "Luo Han Guo", which is the best known common name for it when used in Traditional Chinese Medicine, but when used in foods and DSs as a natural low-calorie sweetener it may be better known as "Monk Fruit". In these cases, using the Latin binomial in the DS monograph title helps avoid confusion.

Any name in Latin form shall be in accordance with internationally accepted rules on nomenclature, such as those found in the *International Code of Nomenclature for Algae, Fungi, and Plants (Melbourne Code)* (the 2011 edition replaced the document previously known as the

International Code of Botanical Nomenclature) (*4*). Normally, Latin binomials and subspecies or variety names are italicized (*4*).

For brevity, it is not necessary to include the author citation of a Latin binomial in the DS monograph title; it will be provided in the *Definition* section of the monograph. The citation of the author or authors who validly published the Latin binomial is a key part of the scientific name of an organism. The authors' names follow directly after the Latin binomial, e.g., *Andrographis paniculata* (Burm.f.) Nees. The reason the Latin binomial needs to be followed by the author citation is that the author citation helps in locating the original published plant description, which helps determine the "type species" (from which the original description was created), and the date (priority) of publication of the name; these are key criteria used to determine which name for a particular species is correct. The author citation also identifies the source of the name to prevent confusion over duplicate names and helps trace changes in names. For example, the author citation for the plant name *Andrographis paniculata* (Burm.f.) Nees indicates that Christian Gottfried Daniel Nees von Esenbeck (internationally standardized abbreviation, "Nees") transferred this species to the genus *Andrographis* after re-examining and reclassifying the same type specimen from which was derived the original name *Justicia paniculata* Burm.f. published by Nicolaas Laurens Burman ("f." stands for *filius* because he was the son of another botanist, Johannes Burman, whose abbreviation is "Burm").

A detailed explanation of how authors are cited and the meaning of terms such as "ex" or "in" found within the author citation is provided in Chapter VI of the *International Code of Nomenclature for Algae, Fungi, and Plants* (*4*). In the context of the details to be provided in the DS monograph *Definition* section, the author citation becomes critical when a positive identification of the article cannot be made in its absence (e.g., see discussion of *Illicium anisatum* below). This would also be an issue on a product label, on a raw material order form, or in a master formula. Thus, the level of detail in the DS monograph *Description* section will be consistent with the labeling regulations that require inclusion of the designation of the author or authors who published the Latin name.

In the DS monograph title, the name of the plant part follows the name (common or Latin binomial) of the article. For example, *Echinacea purpurea Aerial Parts* is a separate monograph from "*Echinacea purpurea* Root". This is consistent with 21 CFR101.4(h)(1), which requires the DS label to list the part of the plant (e.g., root, leaf) from which the dietary ingredient is derived [e.g., "Garlic bulb" or "Garlic (bulb)"]. The name of the part of the plant shall be expressed in English (e.g., "flower" rather than the Latin term "flos" used in some pharmacopeias).

All titles of dietary ingredient monographs and DS monographs are approved by the appropriate Expert Committee (EC), based on USP staff research and the best scientific judgment of the EC. There have been many considerations in naming dietary ingredients and DSs including, but not limited to: USP's historical and scientific practices, industry convention, international similarities and differences, regulatory status, and environmental and agricultural practices.

The guideline below was developed with input from the Nomenclature, Safety, and Labeling (NSL) EC and the Monographs—Dietary Supplements and Herbal Medicines (DSHM) EC as a complement to *Nomenclature* ⟨1121⟩. The guideline is intended to provide a systematic approach to developing monograph titles for dietary ingredients and DS dosage forms admitted to the compendium. To minimize the potential for confusion and controversy, the naming of monographs in this guideline is guided by available scientific conventions, the practices of the DS industry, and the labeling requirements of applicable federal regulations.

Some DS monographs define and characterize plant, fungal, algal, animal, and certain bacterial

materials. Botanical materials are often processed to some extent, such as by drying and milling (cutting, sifting, particle sizing, and density adjustment). Other DS monographs describe extracts, processed extracts, partially purified natural complexes, or purified substances of botanical materials. There are also monographs for single chemical entities and for finished oral dosage forms. This guideline indicates how DS monograph titles shall be developed for the different types of articles included below, with examples. It is preferable that existing monograph titles that do not conform to the new approach be revised on an as-needed, case-by-case basis.

DIETARY INGREDIENT MONOGRAPH TITLES

A "dietary ingredient", as defined by DSHEA, is a substance intended for use in the manufacture of DS finished dosage forms. Some of these articles may in fact be raw materials (as described in *Identification of Articles of Botanical Origin* ⟨563⟩) that are subject to further processing for the manufacture of dietary ingredients, or they may be dietary ingredients when used directly in the manufacture of DSs. Dietary ingredients can be broadly categorized into the following groups: complex articles of botanical origin, complex articles of animal origin, other complex dietary substance articles, and single chemical entities (including vitamins, minerals, amino acids, and other examples that will be provided below).

Titles for Monographs of Complex Articles of Botanical Origin

These articles include plant (or fungal, algal, or certain bacterial) materials such as the whole plant or a specific plant part (e.g., leaf, root, stem, fruiting body of a fungus, thallus of an alga, and others) and plant products, which are substances produced naturally by a plant or plant part that do not require processing beyond pressing or cutting and scraping to be obtained, such as a seed oil, gum, latex, or resin.

Each monograph shall have a title that is consistent with its *Definition* and *Identification* sections. The monograph title shall include the SCN (or OCN in the cases explained above) from *Herbs of Commerce* or the Latin binomial where necessary (in the cases explained above), followed by the name of the botanical part(s) or botanical product, except in the case of single-celled or colonial organisms such as yeasts (e.g., *Saccharomyces cerevisiae*, *Monascus purpureus*), certain algae (e.g., *Chlorella*), and cyanobacteria (also known as blue-green algae, e.g., Spirulina, *Nostoc*), which have no parts. The part name is followed, where applicable, by the processed form. The botanical part name, botanical product name, and processed form name shall be written in English and in singular form.

In cases where more than one species of a genus are represented in a monograph, the genus name shall be used followed by the word Species[2] unless there is one SCN for all the included species and there is no need to distinguish among them for the purposes of the monograph. For example, *Herbs of Commerce* has a separate SCN for each of 11 different species of willow, but in commerce the barks of various species of *Salix* are used alone or mixed to make "willow bark" or "willow bark extract" supplements (*2*). Due to substantial anatomical and chemical similarities and hybridization between species, distinguishing them by microscopic, chemical, or genetic tests is neither readily feasible nor necessary. Because the use of any one willow SCN in the DS monograph title will not accurately reflect the composition of the article of commerce, a more appropriate title would be "*Salix* Species Bark".

Additional information about the DS article that is the subject of the monograph, e.g., the Latin binomial(s), with their corresponding author(s) and the family, common name(s), identity and

strength of solvent(s), range of ratios of crude plant material to extract, and range of concentration of marker compound(s), shall be included under its *Definition*.

Inclusion of the variety or subspecies in the title of a DS monograph depends on whether or not it is relevant to the accurate definition of the article of commerce. Phytochemical differences, safety differences, and traditional use differences at the variety or subspecies level should be evaluated to determine whether the variety or subspecies should be included in the monograph title. For example, if the fruit with the SCN "Jujube" did not have an SCN, then to accurately reflect the identity of the article used in Traditional Chinese Medicine it would be necessary for the DS monograph title to include the variety name: "*Ziziphus jujuba* var. *spinosa* Seed". When a variety or subspecies is not relevant to the article's definition and characterization, it should not be used in the title of the monograph.

Occasionally, in the absence of an SCN or OCN from *Herbs of Commerce*, the Latin binomial most widely known in commerce will be used in the monograph title even if it does not represent current accepted taxonomic nomenclature. For example, if a DS monograph were to be developed for the fungus *Antrodia camphorata* (which is an article in the *Herbal Medicines Compendium*), the DS monograph title would be *Antrodia camphorata* Fruiting Body, even though the Index Fungorum—Species Fungorum database indicates that the current name should be *Taiwanofungus camphoratus*. The monograph *Description* would give the authors of the Latin binomial, i.e., *Antrodia camphorata* (M. Zang & C.H. Su) Sheng H. Wu, Ryvarden & T.T. Chang, to clarify that the currently accepted name is *Taiwanofungus camphoratus* (M. Zang & C.H. Su) Sheng H. Wu, Z.H. Yu, Y.C. Dai & C.H. Su, and indicate that another synonym is *Ganoderma camphoratum* M. Zang & C.H. Su. By providing these details in the *Definition* of the monograph, the connection is maintained between the article of commerce and its various Latin binomials which are subject to revision by taxonomists.

Since a synonym may be used in a DS monograph title, it is important to be pragmatic in selecting which other taxonomic synonyms to be included in the monograph text for clarification of the article's identity, since there may be more than one commonly used synonym for an article of commerce. Taxonomic web sites such as The Plant List (developed through a collaboration between the Royal Botanic Gardens, Kew; the Missouri Botanical Garden; and other authoritative institutions) (*5*) and the U.S. Department of Agriculture, Agricultural Research Service Germplasm Resources Information Network (GRIN) online database (*6*) can be checked for a reasonably comprehensive list of synonyms, so it will not be necessary to duplicate all of that information in a DS monograph.

The following criteria may be helpful in deciding how to select synonyms for inclusion in the DS monograph *Definition*:

1. If the Latin binomial selected for use in the DS monograph title or associated with the DS monograph title's SCN is a synonym according to the current nomenclature set out in The Plant List (*5*) or the USDA GRIN database (*6*), then clarification of the synonymy should be included in the DS monograph *Definition*. For example, *Polygonum multiflorum* Thunb. is the Latin binomial associated with the SCN "Fo-Ti" but it is a synonym for *Reynoutria multiflora* (Thunb.) Moldenke, so both this synonym and the current correct Latin binomial should be included in the monograph for Fo-Ti. As another example, *Garcinia cambogia* (SCN: Garcinia) is a synonym used currently as a DS monograph title; both*Garcinia cambogia* (Gaertn.) Desr. and the accepted Latin binomial name *Garcinia gummi-gutta* (L.) Roxb. (except with the author N. Robson, which has since been revised

to Roxb.) are included in the *Definition*. To determine which synonyms are well-established in commerce, references to consult include key compendia or pharmacopeias from authoritative sources (e.g., labeling standards or monographs published by the *European Medicines Agency*, or compendia such as the *Food Chemicals Codex, European Pharmacopoeia, Pharmacopoeia of the People's Republic of China*, or the *Herbal Medicines Compendium*).

2. Where key compendia or pharmacopeias from authoritative sources provide multiple synonyms, the presence of a synonym in two or more compendia/pharmacopoeias may be evidence that it is well-known enough to cite in the DS monograph *Definition* [e.g., *Momordica grosvenorii* Swingle and *Thladiantha grosvenorii* (Swingle) C. Jeffrey are commonly cited synonyms for *Siraitia grosvenorii* (Swingle) C. Jeffrey ex A.M. Lu & Zhi Y. Zhang]. Setting a criterion that synonyms must be found in two or more references may help avoid unnecessary listings, if the sources give multiple synonyms that are not necessarily used in commerce. This criterion can be revisited if too long a list is obtained in too many cases.
3. If a synonym is not listed in one of these official compendia but other peer-reviewed literature suggests there is a risk of confusion, such as happened in the case of the potentially hazardous confusion between the edible Chinese star anise, *Illicium verum* Hook. f., synonym *Illicium anisatum* Lour., and the toxic Japanese star anise, *Illicium anisatum* L. (only the authors of these last two Latin binomials differ), then this synonymy should be included in the monograph text as it is relevant to safety.

Below are examples indicating how monograph titles shall be developed for the different types of complex dietary ingredients of botanical origin including botanical materials, botanical products, and botanical processed forms.

TITLES FOR BOTANICAL MATERIAL MONOGRAPHS

DS plant articles (or fungal, algal, or bacterial material articles) include the whole plant or a specific part of the plant, with the exception noted above for single-celled or colonial organisms. The term "botanical material" is used here to indicate material derived directly from a plant and does not include articles that may be obtained from these materials when processed, such as extracts, juices, oils, and others. The examples provided in *Table 1* illustrate how titles for botanical material monographs will be derived when following the new guideline, compared to how current monograph titles were derived.

Table 1. Current and Proposed Nomenclature Formats for Botanical Material Monograph Titles

Current Examples	Proposed Examples[a]
[{SCN} OR {LATIN BINOMIAL W/O AUTHORITY}][b] {BOTANICAL PART(S)}	**[{SCN} OR {LATIN BINOMIAL W/O AUTHORITY}] [BOTANICAL PART(S)]**
Andrographis	Andrographis Stem and Leaf
Asian Ginseng	Asian Ginseng Root
Capsicum	*Capsicum* Species Fruit
Centella asiatica	Gotu Kola Aerial Parts
Chamomile	Chamomile Flower Head

NA[c]	Chlorella
Ganoderma lucidum Fruiting Body	Reishi Fruiting Body
NA	Kelp Thallus[d]
Rhodiola rosea	*Rhodiola rosea* Root and Rhizome
Senna Leaf	Senna Leaf
Senna Pods	Senna Pod
Spirulina	Spirulina Species
Valerian	Valerian Rhizome, Root and Stolon

[a] Some examples provided are hypothetical, solely to show what the new titles would look like.

[b] Items within brackets [ ] are required, whereas those within braces { } are to be used as appropriate, e.g., one should use {SCN} where an unambiguous SCN is provided in *Herbs of Commerce* but use {Latin binomial} in other cases as explained above.

[c] *NA*, title not available because currently no USP monograph exists for this article.

[d] As an example of an unusual case, *Kelp* is the SCN for various species of brown algae: *Alaria marginata, Ascophyllum nodosum, Laminaria digitata, L. hyperborea* (synonym *L. cloustonii*), *L. setchellii, L. sinclairii,* and *Macrocystis pyrifera*. Not all of these species have assigned OCNs. Another species, *L. saccharina*, has "Sugar Kelp" as the SCN. *Kelp* is defined in 21CFR172.365 as the dehydrated, ground product prepared from *Macrocystis pyrifera, Laminaria digitata, Laminaria saccharina*, and *Laminaria cloustoni* [sic] for special dietary and nutritional additives as a source of the essential mineral iodine. Therefore, using *Kelp* as the SCN in a DS monograph title might be interpreted to capture only three of the four species set out in 21CFR172.365, and could include other genera and species not permitted as *Kelp* under the conditions set out in this regulation. To resolve this rare exception to the general approach, a DS monograph entitled "Kelp Thallus" could specify the four species from 21CFR172.365 in the *Definition*, while a monograph for *Ascophyllum nodosum* could have the title "Kelp (*Ascophyllum nodosum*) Thallus" to include the SCN and be distinguishable from the other monograph.

TITLES FOR BOTANICAL PRODUCT MONOGRAPHS

Articles referred to as plant (or fungal, algal, or bacterial) products include substances produced naturally by a plant or plant part that do not require processing beyond pressing or cutting and scraping to be obtained, such as seed oil, gum, latex, resin, and others. The examples provided below illustrate how titles for plant product monographs will be derived following the guideline, compared to how current monograph titles were derived.

Table 2. Current and Proposed Nomenclature Formats for Botanical Product Monograph Titles

Current Examples	Proposed Examples
[{SCN} OR {LATIN BINOMIAL W/O AUTHORITY}] {BOTANICAL PART (S)} {BOTANICAL PRODUCT}	**[{SCN} OR {LATIN BINOMIAL W/O AUTHORITY}] [{BOTANICAL PART(S)} AND/OR {BOTANICAL PRODUCT}]**
Almond Oil	Almond Seed Oil
Castor Oil	Castor Seed Oil
Aromatic Castor Oil	Castor Seed Aromatic Oil[a]
Crypthecodinium cohnii Oil	*Crypthecodinium cohnii* Oil

Boswellia serrata	*Boswellia serrata* Oleo-gum-resin
Evening Primrose Oil	Evening Primrose Seed Oil
Flax Seed Oil	Flax Seed Oil
Guggul	Guggul Oleo-gum-resin
Myrrh	Myrrh Oleo-gum-resin
Palm Oil	Palm Fruit Oil
Palm Oil	Palm Kernel Oil
Schizochytrium Oil	Schizochytrium Species Oil
[a] An aromatic botanical product article is created by the addition of essential oils as flavoring agents, so the DS monograph title follows the proposed format with the addition of the adjective "Aromatic".	

TITLES FOR BOTANICAL PROCESSED FORM MONOGRAPHS

Articles referred to as plant (or fungal, algal, or bacterial) processed forms include plant powders, dry extracts, dry juices, liquid articles, and fractions, but do not include isolated pure compounds. The examples provided below illustrate how titles for plant processed form monographs will be derived when following the new guideline, compared to how current monograph titles were derived.

Titles for botanical powder monographs: The term "powder" often indicates that the botanical material has been milled (comminuted) into a powder, but some materials such as spores and pollen occur naturally as powders. Botanical powders (see *Table 3* for examples) include powdered botanical materials but are not meant to include other botanically derived ingredients that may be powdered or present in powder form, such as dry extracts and dry juices.

Table 3. Current and Proposed Nomenclature Formats for Botanical Powders

Current Examples	Proposed Examples
{PROCESS } [{SCN} OR {LATIN BINOMIAL W/O AUTHORITY}] {BOTANICAL PART(S)}	**[{SCN} OR {LATIN BINOMIAL W/O AUTHORITY}] [BOTANICAL PART(S)] [{POWDER} OR {SPORE} OR {POLLEN}]**
Powdered Andrographis	Andrographis Stem and Leaf Powder
Powdered Ashwagandha Root	Ashwagandha Root Powder
Powdered Asian Ginseng	Asian Ginseng Root Powder
Powdered Black Cohosh	Black Cohosh Rhizome and Root Powder
NA	Clubmoss Spore
Powdered Centella asiatica	Gotu Kola Aerial Parts Powder
Powdered Garlic	Garlic Bulb Powder
Powdered Hawthorn Leaf with Flower	Hawthorn Leaf with Flower Powder
Powdered Horse Chestnut	Horse Chestnut Seed Powder
NA	Pine Pollen

Titles for botanical extract monographs: Extracts obtained from botanical materials are classified and named based on their physical state or consistency, such as liquid (liquid extracts), semisolid (soft extracts), or dry (extracts in solid form, e.g., powders, granules, or flakes) (see *Botanical Extracts* ⟨565⟩). The examples provided in *Tables 4* and *5* illustrate how titles for botanical extract

monographs will be derived when following the new guideline compared to how current monograph titles were derived. For the sake of clarity, in the following tables the format terms: **[{SCN} OR {LATIN BINOMIAL W/O AUTHORITY}] [{BOTANICAL PART(S)} AND/OR {BOTANICAL PRODUCT}]** used above to describe botanical materials, products, and powders will be simplified to **[SOURCE MATERIAL NAME]**, which incorporates all of the above terms.

Table 4. Current and Proposed Nomenclature Formats for Botanical Dry Extracts

Current Examples	Proposed Examples
[{PROCESS} {TYPE}] [SOURCE MATERIAL[a] NAME] [{EXTRACT}]	**[SOURCE MATERIAL NAME {FRESH}[b]] [{TYPE}[c] DRY EXTRACT]**
Powdered Andrographis Extract	Andrographis Stem and Leaf Dry Extract
Powdered Asian Ginseng Extract	Asian Ginseng Root Dry Extract
Powdered Centella asiatica Extract	*Centella asiatica* Aerial Parts Dry Extract
Powdered Goldenseal Extract	Goldenseal Root and Rhizome Dry Extract
NA	Oat Fresh Seed Dry Extract
NA	Rosemary Leaf Aqueous Dry Extract
Powdered Valerian Extract	Valerian Rhizome, Root and Stolon Dry Extract
Yeast Extract	Yeast Dry Extract

[a] Source material refers to the unprocessed botanical material or product used to prepare an extract or other processed botanical materials. Crude herb, or raw material would be synonymous terms the naming of which is exemplified in *Tables 1* and *2*.

[b] If fresh plant material is used to prepare the extract, the word "Fresh" is included after the SCN or Latin binomial and before the plant part. Otherwise, dry material is assumed.

[c] "**TYPE**" is an additional term that further identifies the article. The solvent is specified when two articles need to be differentiated based on their chemical profile due to the solvent used. For example, the terms aqueous or hydroalcoholic specify the type of extraction solvent used, which will create a unique article.

Table 5. Current and Proposed Nomenclature Formats for Botanical Soft Extracts

Current Examples	Proposed Examples
[SOURCE MATERIAL NAME] [{EXTRACT}]	**[SOURCE MATERIAL NAME {FRESH}] [{TYPE} {OLEORESIN} OR {TYPE} {SOFT EXTRACT}]**
Capsicum Oleoresin	*Capsicum* Species Fruit Oleoresin
NA	Turmeric Rhizome Ethanol Oleoresin
NA	Ginger Rhizome CO_2 Soft Extract
NA	Lemon Balm Leaf Soft Extract
NA	Valerian Fresh Rhizome, Root and Stolon Soft Extract

The term "botanical liquid articles" is intended to capture a variety of types of extracts, including not only fluidextracts and tinctures, which are described in ⟨565⟩, but also articles such as essential oils, essential oil spirits, and essential oil waters. Examples are provided in *Table 6*.

Table 6. Current and Proposed Nomenclature Formats for Botanical Liquid Articles

Current Examples	Proposed Examples
[SOURCE MATERIAL NAME]	**[SOURCE MATERIAL NAME {FRESH}]**

[{EXTRACT}]	[LIQUID ARTICLE]
Belladonna Tincture	Belladonna Leaf Tincture
Black Cohosh Fluidextract	Black Cohosh Root and Rhizome Fluidextract
Aromatic Cascara Fluidextract	Cascara Sagrada Bark Aromatic Fluidextract[a]
Garlic Fluidextract	Garlic Bulb Fluidextract
Ginger Tincture	Ginger Rhizome Tincture
Licorice Fluidextract	Licorice Root, Rhizome and Stolon Fluidextract
NA	Oat Fresh Seed Tincture
Peppermint Oil	Peppermint Leaf Essential Oil
Peppermint Spirit	Peppermint Leaf Essential Oil Spirit
Peppermint Water	Peppermint Leaf Essential Oil Water
Rhodiola rosea Tincture	*Rhodiola rosea* Root and Rhizome Tincture
Valerian Tincture	Valerian Rhizome, Root and Stolon Tincture

[a] An aromatic botanical product article is created by the addition of essential oils as flavoring agents, so the DS monograph title follows the proposed format with the addition of the adjective "Aromatic".

Juices are distinguished from other botanical liquid articles because while they are liquid to start, they may be subsequently concentrated or dried to make the article of commerce. In most cases the ability to extract the juice depends upon the plant material being fresh, so {FRESH} can be assumed unless otherwise specified. Examples are provided in *Table 7*.

Table 7. Current and Proposed Nomenclature Formats for Plant Juices

Current Examples	Proposed Examples
[SOURCE MATERIAL NAME] [{EXTRACT}]	**[SOURCE MATERIAL NAME] [JUICE] OR [DRY JUICE]**
Cranberry Liquid Preparation	Cranberry Fruit Juice
NA	*Echinacea purpurea* Aerial Parts Dry Juice
NA	European Elder Fruit Dry Juice

Chapter ⟨565⟩ states that certain botanical extracts may be referred to as "native extracts", which are extracts with no added inert substances and not processed beyond initial extraction. The only DS monographs with the word "native" in the title are *Native Guggul Extract* and *Native Gymnema Extract*, both of which have a contrasting monograph, *Purified Guggul Extract* and *Purified Gymnema Extract*. Other monographs indicate in the *Definition* rather than the title if suitable added substances such as carriers may be added (e.g., *Powdered Holy Basil Leaf Extract* or *Powdered Red Clover Extract*) or if the extract has no added substances (e.g., *Cranberry Liquid Preparation* or *Saw Palmetto Extract*). Another possibility is that the *Definition* may say nothing about the presence or absence of added substances (e.g., *Maritime Pine Extract*, or *Powdered St. John's Wort Extract*).

Some extracts are subject to additional processes that increase the content of characterized constituents, decrease the content of unwanted constituents, or both. The percentage of characterized or unwanted constituents in a processed extract may vary and will be specified in the *Definition* of the article. For example, the *Powdered Garcinia Hydroxycitrate Extract*

monograph specifies NLT 40% (−)-hydroxycitric acid. *Powdered Decaffeinated Green Tea Extract* serves as an example of a monograph for an article with a reduction of the level of a constituent, by its caffeine specification of NMT 0.1%. Another potential example would be "Deglycyrrhizinated Licorice Root Extract" which is processed to remove glycyrrhizin (glycyrrhizic acid or glycyrrhizinic acid).

In other cases, the specification may be for a class of compounds rather than a single characterized constituent, e.g., NLT 90.0% *Centella asiatica* triterpene derivatives in the monograph *Centella asiatica Triterpenes*; NLT 75.0% oligomeric proanthocyanidins in *Grape Seeds Oligomeric Proanthocyanidins*; NLT 90.0% and NMT 110.0% of the labeled amount of the sum of guggulsterones *E* and *Z* calculated as guggulsterone *Z* in *Purified Guggul Extract*; and NLT 90.0% and NMT 110.0% of the labeled amount of the sum of a specific list of isoflavones in *Powdered Soy Isoflavones Extract*.

As a very complex example, the *Saw Palmetto Extract* monograph allows for three types of extraction solvent: hydroalcoholic mixtures to produce a hydrophilic extract; hexane to produce a lipophilic extract; and supercritical carbon dioxide to produce extracts that are also lipophilic, although their composition can be altered by variations in temperature, pressure, time, and other factors. The hydroalcoholic extract contains NLT 0.01% and NMT 0.15% of long-chain alcohols, whereas the lipophilic extract contains NLT 0.15% and NMT 0.35% of long-chain alcohols; all extracts are required to contain NLT 80.0% of fatty acids, NLT 0.2% of sterols, and NLT 0.1% of *β*-sitosterol, all on the anhydrous basis.

Titles of monographs for extracts that have been processed for specified content ranges of particular constituents are made more precise by identifying the class of compounds whose content in the extract has been increased or decreased, as demonstrated in the examples provided in *Table 8* with comparisons to current monograph titles.

Table 8. Current and Proposed Nomenclature Formats for Additionally Processed Botanical Extracts

Current Examples	Proposed Examples
[{PROCESS} {TYPE}] [SOURCE MATERIAL NAME] [{CONSTITUENT OR CLASS OF COMPOUNDS} {EXTRACT}]	**[SOURCE MATERIAL NAME] [{CONSTITUENT OR CLASS OF COMPOUNDS} {TYPE} {DRY EXTRACT} OR {SOFT EXTRACT} OR {LIQUID ARTICLE} OR {BOTANICAL PRODUCT}]**
Powdered Garcinia Hydroxycitrate Extract	Garcinia Pericarp Hydroxycitrate Dry Extract
Centella asiatica Triterpenes	Gotu Kola Aerial Parts Triterpenes Dry Extract
Grape Seed Oligomeric Proanthocyanidins	Grape Seed Oligomeric Proanthocyanidins Dry Extract
Powdered Decaffeinated Green Tea Extract	Green Tea Leaf Decaffeinated Dry Extract
Purified Guggul Extract	Guggul Guggulsterones Dry Extract
Purified Gymnema Extract	Gymnema Leaf Gymnemic Acids Dry Extract
NA	Licorice Root Deglycyrrhizinated Soft Extract
Psyllium Hemicellulose	Psyllium Seed Husk Hemicellulose Dry Extract
Saw Palmetto Extract	Saw Palmetto Fruit Hydroalcoholic[a] Dry Extract
NA	Saw Palmetto Fruit Lipophilic[a] Soft Extract

NA	Saw Palmetto Fruit CO_2[a] Soft Extract
Powdered Soy Isoflavones Extract	Soy Seed Isoflavones Dry Extract
Tomato Extract Containing Lycopene	Tomato Fruit Lycopene Dry Extract
	Echinacea angustifolia Root Alkylamides Fluidextract
	Evening Primrose Seed Gamma-Linolenic Acid Oil

[a] For some articles the targets of additional processing include several constituents or classes of compounds, e.g., Saw Palmetto Fruit fatty acids, sterols, and long-chain alcohols, with different specifications for different types of extracts, e.g., with respect to the long-chain alcohols content. In such cases, the type of extract may be used in the DS monograph title for brevity and the details of the associated targeted constituents or classes of compounds provided in the *Definition*.

Further processing of plant extracts can lead to the production of "partially purified natural complexes", as opposed to the processed/semi-purified extracts just described. It would be arbitrary to set any numerical concentration threshold to distinguish between a plant extract processed with regard to particular constituents and a partially purified natural complex—they are all complex articles. However, the *Definition* section of currently monographed articles explicitly makes the distinction that partially purified natural complexes are comprised mainly of particular characterized constituents and their closely related congeners, whereas the processed extracts are characterized as fractions of an extract enriched or depleted in a particular substance or group of related substances. In practice, the degree of purification of natural complexes may overlap with that of processed extracts, but the intent of a monograph for a partially purified natural complex is to provide quality specifications for a complex article that is more akin to a single chemical entity than an unprocessed botanical extract.
The format for monograph titles for partially purified natural complexes is simply **[CLASS OF COMPOUNDS]**. For example, *Sennosides* is defined as a partially purified natural complex of anthraquinone glucosides isolated from senna leaf and/or senna pod, with NLT 90.0% and NMT 110.0% of the labeled amount of sennosides, and the labeled amount should be NLT 60.0% (w/w) of the article. *Curcuminoids* is defined as a partially purified natural complex of diaryl heptanoid derivatives isolated from turmeric, with NLT 95.0% of curcuminoids, calculated on the dried basis as a sum of curcumin (70.0%–80.0%), desmethoxycurcumin (15.0%–25.0%), and bisdesmethoxycurcumin (2.5%–6.5%).

Titles for Monographs of Complex Articles of Animal Origin

Monograph titles for dietary ingredients of animal origin should follow the directives in 21CFR101.4 *Food; designation of ingredients*, which is consistent with DSHEA with respect to the requirement to use common or usual English names where available. Taxonomic details may be provided in the article's *Definition*, e.g., the families of fish that may be used to produce fish oil are provided in the *Definition* because it is not feasible to identify each individual species in the monograph title or *Definition*. The general nomenclature convention for DS monograph titles is **[ANIMAL NAME] {ANIMAL ORGAN(S)} [ANIMAL PRODUCT] {MAJOR CONSTITUENT}**. Examples include *Cod Liver Oil*, *Krill Oil*, "Oyster Shell", and "Shark Cartilage".
As with partially purified natural complexes from plants, some complex articles of animal origin may be comprised mainly of particular characterized constituents and their closely related

congeners, so the format of the monograph titles can be similar to those for processed botanical articles (see *Table 9*). An added benefit of including the source material is that greater precision is provided, e.g., fish is not the only commercial source of omega-3 fatty acid triglycerides from which ethyl esters can be made. α-Linolenic acid can be sourced from the oils of flaxseeds, walnuts, or soybeans, and there are DS monographs for docosahexaenoic acid (DHA) from algal oil sources (*Crypthecodinium cohnii* and *Schizochytrium* spp.).

Table 9. Current and Proposed Nomenclature Formats for Processed Animal Products

Current Examples	Proposed Examples
{PROCESS} {TYPE} {SOURCE MATERIAL NAME} [CLASS OF COMPOUNDS]	**[SOURCE MATERIAL NAME] [CLASS OF COMPOUNDS]**
Fish Oil Containing Omega-3 Acids	Fish Oil Omega-3 Acids
Omega-3 Acids Triglycerides	Fish Oil Omega-3-Acid Triglycerides

The format for monograph titles for partially purified natural complexes from animal source materials, as with that type of botanical monograph title, is simply **[CLASS OF COMPOUNDS]**, e.g., *Pancreatin*, where the source material name (hog or ox) is provided in the *Definition* and can be specified in labeling, e.g., to allow consumers to make informed choices with respect to kosher or halal products.

Titles for Monographs of Other Complex Dietary Substances

In contrast to the examples cited above of cyanobacteria, which resemble algae in their growth form and thus fit within the DSHEA dietary ingredient definition part (C) "*a herb or other botanical*", monographs for other bacterial articles such as probiotic species better fit the DSHEA definition part (E), "*a dietary substance* …". Titles for these monographs should follow the format **[LATIN BINOMIAL W/O AUTHORITY] [STRAIN IDENTIFIER]** e.g., *Bacillus coagulans* GBI-30, 6086; *Lactobacillus rhamnosus* GG; or *Lactobacillus johnsonii* NCC 533.

Titles for Single Chemical Entity Monographs

The nomenclature for single chemical entities (e.g., vitamins, mineral nutrients, amino acids, enzymes, and isolated or synthetic substances) is the same as for drug substances, as outlined in ⟨1121⟩. Some examples include *Alanine*, *Ascorbic Acid*, *N-Acetylglucosamine*, *Chromium Picolinate*, *Cyanocobalamin*, *Ergocalciferol*, *Glutathione*, *Lactase*, *Lycopene*, *Magnesium Sulfate*, *Melatonin*, *Quercetin*, *Rutin*, *S-Adenosyl-L-methionine Disulfate Tosylate*, and *Vinpocetine* .
In some cases, "single" chemical entities may in fact be comprised of isomers or derivatives. For example, the *Phytonadione* monograph contains a purity specification of NLT 97.0% and NMT 103.0%, but it is a mixture of the *E*- and *Z*-isomers, of which it contains NMT 21.0% of the *Z*-isomer. To be compliant with the "Vitamin A" monograph, the article must possess NLT 95.0% of the vitamin A activity declared on the label but it may consist of retinol or esters of retinol formed from edible fatty acids, principally acetic and palmitic acids. The "Vitamin E" article consists of alpha-tocopherol and its alpha-tocopheryl acetate or alpha-tocopheryl acid succinate derivatives, and it may be the *RRR*- (previously referred to as *d*-) isomer or the all-racemic (*d,l*-) form. Other tocopherols and tocotrienols are not included in the "Vitamin E" *Definition*—a potential separate monograph could cover mixed tocopherols and tocotrienols.

The Term "Preparation" in Monograph Titles

The term "Preparation" is used in a number of current DS monograph titles. The original intent was to indicate articles that may be intermediates used in formulating finished dosage forms. In comparison, the *European Pharmacopoeia* distinguishes an "Herbal Drug Preparation" as an article obtained by subjecting the herbal drug to processes such as extraction (e.g., liquid extract/tincture/dry extract/soft extract); the class of extract may be further indicated as standardized or quantified.

With regard to current DS monographs, *Cranberry Liquid Preparation* has cranberry juice and no added substances. *Vitamin E Preparation* combines a single form of vitamin E with one or more inert substances. *Dexpanthenol Preparation* contains dexpanthenol and pantolactone, both of which have Reference Standards (RS). *Lutein Preparation* combines lutein (95.0%–130.0% of the labeled amount of lutein, with NLT 85.0% lutein, NMT 9.0% zeaxanthin) with one or more inert substances. *Lycopene Preparation* combines lycopene with one or more inert substances and suitable antioxidants. *Vitamin A Oral Liquid Preparation* consists of either retinyl acetate or retinyl palmitate in an emulsion, suspension, or solution.

The term "Preparation" will not be used in future DS monograph titles. As discussed above, many complex botanical articles may be used either as raw materials to be processed further in formulating DS finished products, or they may be used directly as dietary ingredients. Many current monographs that do not contain the word "Preparation" in the title include provisions in the *Definition* section that allow for the addition of "suitable added substances" (excipients, e.g., *Powdered Andrographis Extract*). Some allow for the addition of "suitable antioxidants" (e.g., *Schizochytrium Oil*), and many allow for multiple ingredients that each have an RS (e.g., *Vitamin E*).

TITLES FOR DIETARY SUPPLEMENT MONOGRAPHS

Dietary supplements are finished oral dosage forms manufactured to include dietary ingredients. Most commonly, DSs are available as tablets, capsules, liquid extracts (e.g., fluidextracts and tinctures), syrups, teas for infusion, and powders to be reconstituted for ingestion or sprinkled on food. DS dosage form nomenclature typically follows the same rules as those for drug products (see general chapter *Pharmaceutical Dosage Forms* ⟨1151⟩).

Some examples are provided below (note that some examples are hypothetical and are provided only to illustrate how titles should be derived). For the sake of clarity, the format terms: **[{SCN} OR {LATIN BINOMIAL W/O AUTHORITY}] [{FRESH}{BOTANICAL PART(S)} AND/OR {BOTANICAL PRODUCT}] [{TYPE} {DRY EXTRACT} OR {OLEORESIN} OR {SOFT EXTRACT} OR {LIQUID ARTICLE} OR {JUICE} OR {DRY JUICE} AND/OR {CONSTITUENT OR CLASS OF COMPOUNDS}]** used above to describe botanical materials and products will be simplified to **[DIETARY INGREDIENT NAME]** which incorporates all of the above terms. The general form is as follows: **[DIETARY INGREDIENT NAME] {RELEASE CHARACTERISTIC} [DOSAGE FORM]**

Tablets: Black Cohosh Rhizome and Root Fluidextract Tablets, Cat's Claw Stem Bark Dry Extract Tablets, *Chondroitin Sulfate Sodium Tablets*, *Glucosamine Tablets*, Gymnema Leaf Dry Extract Tablets, *Methylsulfonylmethane Tablets*.

Capsules: Asian Ginseng Root Powder Capsules, *Fish Oil Omega-3 Acids Capsules*, *Cod Liver Oil Capsules*, Milk Thistle Fruit Dry Extract Capsules.

Lozenges: *Zinc and Vitamin C Lozenges*.
Oral solutions: *Ascorbic Acid Oral Solution*, *Cholecalciferol Solution*, *Oil-Soluble Vitamins with Minerals Oral Solution*, *Water-Soluble Vitamins with Minerals Oral Solution*, *Zinc Acetate Oral Solution*.
Oral suspensions: *Calcium Carbonate Oral Suspension*.
Powders for oral suspension: *Psyllium Hydrophilic Mucilloid for Oral Suspension*.

DRUG VERSUS DIETARY SUPPLEMENT NAMES FOR ARTICLES

In the United States, drugs and DSs conform to different standards and require different testing procedures for identity, purity, strength, and composition. Occasionally, the same substance is used in a drug and in a DS. When used in a drug, the substance is given a US Adopted Name (USAN) or an International Nonproprietary Name (INN), but when the same substance is used in a DS, it may be referred to by another scientific, traditional, or *Herbs of Commerce* name (*2*). Because the articles (drug vs. DS) may have to meet different standards, the use of different names may be important. *Table 10* provides some examples of such multiple names.

Table 10. USAN Names vs. DS Names

USAN Name	DS Name
Ademetionine	*S*-Adenosylmethionine or SAMe
Ubidecarenone	Coenzyme Q_{10}, Co-Q_{10}
Sinecatechins	Green Tea Catechin Extract

GLOSSARY

This glossary does not include terms for plant (or fungal, algal, bacterial, or animal) materials that are defined in standard textbooks. It focuses on terms specific to DS products and ingredients whose definitions are not so readily available elsewhere or that have been defined differently in various sources. Readers are also encouraged to consult ⟨563⟩ and ⟨565⟩ for additional information on terminology that applies to DSs.
Aqueous extract: Articles prepared by extracting materials with water.
Concentrate: Historically, "concentrate" had two meanings. One was simply reflecting a liquid or solid preparation of higher concentration sometimes referred to as "high potency". The other meaning was that the product must be diluted before administration. Not all "high potency" products had to be diluted, so the word "concentrate" lost its definitive meaning and created confusion. The nomenclature committee has recommended that the term "concentrate" be phased out of nomenclature. Instead, the appropriate dosage form terms, e.g., fluidextract or tincture, with the extraction or concentration ratio in the *Definition* and on the label, can be used to indicate potency. If applicable, the statement "must be diluted" should be displayed prominently on the label.
Dry extract: Solid preparations obtained by evaporation of the solvent used in their production.
Dry juice: Dry material obtained by, for example, freeze drying or spray drying juice, often onto a carrier.
Essential oil: Natural aromatic complex mixtures of compounds (there may be 200 or more in one essential oil) belonging mainly to two chemical classes: terpenoids (e.g., monoterpenoid ketones, alcohols, hydrocarbons, and esters such as carvone, menthol, α-pinene, and thymol acetate; sesquiterpenoids such as α-bisabolol and caryophyllene; and less commonly,

diterpenoids such as phyllocladene and (+)-kaurene) and phenylpropanoids (e.g., anethole, cinnamaldehyde, coniferyl alcohol). However, there may also be some phenols such as methyl salicylate (oil of wintergreen) or vanillin, sulfur-containing compounds such as allyl isothiocyanate in mustard oil, or aldehydes such as benzaldehyde in bitter almond essential oil. They are liquid at room temperature and generally immiscible in water but are soluble in alcohol or other organic solvents, so they act like oils. They are called "essential" because they represent the "essence" of the plant in terms of fragrance. Since they evaporate when exposed to the air at room temperature, they are also called volatile oils or ethereal oils. They may be present in the leaf, seed, bark, stem, root, flower, and other plant parts, and may be obtained by steam distillation, extraction using various solvents, or other techniques.

Extract: Preparations with liquid, solid, or semisolid consistency obtained from plant material using solvents (such as ethanol, methanol, and others) to separate constituents of interest from the plant material. Types of extracts are namely: *Dry extract*, *Soft extract*, and *Liquid extract*; each is defined in this *Glossary*. Excipients may be included except for native extracts, which contain no constituents that were not native to the plant from which the extract was made.

Fluid extract: A type of *Liquid extract* preparation of plant matter, containing ethanol as a solvent or as a preservative, or both, so made that each 1 mL contains the extracted constituents of 1 g of the crude dry material that it represents, unless otherwise specified (e.g., 1:2) in the individual monograph.

Fraction: Processed extracts that consist of a specific class of compounds. For example sennosides from Senna, oligomeric proanthocyanidins from Grape Seed, and triterpenes from *Centella asiatica*.

Gum: A water-soluble carbohydrate derivative in the form of a hydrocolloid comprised of an anionic or nonionic polysaccharide or salts of polysaccharides, e.g., tragacanth, arabic (also known as acacia), ghatti, guar, karaya, locust bean, or xanthan.

Latin binomial: A system of nomenclature of animals, plants, and other life forms (developed by Linnaeus) that assigns a two-part Latinized name, the generic and specific epithets, to each species, such as *Harpagophytum procumbens* or *Harpagophytum zeyheri* for the two species of Devil's Claw included in the "Harpagophytum Species Root" monograph.

Latin binomial authority: The author of the Latin binomial, i.e. the individual(s) who first named, or later revised the name of the plant and validly published that binomial. The author information immediately follows the specific epithet, e.g., *Harpagophytum procumbens* (Burch.) DC. ex Meisn. or *Harpagophytum zeyheri* Decne.

Liquid extract: Liquid preparations of plant matter containing ethanol, water, vinegar, vegetable oil, or glycerin (or a mixture, e.g., aqueous ethanol) as a solvent. The term liquid indicates a material that is pourable and conforms to its container at room temperature.

Oleo-gum-resin: A mixture of an oleoresin and a gum, e.g., myrrh.

Plant processed forms: Plant material that has been subjected to processing, e.g., grinding to powder. Examples of processed plant forms include juices, powders, extracts, and fractions, but not isolated pure compounds.

Plant product: Substance produced naturally by a plant or plant part that does not require processing beyond pressing or cutting and scraping to be obtained. Examples include seed oil, gum, latex, resin, and others.

Resin: An amorphous complex mixture of resin acids, resin alcohols, resinotannols, esters and resins, usually hard and transparent or translucent at room temperature, and insoluble in water, e.g., rosin, guaiac, and mastic.

Soft extract: Soft extracts are preparations having consistencies between those of liquid extracts and those of dry extracts, and are obtained by partial evaporation of the solvent (e.g., water, alcohol, or hydroalcoholic mixture) used for extraction.
Tincture: Tinctures are liquid preparations usually prepared by extracting plant materials with alcohol or hydroalcoholic mixtures. Traditionally, tinctures of potent articles of botanical origin represent the activity of 1 g of the drug in each 10 mL of tincture, the strength being adjusted following the test for content of active principles or marker compounds.

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APPENDIX

USP DS and Herbal Medicines Nomenclature Joint Subcommittee (DSHM Nomenclature SC), of the 2010–2015 Monographs—Dietary Supplements and Herbal Medicines Expert Committee (DSHM EC) & Nomenclature, Safety, and Labeling Expert Committee (NSL EC) members were as follows: Robin J. Marles, Ph.D.; Steven J. Dentali, Ph.D. (Subcommittee Chair); Josef A. Brinckmann (Subcommittee Vice-Chair); Richard Ko, Pharm.D.; Joy A. Joseph, M.S., Ph.D.; Dennis K.J. Gorecki, B.S.P., Ph.D.; Paul L. Schiff, Jr., Ph.D.; Gregory A. Pennyroyal; and Kailas Thakker, Ph.D.
Government liaisons:[3] Yana Mille, R.Ph. and Steven Casper, Ph.D.
USP staff: Hellen Oketch-Rabah, Ph.D.; Nandakumara Sarma, Ph.D.; and Gabriel I. Giancaspro, Ph.D.
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[1] See § 201(ff) of DSHEA, 108 Stat. 4325, Public Law 103-471, 103d Congress (1994) for additional details of the definition of a dietary supplement. These provisions are now codified in the Federal Food, Drug, and Cosmetic Act at 21 United States Code § 321(ff).

[2] The Latin term "Species" with an uppercase S has a different meaning in monograph titles of some other currently valid national pharmacopeias, e.g., the pharmacopeias of Austria (*ÖAB*), Switzerland (*PhHelv*), and Hungary (*PhHg*) as well as Formulae Normales (*FoNo*), wherein the term Species is used as a synonym for the German term *Teegemische*, meaning

herbal teas composed of multiple species.

[3] The views presented in this article do not necessarily reflect those of the FDA. No official support or endorsement by the Food and Drug Administration is intended or should be inferred.

Need for Clear Regulation of Pesticide Residue Limits for Articles of Botanical Origin

STIMULI TO THE REVISION PROCESS

Stimuli articles do not necessarily reflect the policies of the USPC or the USP Council of Experts

Need for Clear Regulation of Pesticide Residue Limits for Articles of Botanical Origin

Botanical Dietary Supplements and Herbal Medicines Expert Committee,[a] and USP Staff[a,b]

ABSTRACT *Articles of Botanical Origin* ⟨561⟩ provides limits for common contaminants, including pesticides, aflatoxins, and elemental impurities. The *USP* limits for pesticides specified in this chapter are applicable to botanical drugs, but since dietary supplements (DS) in the United States are regulated as a subset of foods, the U.S. limits for pesticides in botanical DS are set to the same levels as those for food by the Environmental Protection Agency (EPA), or the Food and Drug Administration (FDA) action levels determined on a case-by-case basis.

This creates a divide between two different standards for the same article of botanical origin, which results from the unintended consequences of U.S. regulations initially established for food crops, but now also applicable to botanical ingredients that fall within the DS regulatory framework. In the absence of EPA-established limits for an article, compliance with the *USP* limits is permitted for drugs, whereas zero tolerance is applied when the same ingredient is labeled as a food or as a DS.

The intent of this *Stimuli* article is to provide background about the need for rational limits for pesticides, to ensure the quality of articles of botanical origin, engage the stakeholders to strengthen *USP* standards with regard to contaminants, and solicit public comments that will be reviewed and considered by USP's Botanical Dietary Supplements and Herbal Medicines Expert Committee. It is recommended that *USP*-specified limits for DS be adopted as part of the Good Manufacturing Practices for Dietary Supplements in 21 CFR 111.

INTRODUCTION

When the *USP* article *Psyllium Husk* is labeled and marketed in the United States as a bulk-forming laxative drug product for over-the-counter (OTC) human use at a single daily dose of up to 30 g, as permitted under the Food and Drug Administration (FDA) tentative final monograph (*1*), the pesticide[1] residue limits established in *USP* general chapter *Articles of Botanical Origin* ⟨561⟩ are applicable. However, the *USP* limits are not applicable when the very same *Psyllium Husk* material is intended for use as a food or dietary supplement (*2*) at the same daily serving size; for example, when labeled with an FDA-authorized health claim statement, i.e., soluble fiber from Psyllium Husk, as part of a diet low in saturated fat and cholesterol, may reduce the risk of heart disease (*3*).

Chapter ⟨561⟩ provides methods and limits for common contaminants including pesticides, aflatoxins, and elemental impurities. The applicable limits for pesticides in botanical drugs are covered in *USP* standards, but the limits for pesticides in foods are set by the Environmental

Protection Agency (EPA) and published in the *Code of Federal Regulations* (40 CFR Part 180) or the *Federal Register*. The FDA also sets "action levels"[2] for some pesticides that differ from EPA allowable limits (*4*). In either case, the limits contained in the *USP* are not applicable in the U.S. when articles of botanical origin are intended for food purposes. The *USP* limits, however, may be applicable in other countries where the *USP* is recognized as an acceptable pharmacopoeia, as the basis of specifications established for botanicals used as ingredients of licensed, listed, or registered herbal health products; for example, in Australia and Canada. For pesticide chemicals without EPA-established tolerance levels, their allowance on or in food is defined in 40 CFR Part 180.5 as "zero tolerance" (*5*), which is recognized to be below the limit of detection[3] using the applicable analytical method contained or referenced in the FDA's "Pesticide Analytical Manual" (*6*,*7*).

There are no pesticide residue tolerances established by the EPA for psyllium husk and for most of other plant species (other than the major commodity groups such as grains, nuts, oil seeds, fruits, vegetables, culinary herbs and spices, mushrooms and fodder) when sold in the U.S. as a food or supplement. Therefore, the detection of any pesticide, whether its presence is due to intentional pesticide application or minor contamination from pesticide application to nearby crops, or from any other cause, especially nonpoint source pesticide pollution, is detection of the presence of an unapproved pesticide residue.

The Pesticide Data Program of the United States Department of Agriculture (USDA) reported in their Annual Summary, Calendar Year 2014 (*8*), pesticide residue testing results for a variety of foods, including fresh and processed fruit and vegetables, grains, nuts, dairy products, meat, poultry and fish, eggs, honey, drinking water, and infant formula and baby foods. They noted that "Residues with no established tolerance were found in 2.6% (281 samples) of the total samples tested (10,619 samples). Of these 281 samples, 138 were domestic (49.1%), 140 were imported (49.8%), and 3 were of unknown origin (1.1%)." Given the total absence of tolerance limits for pesticides on the majority of botanicals, if these were subject to USDA testing for a future report, the noncompliance rate could be predicted to be close to 100%.

The FDA's *Compliance Policy Guide* Section 575.100 notes that food or feed may contain a pesticide residue from sources of contamination that cannot be avoided by good agricultural or manufacturing practices, such as contamination by a pesticide that persists in the environment. In the absence of a tolerance, tolerance exemption, or food additive regulation, FDA may establish an "action level" for such unavoidable pesticide residues. An action level specifies the level below which FDA exercises its discretion not to take enforcement action. An action level established by FDA is based on EPA's recommendation, which follows the criteria of Section 406 of the Federal Food, Drug, and Cosmetic Act (FFDCA). Food or feed found to contain an unavoidable pesticide residue at a level that is at or greater than an action level is subject to FDA enforcement action. In this Guide, certain pesticides are explicitly identified as having a zero tolerance while others are listed with an FDA action level for unavoidable pesticide residues in food and feed. However, the Guide also notes that none of the action levels listed there is binding on the agency, the regulated industry, or the courts. In any given case, FDA may decide to initiate an enforcement action below the action level or decide not to initiate an enforcement action if the level is exceeded (*4*).

In contrast, the Canadian *Food and Drug Regulations* [section B.15.002(1)(a)] states that a food is adulterated if a pest control product or its components or derivatives, for which no maximum residue limit (MRL) has been specified under sections 9 or 10 of the *Pest Control Products Act* for that food, are present in or on the food, singly or in any combination, in an amount exceeding 0.1 part per million (ppm) (*9*). Thus, in Canada there is no zero tolerance approach where no MRL has been set; instead there is a general MRL (GMRL) of 0.1 ppm.

Control for pesticide limits in botanical articles are amongst the limits for contaminants in the World Health Organization publication "Guiding principles for assessing safety of herbal medicines with reference to contaminants and residues" (*10*). The analytical methods and the limits for pesticides in this publication align with those elaborated in ⟨561⟩.

CONSIDERATIONS FOR ESTABLISHING PESTICIDE RESIDUE LIMITS

Since the recommended daily dose (as a drug) or serving size (as a food or supplement) are the same in the example of Psyllium Husk mentioned above, the requirement of zero tolerance in one case, but not the other, does not appear to be a toxicologically sound decision, based on human exposure to pesticide residues. This example illustrates how two very different standards apply for the same article of botanical origin based on product categorization, not practical analytical data.

The American Herbal Products Association's *Herbs of Commerce 2nd Edition* lists 2,048 separate species in U.S. commerce, which are used in various processed forms as ingredients of cosmetic, DS, food, and/or drug products (*11*). The International Union for Conservation of Nature estimates that about 3,000 medicinal and aromatic plant species are traded internationally, of which only about 900 are cultivated on farms, while the majority are wild-collected (*12*). Forty-five years after the establishment of the EPA, the majority of botanical species in commerce remain without EPA-established tolerances, meaning a zero tolerance is in effect for most species, even for many of the most widely used herbs, like the German chamomile flower [*Matricaria recutita* L., (currently accepted name *M. chamomilla* L.); Fam. Asteraceae][4]. Notable exceptions of herbs that do have EPA-established limits include certain aromatic or culinary herbs (EPA Crop Group 19) that are cultivated in the U.S. on a large scale, e.g., spearmint tops (*Mentha spicata* L; Fam. Lamiaceae), as well as a few important economic herb crops like hop dried cones (strobiles) (*Humulus lupulus* L.; Fam. Cannabaceae), which are used mainly in beer production. Such allowances are due to successful applications by industry for tolerances of specific pesticides on specific crops.

De minimis (trace yet detectable) levels of pesticide residues of unknown origin (nonpoint source) are increasingly a global environmental contamination problem. Zhang et al. reported that residues of "legacy pesticides" (e.g., DDT) and also "current use pesticides" have been detected in Arctic ice caps, which is evidence of long range atmospheric transport (*13*). Similarly, David et al. observed that the source of exposure to multiple pesticides in wild flowers is through long range transportation through bees (*14*). In recognition of this fact, action levels were set by the FDA in consultation with the EPA for residues of cancelled pesticide chemicals that persist in the environment and that were considered to be unavoidable in food and feed, including DDT, although only for specified crop groups or commodities. Nonpoint source pesticide detection is

also an increasing problem with certified organically grown and/or wild-collected botanicals.

In reality, cultivated and wild crops[5] alike are facing unavoidable contamination from nonpoint source pesticides and other contaminants, especially in the case of wild collected botanicals. These articles are unlikely to ever have pesticide tolerance levels established by the EPA, primarily because they are not food crops that would be subjected to intentional application of pest protection products. There is, then, no reason to establish a tolerance under the food crop framework. If pesticide tolerances were to be established for all botanicals sold in the U.S., it remains unpredictable as to which nonpoint source pesticide residues may occur.

A review of FDA import alerts concerning pesticide residues that are detected on raw agricultural botanical products can also illustrate the problems created by the absence of EPA-established tolerances for most botanicals that have a requirement to comply with EPA limits. The U.S. regulatory framework for pesticide chemical tolerances has not been "adaptive" to the changing environment, in that the realities of unpredictable nonpoint source residues, coupled with improved lower detection limits, have not been adequately accounted for in FDA's rulemaking or enforcement policy. This suggests that a more rational scientific approach to articles of botanical origin is clearly needed.

According to test data of the Canadian Food Inspection Agency (CFIA), during the period from April 1, 2012 to March 31, 2013, 35 out of 75 (47%) samples of organically grown fresh fruits and vegetables tested positive for a trace, yet detectable, level of pesticide residues of unknown origin (*15*). Eighteen samples (24%) had one residue detected and 17 (23%) had multiple residues detected. Out of 306 samples of imported organic fruits and vegetables, 148 (48%) tested positive for pesticide residues: 77 samples (25%) had one residue detected and 71 (23%) had multiple residues detected. Thus, there were no significant differences in rates of pesticide residue detection between domestic and imported organic fruits and vegetables. To put this in the context of consumer safety, only two of these domestic organic produce samples and only four of the imported organic produce samples were in violation of Canada's GMRL of 0.1 ppm used when the pesticide has no specific MRL established. Thus, compliance with Canadian regulatory limits for pesticides was 97.3% for domestic and 98.7% for imported organic fruits and vegetables. As a specific example, one sample of organic fine herbs grown in the U.S. was found to have residue of the pesticide tebufenpyrad (not listed in 40 CFR 180 but registered by the EPA for use on ornamental plants grown in commercial greenhouses), but the level was only 0.00167 ppm. The CFIA recognizes that while the detection of pesticide residues in products labeled as organic may reflect intentional use of pesticides, low level residues may also occur as a result of pesticide spray drift from nearby fields or post-harvest contamination during handling or storage.[6]

A case example for the rational need for pesticide limits occurred during consideration of *USP* compendial limits for inorganic bromide, which is a surrogate test for exposure to fumigation with methyl bromide gas. USP received a request, with supporting data, to delete the limit of bromide in ⟨561⟩ because some articles of botanical origin listed in *USP–NF* fail the current requirements, even when grown in organic conditions due to naturally occurring bromide in the source plants. The USP Botanical Dietary Supplements and Herbal Medicines Expert Committee recognized that the natural occurrence of bromide in some pharmacopeial articles of botanical origin may exceed

the then official limit of 50 mg/kg. However, the Expert Committee was not convinced that removal of the bromide limit was a rational approach, due to concern about toxicity arising from methyl bromide use as a pesticide.

Based on a *USP* revision proposal published in *Pharmacopeia Forum* 40(5), the Expert Committee revised the limit for bromide from 50 mg/kg to 125 mg/kg to allow the presence of naturally occurring bromide, while still addressing the possible use of methyl bromide as a fumigant. In view of the above decision, USP issued a Revision Bulletin, incorporated in the *First Supplement to USP 38–NF 33*. This approach of retaining an upper limit for inorganic bromide as a marker for methyl bromide fumigation is different from the *European Pharmacopoeia* (*Ph. Eur.*) approach, which, in fact, deleted the limit requirement[7]. The Canadian *Food and Drug Regulations* [section B.15.003(2)] also explicitly state that a food is exempt from the regulatory definition of "adulterated" if an inorganic bromide salt residue is present, i.e., there is neither a specific nor a general MRL for inorganic bromide (*9*).

For these reasons, and in consideration of data presented to USP, the Expert Committee revised the limit for bromide as an indication for its use as a fumigant. The new limit of 125 kg/mg is harmonized with the EPA requirements set in 40 CFR 180.123(a)(2)(i)(D) for processed foods not otherwise listed under 40 CFR 180.123(a)(2)(i), and under 40 CFR 180.521(a)(3), which would include some of the herbal drugs listed in the *USP*.

Another consideration in specifying limits for pesticides in articles of botanical origin is that botanical extracts, tinctures, or other pharmaceutical forms might contain pesticide residues at either enriched or reduced levels compared to their native plant material forms, because the preparation method may modify the pesticide content in finished products. For the pesticides listed in *Botanical Extracts* ⟨565⟩, the limits in extracts of botanical material are calculated by the following formula:

$$\text{If } E \le 10,\ \textit{Limit} = L \times E$$

$$\text{If } E > 10,\ \textit{Limit} = AM/100B$$

E = extraction factor of the pesticide in preparation method (determined experimentally)
L = the limit in the original article as listed in ⟨561⟩*, Table 4* or the EPA tolerance or the FDA action level
A = acceptable daily pesticide intake (mg/kg body weight), as published by FAO/WHO
M = body weight (kg)
B = daily dose of the article (kg)

The higher pesticide limits for extracts of botanical ingredients may be justified if the suggested intake or dose of the extract is reduced by a factor which is higher than the extraction factor *E*. The limits for suspected pesticides that are not listed in ⟨561⟩ must comply with the regulations of the EPA. For instances in which a pesticide is not listed in ⟨561⟩ or in EPA regulations, limits are calculated by the formula:

$$\textit{Limits} = A \times M/100B$$

A = acceptable daily pesticide intake (mg/kg body weight), as published by FAO/WHO
M = body weight (kg)
B = daily dose of the article (kg)

If the article is intended for the preparation of extracts, tinctures, or other pharmaceutical forms of which the preparation method modifies the content of pesticides in the finished product, the limits are calculated by the formula:

$$Limit = A \times M \times E/100B$$

A = acceptable daily pesticide intake (mg/kg body weight), as published by FAO/WHO
M = body weight (kg)
E = extraction factor of the pesticide in preparation method (determined experimentally)
B = daily dose of the article (kg)

ARTICLES OF BOTANICAL ORIGIN PRIOR TO DSHEA

Prior to the passage of the Dietary Supplement Health and Education Act of 1994 (DSHEA), articles of botanical origin were regulated as ingredients in foods, drugs, or non-drug cosmetics. To be permitted for use as a food ingredient, the botanical had to have been recognized by the FDA as Generally Recognized as Safe (GRAS) for an intended use in food products and/or as an approved color additive or other direct food additive. Currently, the vast majority of medicinal plant species are not recognized by FDA as GRAS, though their former treatment as drug ingredients in the U.S. market continued during the 1970s and 1980s, which were not subject to EPA-tolerances established for food crops.

In the 1970s, FDA established its Over-the-Counter (OTC) Drug Review process with expert advisory review panels to evaluate the safety and efficacy of OTC drug products marketed in the U.S. before May 11, 1972. The panels were charged with reviewing the active ingredients in OTC drug products (including a large number of botanicals) to determine whether these ingredients could be classified as Generally Recognized as Safe and Effective (GRASE) for use in self-treatment for the labeled indications for use at the recommended dosages. The panels classified ingredients into three categories:

- Category I: generally recognized as safe and effective for the claimed therapeutic indication;
- Category II: not generally recognized as safe and effective or unacceptable indications;
- Category III: insufficient data available to permit final classification (*16*).

Over a period of about two decades, from the mid-1970s until passage of DSHEA in 1994, FDA's review process resulted in the systematic removal of most articles of botanical origin as active ingredients of OTC drug products in the U.S. market and placed them into either Category II or III. As this process unfolded in the years leading up to DSHEA, many botanical articles had no legal safe harbor, i.e., they could not be used as food ingredients (not GRAS) nor as drug ingredients (not GRASE) as the panels determined them to be a "non-monograph," therefore requiring an approved New Drug Application (NDA) for marketing authorization.

Very few of the articles of botanical origin survived the review process and continued to be classified as OTC drug active ingredients, and, as such, are the only cases where ⟨561⟩ pesticide residue limits may be applicable in the U.S. However, several of the remaining botanical OTC active ingredients are now also permitted for use as DS ingredients. Thus, the previously illustrated example of different pesticide residue rules in effect for *Psyllium Husk*, depending on whether it is marketed as a DS or as a drug, holds true for other botanical OTC drug ingredients including, for example, *Elm* (dried inner bark of *Ulmus rubra* Muhl.; Fam. Ulmaceae) and *Senna Pods* (dried ripe fruits of *Senna alexandrina* Mill.; Fam. Fabaceae), among others.

ESTABLISHMENT OF THE EPA

When the EPA was established in 1970, the functions of establishing tolerances for pesticide chemicals on food crops, formerly vested in the Secretary of Health, Education, and Welfare, were transferred to the EPA (*17*). Today, EPA pesticide regulations (published in 40 CFR Part 180) are limited in scope to tolerances and exemptions for pesticide chemical residues in food. Articles of botanical origin used as ingredients of OTC or prescription drug products are outside of the scope of these EPA regulations. Limits for pesticides in botanical drugs are established by USP, as are limits for other contaminants such as microbial load and elemental impurities.

In 1970, it was not envisioned that 24 years later a new regulatory framework would be established for a class of oral ingestion DS products as a subset of foods. With the passage of the DSHEA, many herbal products formerly regulated as OTC or prescription drug products were available under the new framework as DS. For these herbs that were once available as OTC or prescription drug ingredients, the protection afforded by the *USP* quality standards did not transfer with them. They were now treated as food crops and therefore subject to the EPA-tolerances, which for most botanical articles are nonexistent.

U.S. REGULATORY FRAMEWORK FOR PESTICIDE RESIDUES

The FDA is responsible for the enforcement of pesticide tolerances and food additive regulations established by the EPA as per section 402(a)(2)(B) of the FFDCA. Under this section, a raw agricultural commodity or a processed food or feed is deemed to be adulterated and subject to FDA enforcement action if it contains either:

- A pesticide residue at a level greater than that specified by a tolerance or food additive regulation; or
- A pesticide residue for which there is no tolerance, tolerance exemption, or food additive regulation (*4*).

Furthermore, as per FDA regulation 21 CFR Part 111 (Current Good Manufacturing Practice in Manufacturing, Packaging, Labeling, or Holding Operations for Dietary Supplements) (*18*):

- Specifications are required to ensure that a dietary supplement derived from a botanical source does not contain contaminants such as an unlawful pesticide; and
- FDA samples individual lots of domestically produced and imported botanicals and analyzes them for pesticide residues to enforce the tolerances established by EPA.

- The preamble for the cGMPs section on the "Written procedures for laboratory operations (subpart J)" notes that the "failure to consider that specifications are needed to ensure that a dietary supplement derived from a botanical source does not contain contaminants, such as an unlawful pesticide, could result in a dietary supplement that contains unsafe levels of a contaminant."

In the case of certified organic products, such as organic herbal DS products (e.g., organic herbal teas, tinctures, capsules, and tablets), there are additional regulations to consider. For botanical ingredients or products that are certified organic as per the USDA National Organic Program regulations, the maximum allowable limit for pesticide residues of unknown origin is 5% of the EPA-established tolerance.

According to USDA regulation 7 CFR 205.671 ("Exclusion from organic sale"), when residue testing detects prohibited substances in certified organic botanicals at levels that are greater than 5% of the EPA-tolerance for the specific residue detected or unavoidable residual environmental contamination, the agricultural product must not be sold, labeled, or represented as organically produced. The USDA, the applicable State organic program's governing State official, or the certifying agent may conduct an investigation of the certified operation to determine the cause of the prohibited substance (*19*).

Obvious problems with the aforementioned FDA and USDA enforcement policies, respectively include the facts that most botanical articles have no EPA-established tolerance, and as such, in the case of certified organic botanicals, the 5% rule provides no relief. Five percent of a zero value is still zero.

As mentioned in the introduction of this article, the *USP*-established limits for pesticide residues in ⟨561⟩ for those articles of botanical origin are only applicable if:

- The botanical article is being used as an active ingredient of an OTC drug product (e.g., *Psyllium Husk USP*) or of a prescription botanical drug (e.g., *Digitalis USP*); or
- The botanical article is being used as an active ingredient of a medicinal product listed, licensed or registered in another country where the *USP–NF* is recognized as Official Compendia (e.g., Listed Complementary Medicines in Australia or Licensed Natural Health Products in Canada, among others).

Table 1 shows articles of botanical origin with *USP 37–NF 32* monographs in alphabetical order and indicates whether there are any EPA-established tolerances for each species. It is important to note that even if an article has some EPA-established tolerances, they may or may not be comprehensive and representative of the range of residues of unknown origin that may be detectable.

Table 1. Articles of Botanical Origin with *USP–NF* Monographs—EPA Tolerance Status (No or Yes)

Article of Botanical Origin with *USP–NF* Monographs	EPA Tolerances
Acacia (*Acacia senegal* or other related African species of Acacia)	No

Aloe (*Aloe vera*, *A. ferox*, or hybrids with *A. africana* and *A. spicata*)	No*
American Ginseng (*Panax quinquefolius*)	Yes
Andrographis (*Andrographis paniculata*)	No
Ashwagandha Root (*Withania somnifera*)	No
Asian Ginseng (*Panax ginseng*)	No
Aztec Marigold (*Tagetes erecta*)	No
Bacopa (*Bacopa monnieri*)	No
Belladonna Leaf (*Atropa belladonna*)	No
Benzoin (*Styrax benzoin*, *S. paralleloneurus*, *S. tonkinensis*)	No
Bilberry (*Vaccinium myrtillus*)	Yes
Black Cohosh (*Actaea racemosa*)	No
Black Pepper (*Piper nigrum*)	Yes
Boswellia serrata (*Boswellia serrata*)	No
Candelilla Wax (*Euphorbia antisyphilitica*)	No
Capsicum (various *Capsicum* species)	Yes
Caraway (*Carum carvi*)	Yes
Cardamom Seed (*Elettaria cardamomum*)	Yes
Carnauba Wax (*Copernicia cerifera*)	No
Cascara Sagrada (*Frangula purshiana*)	No
Cat's Claw (*Uncaria tomentosa*)	No
Centella asiatica (*Centella asiatica*)	No
Chamomile (*Matricaria recutita*)	No**
Chaste Tree (*Vitex agnus-castus*)	No
Cherry Juice (*Prunus cerasus*)	Yes
Chinese Salvia (*Salvia miltiorrhiza*)	No
Chocolate (*Theobroma cacao*)	Yes
Cranberry Liquid Preparation (*Vaccinium macrocarpon*, *V. oxycoccos*)	Yes
Digitalis (*Digitalis purpurea*)	No
Echinacea (*Echinacea angustifolia*, *E. pallida*, *E. purpurea*)	No
Eleuthero (*Eleutherococcus senticosus*)	No
Elm (*Ulmus rubra*)	No
Feverfew (*Tanacetum parthenium*)	No
Forskohlii (*Plectranthus barbatus*)	No
Garcinia cambogia (*Garcinia gummi-gutta*)	No
Garcinia indica (*Garcinia indica*)	No
Garlic (*Allium sativum*)	Yes
Ginger (*Zingiber officinale*)	Yes
Ginkgo Leaf (*Ginkgo biloba*)	No
Goldenseal (*Hydrastis canadensis*)	No
Green Tea Extract (*Camellia sinensis*)	No
Guar gum (*Cyamopsis tetragonolobus*)	No

Guggul (*Commiphora wightii*)	No
Gutta Percha (*Palaquium gutta* and Payena spp.)	No
Gymnema (*Gymnema sylvestre*)	No
Hawthorn Leaf with Flower (*Crataegus monogyna*, *C. laevigata*)	No
Holy Basil Leaf (*Ocimum tenuiflorum*)	No
Horse Chestnut (*Aesculus hippocastanum*)	No
Ipecac (*Cephaëlis acuminata*, *C. ipecacuanha*)	No
Juniper Tar (*Juniperus oxycedrus*)	No
Licorice (*Glycyrrhiza glabra*, *G. uralensis*)	No
Malabar-Nut-Tree Leaf (*Justicia adhatoda*)	No
Maritime Pine (*Pinus pinaster*)	No
Milk Thistle (*Silybum marianum*)	No
Myrrh (*Commiphora molmol*)	No
Opium exudate (*Papaver somniferum*)	No***
Peppermint (*Mentha* × *piperita*)	Yes
Phyllanthus amarus (*Phyllanthus amarus*)	No
Plantago Seed (*Plantago psyllium*, *P. indica*, *P. ovata*)	No
Podophyllum (*Podophyllum peltatum*)	No
Psyllium Husk (*Plantago ovata*, *P. arenaria*)	No
Pygeum (*Prunus africana*)	No
Rauvolfia serpentina (*Rauvolfia serpentina*)	No
Red Clover (*Trifolium pratense*)	No
Rosemary leaves with stems (*Rosmarinus officinalis*)	Yes
Saw Palmetto (*Serenoa repens*)	No
Senna (*Senna alexandrina*) leaf or pods	No
St. John's Wort (*Hypericum perforatum*)	No
Stinging Nettle (*Urtica dioica*, *U. urens*)	No
Storax (*Liquidambar orientalis*, *L. styraciflua*)	No
Tolu Balsam (*Myroxylon balsamum*)	No
Tomato Extract (*Lycopersicon esculentum*)	Yes
Tragacanth (*Astragalus gummifer*)	No
Turmeric (*Curcuma longa*)	Yes
Valerian (*Valeriana officinalis*)	No
Vanilla (*Vanilla planifolia*, *V. tahitensis*)	Yes
Witch Hazel (*Hamamelis virginiana*)	No

* Only glyphosate for *Aloe vera*.
** Only *Anthemis nobilis*.
*** Only Poppy Seed.

Table 2 lists the *USP*-established limits for pesticide residues on articles of botanical origin

listed in ⟨561⟩. Unless otherwise indicated in the monograph, the article to be examined complies with the limits indicated in *Table 2*. The limits for suspected pesticides that are not listed in *Table 2* must comply with the regulations of the EPA. It is also worth noting that the *USP*-established limits, while not identical, are comparable to those established by the *Ph. Eur*. for "herbal drugs" and "herbal drug preparations" marketed in the European Union (EU).

Table 2. Pesticide Residue Limits Listed in *⟨561⟩*

Substance	Limit (mg/kg)
Acephate	0.1
Alachlor	0.05
Aldrin and dieldrin (sum of)	0.05
Azinphos-ethyl	0.1
Azinphos-methyl	1
Bromide, inorganic (calculated as bromide ion)	125
Bromophos-ethyl	0.05
Bromophos-methyl	0.05
Bromopropylate	3
Chlordane (sum of *cis*-, *trans*-, andoxychlordane)	0.05
Chlorfenvinphos	0.5
Chlorpyriphos-ethyl	0.2
Chlorpyriphos-methyl	0.1
Chlorthal-dimethyl	0.01
Cyfluthrin (sum of)	0.1
λ-Cyhalothrin	1
Cypermethrin and isomers (sum of)	1
DDT (sum of *o,p*′-DDE, *p,p*′-DDE, *o,p*′-DDT, *p,p*′-DDT, *o,p*′-TDE, and *p,p*′-TDE)	1
Deltamethrin	0.5
Diazinon	0.5
Dichlofluanid	0.1
Dichlorvos	1
Dicofol	0.5
Dimethoate and omethoate (sum of)	0.1
Dithiocarbamates (expressed as CS2)	2
Endosulfan (sum of isomers and endosulfan sulphate)	3
Endrin	0.05
Ethion	2
Etrimphos	0.05
Fenchlorophos (sum of fenchlorophos and fenchlorophos-oxon)	0.1
Fenitrothion	0.5
Fenpropathrin	0.03
Fensulfothion (sum of fensulfothion, fensulfothion-oxon, fensulfothion-oxon	

sulfone, and fensulfothion sulfone)	0.05
Fenthion (sum of fenthion, fenthion-oxon, fenthion-oxon sulfone, fenthion-oxon sulfoxide, fenthion sulfone, and fenthion-sulfoxide)	0.05
Fenvalerate	1.5
Flucythrinate	0.05
τ-Fluvalinate	0.05
Fonophos	0.05
Heptachlor (sum of heptachlor, *cis*-heptachlorepoxide, and *trans*-heptachlorepoxide)	0.05
Hexachlorbenzene	0.1
Hexachlorocyclohexane (sum of isomers α-, β-, δ-, ε-)	0.3
Lindane (γ-hexachlorocyclohexane)	0.6
Malathion and malaoxon (sum of)	1
Mecarbam	0.05
Methacriphos	0.05
Methamidophos	0.05
Methidathion	0.2
Methoxychlor	0.05
Mirex	0.01
Monocrotophos	0.1
Parathion-ethyl and Paraoxon-ethyl (sum of)	0.5
Parathion-methyl and Paraoxon-methyl (sum of)	0.2
Pendimethalin	0.1
Pentachloranisole	0.01
Permethrin and isomers (sum of)	1
Phosalone	0.1
Phosmet	0.05
Piperonyl butoxide	3
Pirimiphos-ethyl	0.05
Pirimiphos-methyl (sum of pirimiphos-methyl and *N*-desethyl-pirimiphos-methyl)	4
Procymidone	0.1
Profenophos	0.1
Prothiophos	0.05
Pyrethrum (sum of cinerin I, cinerin II, jasmolin I, jasmolin II, pyrethrin I, and pyrethrin II)	3
Quinalphos	0.05
Quintozene (sum of quintozene, pentachloraniline, and methylpentachlorphenyl sulfide)	1
S-421	0.02
Tecnazene	0.05
Tetradifon	0.3

Vinclozolin	0.4

European herbal drugs must test in compliance with the pesticide residue limits for those pesticides provided in Table 2.08.13 of the *Ph. Eur.* (*20*). For pesticides not included in the table, the herbal drug must test in compliance with the limits cross referenced by regulation (EC) No. 396/2005, including annexes and updates. Furthermore, for pesticides not listed in the *Ph. Eur.*, nor in EU official documents, a calculation based on toxicological information is provided to make a determination of whether its level of detection is acceptable or not (*20*).

In Canada, articles of botanical origin sold as natural health products (NHPs) must comply with either *USP* limits, *Ph. Eur.* limits, or if the ingredient is also used as a food in Canada, limits set out in Health Canada's MRL Database,[8] formerly the "List of Maximum Residue Limits Regulated Under the *Pest Control Products Act*"(*21*), including the GMRL of 0.1 ppm.

These appear to be rational and pragmatic approaches to the regulation of low levels of pesticides residues that may be present on articles of botanical origin. It is important to note that a total or partial exemption from the test may be granted when the complete history (the nature and quantity of the pesticides used and the date of each treatment during cultivation and after harvest) of the treatment of the batch is known and can be checked precisely according to good agricultural and collection practices.

DISCUSSION

An unfortunate situation exists where pesticide residues are now widespread in the natural environment and detectable in ice, snow, soil and water, as well as on crops from certified organic land where no pesticide chemicals have been applied, and even in the remotest areas of the world where wild plant species are gathered for domestic consumption and export trade.

Many countries have developed a rational framework for the establishment of maximum allowable limits for a wide range of pesticide chemical residues broadly applicable to articles of botanical origin. This includes, for example, herbal medicinal products in the EU subject to the reasonable pesticide residue limits of the *Ph. Eur*. The U.S. has a similarly rational framework available through the *USP*-established limits that are currently applicable only to OTC botanical drugs and prescription botanical drugs. However, there are relatively few of these types of drugs, due to the different regulatory framework for herbal products in the U.S. compared to the rest of world.

When considering the basis for establishing limits in the context of human health, it is important to note that products regulated as herbal DS in the U.S. (and therefore subject to the EPA-established tolerances for conventional food crops) are ostensibly the same products that are regulated as registered herbal medicinal products in the EU (and therefore subject to the *Ph. Eur.*-established limits that are specifically intended for herbal drugs and herbal drug preparations, rather than for food crops). Furthermore, these are also the same products that are regulated in Canada as licensed (NHPs) for which Health Canada, in its general finished product specifications for NHPs, specifies the *USP* as an accepted source of limits for pesticide residues (*21*).

Recent technological advancements in pesticide analysis have substantially improved the sensitivity of detection, identification, and quantitation of pesticide residues. As a result, a zero tolerance criterion, based on earlier nonspecific analytical methods, is vastly different from the criteria applied with results of pesticides at levels in the parts per billion range, which are of such low levels that they are not toxicologically relevant. This change in technology highlights the need for more rational limits, based on current knowledge and compendial quality standards.

Different standards with regard to pesticide residues between the U.S. and their main trading partners, such as Canada and the EU, for ostensibly the same herbal products (albeit regulated differently), is also problematic in that it puts U.S. companies at a competitive disadvantage in the global market. For example, Canadian herbal product companies may import and use articles of botanical origin that test in compliance with either the *Ph. Eur*. or *USP* limits, whereas U.S. companies may experience FDA detentions and import refusals for articles of the same pharmacopeial quality due to the zero tolerance requirement for the vast majority of botanical articles with no EPA-established tolerances. Any move to increase enforcement for botanical articles without EPA tolerances would have a significant negative impact on the global herbal trade as the U.S. is one of the major destination markets for medicinal and aromatic plants.

CONCLUSION AND RECOMMENDATION

Rational limits for pesticides are very important to help ensure the quality of articles of botanical origin, whether they are used as components of prescription drugs, DS, or foods. The acceptance and incorporation of internationally recognized, official pharmacopeial quality standards such as the limits set out in ⟨561⟩ could be a workable solution to establish pesticide residue levels that are consistent with herbal materials of pharmacopeial quality.

It appears unrealistic to expect that the EPA will be mandated to prioritize the establishment of rational pesticide residue tolerances for each of the thousands of botanical articles of commerce presently not specified in 40 CFR Part 180. One possible solution to this gap would be the legal recognition in 21 CFR of ⟨561⟩, applied broadly to all herbs of commerce. This would:

- Help resolve a major unintended omission in the U.S. regulatory framework, i.e., the absence of rational limits for an entire class of ingredients, such as herbal DS ingredients;
- Provide a rational, scientific approach to regulation that would serve the public interest while reducing undue risk to businesses that import and use pharmacopeial quality herbal ingredients in their DS products; and
- Harmonize the U.S. with trading partners like Canada where ⟨561⟩ is accepted for NHP ingredient specifications, and with the EU where the comparable *Ph. Eur.* pesticide residue limits are applied.

Other possible solutions could include expanding the list of "Unavoidable Pesticide Residues" exceptions when enforcing an adulteration violation under Section 402 of the FFDCA for a pesticide residue in a food (or dietary DS component) that is not subject to an EPA-tolerance. In the absence of a tolerance, FDA may establish an "action level" for unavoidable pesticide residues. An action level specifies the level below which FDA exercises its discretion not to take enforcement action.

In view of the widespread environmental contamination caused by the use of pesticide chemicals throughout the world and their persistence in the environment, this article suggests that the most effective long-term solution would be an amendment of FDA regulations to replace the existing incorporation by reference of EPA-established tolerances for botanical DS components with the pesticide residue limits set forth in ⟨561⟩.

APPENDIX

USP Botanical Dietary Supplements and Herbal Medicines Expert Committee were as follows: Josef A. Brinckmann; Steven Dentali, Ph.D.; Edward Fletcher; Stefan Gafner, Ph.D.; and Robin J. Marles, Ph.D.

USP staff: Christopher Okunji, Ph.D.; Nandakumara Sarma, Ph.D.[b]; and Gabriel I. Giancaspro, Ph.D.

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[1] Pesticides are defined, according to ⟨561⟩, as a substance or mixture of substances intended to prevent, destroy, or control any pest, unwanted species of plants, or animals causing harm during or otherwise interfering with the production, processing, storage, transport, or marketing of pure articles. The designation includes substances intended for use as growth regulators, defoliants, or desiccants, and any substance applied to crops before or after harvest to protect the product from deterioration during storage and transport.

[2] An FDA action level is an enforceable regulatory limit for unavoidable pesticides residues in or on a food or animal feed. Its purpose is to protect the general public from contaminants. FDA action levels exist only for pesticides without U.S. EPA tolerances. Action levels and tolerances are established based on the unavoidability of pesticides residues and do not represent permissible levels of contamination where it is avoidable. The FDA works with the EPA to set action levels or enforcement guidelines for residues of pesticides, such as DDT, that may remain in the environment after their use is discontinued. These guidelines are set at levels to protect public health.

[3] Limit of Detection (LOD) is defined in *Validation of Compendial Procedures* ⟨1225⟩.

[4] The EPA has, however, established tolerances for the far less commonly used "Roman chamomile" (*Anthemis nobilis*, Syn.; *Chamaemelum nobile*), which are not applicable to the far more commonly used "German chamomile" (*Matricaria recutita*, Syn.; *Chamomilla recutita*).

[5] USDA. 7 CFR §205.2. Wild crop: Any plant or portion of a plant that is collected or harvested from a site that is not maintained under cultivation or other agricultural management.

[6] Canadian Food Inspection Agency. *National Chemical Residue Monitoring Program*: 2012–2013 Report. Available at: http://www.inspection.gc.ca/food/chemical-residues-microbiology/chemical-residues/ncrmp-report/eng/1415838181260/1415838265896 (accessed October 29, 2015).

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Factors to Consider in Setting Adequate Overages of Vitamins and Minerals in Dietary Supplements

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Factors to Consider in Setting Adequate Overages of Vitamins and Minerals in Dietary Supplements

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ABSTRACT

Currently, U.S. law requires that all fortified foods, including dietary supplements, containing a Class I nutrient, e.g., vitamin, mineral, protein, or dietary fiber must contain, at minimum, 100% of the label-claimed amount of the Class I nutrient. Thus, it is important for dietary supplement manufacturers to ensure that the content of nutrients in a dietary supplement meets the requirement of 100% of the label-claimed amount throughout the shelf life of the product. Dietary supplement manufacturers typically formulate products to contain nutrients in amounts greater than the label-claimed amount (i.e., overage amounts or overages) to compensate for loss due to degradation of the nutrients during the product's shelf life, and to compensate for the inherent variability of the manufacturing process and product testing. However, it is desirable for manufacturers to minimize overages, to help prevent individuals from consuming higher amounts of nutrients than desired, especially amounts that exceed, without warning, the tolerable upper intake levels (ULs). The use of USP public quality standards, detailed in compendial monographs, can assist manufacturers in reducing overages. This *Stimuli* article discusses factors, such as nutrient degradation, analytical testing, and manufacturing process variabilities, for dietary supplement manufacturers to consider when determining overages of nutrients in products. Furthermore, this *Stimuli* article recommends several strategies, such as the use of stabilized ingredients, formulation adjustment by strength, and improved manufacturing processes, to minimize manufacturing variability that may assist manufacturers reduce nutrient overages in their products.

INTRODUCTION

The Nutrition Labeling and Education Act of 1990 provided the U.S. Food and Drug Administration (FDA) with specific authority to require nutrition labeling of most foods regulated by the FDA. In order to evaluate the accuracy of nutrition labeling information for compliance purposes, the FDA regulations in 21 Code of Federal Regulations (CFR) §101.9(g)(3) and (g)(4) defined two classes of nutrients, Class I and Class II. Nutrients are specific dietary ingredients for which the Recommended Daily Intake or Daily Reference Values have been established by the Institute of Medicine (IOM) and the FDA, respectively, and include vitamins, minerals, protein, dietary fiber, total carbohydrate, polyunsaturated or monounsaturated fat, and potassium. Class I nutrients are those that are added to fortified or fabricated food, and the content of those nutrients has been controlled in some fashion. Class I nutrient content needs to be at least equal to the value for that nutrient declared on the label, i.e., not less than (NLT) 100% of the label-

claimed amount. Class II nutrients are naturally occurring nutrients whose content needs to be NLT 80% of the label-claimed amount. However, FDA regulations indicate that no action will be taken against Class II nutrients based on a determination of a nutrient value that falls below the label-claimed amount by a factor less than the variability that is generally recognized for the analytical method used on that food at the level involved.

The FDA established specific nutrition requirements and guidelines for nutrition labeling of dietary supplements in 21 CFR §101.36. In 21 CFR §101.36(f)(1), the regulations state that compliance with the nutrition labeling of dietary supplements will be determined according to the nutrient labeling requirements in 21 CFR §101.9(g)(1) through (g)(8), and further stated in 21 CFR §101.36 (b)(3)(i) that the requirements on Class I and Class II nutrients are also applicable to other dietary ingredients, for which adequate daily values have not been established. Because the degradation of a dietary ingredient in a dietary supplement is foreseeable, the FDA expects that manufacturers will take this into account when formulating dietary supplements with dietary ingredient overages, while adhering to dietary supplement Current Good Manufacturing Practices (GMPs). Consequently, the acceptance criteria that the FDA considers to be acceptable for dietary ingredients are variable at the lower acceptance limit, based on analytical method variability (for Class II nutrients), and at the upper limit based on reasonable excesses of dietary ingredients due to manufacturing variability and the degradation to an extent considered acceptable within GMPs (for Class I and II nutrients). An alternative approach was proposed by the Council for Responsible Nutrition, who petitioned the FDA to recognize the 90% minimum acceptance criteria to provide the expected level of a dietary ingredient, as in the *United States Pharmacopeia–National Formulary* (*USP–NF*) monographs, given the inherent variability in manufacturing and analytical testing (*1*).

Dietary supplement GMPs (21 CFR §111) require a manufacturer to use manufacturing processes in a manner that will ensure that a product meets established specifications. As stated in 21 CFR §111.210(e), GMP regulations require master manufacturing records to include a statement of any intentional overage amount of a dietary ingredient. The amount of overage should be limited to the amount needed to meet the weight or measure of each dietary ingredient that will be declared on the supplement facts label of the dietary supplement (*2*). Although the GMPs retain a requirement to state any intentional overage of a dietary ingredient, it does not require the manufacturers to provide an explanation on how the overage amount was determined.

USP–NF monographs define the quality of dietary ingredients and dietary supplements in terms of science-based specifications (analytical methods and specific acceptance criteria) for the identity, composition/ assay, and limit for contaminants. These public standards allow for analytical variability and for degradation of dietary ingredients to the extent considered acceptable under practical conditions. An official article must be formulated with the intent to provide 100% of the quantity of each dietary ingredient declared on the label. In most cases for a dietary supplement containing a single dietary ingredient, the *USP–NF* monograph acceptance criteria are set at NLT 90.0% and not more than (NMT) 110.0% of the declared amount on the label. However, per USP *General Notices and Requirements, 4.10.20. Acceptance Criteria* (*3*), where the minimum amount of a substance present in a dietary supplement is required by law to be higher than the lower acceptance criterion allowed for in the monograph, the upper

acceptance criterion contained in the monograph may be increased by a corresponding amount in the U.S. Therefore, for example, although the *USP* monograph states that *Folic Acid Tablets* (*4*) contain NLT 90.0% and NMT 110.0% of the labeled amount of folic acid, because of federal regulations in 21 CFR Part §101.9(g)(3) and (g)(4), the acceptance criteria become NLT 100.0% and NMT 120.0% of the labeled amount of folic acid to meet the federal regulations.

USP has established public standard monographs for dietary ingredients and dietary supplements, such as tablets or capsules containing a single vitamin or mineral as well as multiple vitamin and mineral combinations. The lower and upper acceptance limits of dietary ingredients are stated in the monographs to maintain the quality and accuracy of the content in the dietary supplement against the declared amount on the product label. For example, the acceptance criteria for *Ascorbic Acid* (*5*) as a dietary ingredient are NLT 99.0% and NMT 100.5% of ascorbic acid ($C_6H_8O_6$). Dietary supplement products that claim compliance with *Ascorbic Acid Tablets* (*6*) should contain NLT 90.0% and NMT 110.0% of the labeled amount, whereas the content of ascorbic acid in *Water-Soluble Vitamins Tablets* (*7*) should be NLT 90.0% and NMT 150.0%. The range of the lower and upper limits is wider in *Water-Soluble Vitamins Tablets* (*7*) to account for the increasing complexity under practical conditions and the stability of the ingredient while maintaining the accuracy of the label. In these defined limits, proper overages based on scientific assessment, such as stability profile and/or testing variability, have been incorporated into the upper and lower limits in the *USP* monographs.

As analytical instrument technology has evolved in recent decades, the variability of results from test procedures using advanced analytical instrumentations, such as high performance liquid chromatography or gas chromatography, has been smaller than with previous results using quantitative microbiological assays. USP acknowledges that, as a part of the USP monograph modernization activities, the lower and upper acceptance limits in the current *USP* monographs for dietary ingredients and dietary supplements need to be adjusted to account for the advancement of current analytical instruments that have reduced testing variabilities. Revision of these *USP* monographs to adjust the lower and upper acceptance limits requires scientific justification based on supporting data, followed by a period of public review and comment, and subsequent approval by an Expert Committee composed of independent experts from government, academia, and industry.

Since *USP* monograph acceptance criteria are defined for each dietary ingredient based on the review of available information and public comment, the adoption of *USP* standards will help ensure the quality of dietary ingredients and promote transparency among the users of the test methods and acceptance criteria for the selection of quality ingredients used in the manufacturing of dietary supplements. Accordingly, *USP* standards can help control any uncertainty with the quality and the analytical variabilities of incoming raw materials.

Understanding health risks associated with an excessive overage is critical to ensuring that the final dosage form of a dietary supplement is safe for consumers. For example, excessive intake of vitamin D above the upper intake levels (ULs) for an extended period of time can lead to nonspecific symptoms that may include anorexia, weight loss, polyuria, and heart arrhythmias. This situation could eventually cause more serious adverse events over time, such as vascular and tissue calcification with subsequent renal and cardiovascular damage, as well as increased

risk of pancreatic cancer (*8*). As another example, significantly higher amounts of folic acid above the tolerable ULs may mask and potentially delay the diagnosis of vitamin B_{12} deficiency. Eventually, it may lead to an increased risk of progressive, unrecognized neurological damage (*9*).

Tolerable ULs established by the IOM are the highest levels of daily consumption of nutrients within which any adverse health effect is unlikely to take place in almost all individuals in the general population, based on scientific data (*10*). Also, the UL is meant to be a caution against excessive intake of nutrients for an extended period of time, which could lead to undesirable health risks in the general population. The IOM has established ULs for vitamin A, vitamin C, vitamin D, vitamin E, niacin, vitamin B_6, folate, and choline. ULs have also been established for boron, calcium, copper, fluoride, iodine, iron, magnesium, manganese, molybdenum, nickel, phosphorus, selenium, vanadium, zinc, sodium, and chloride. The ULs established by the IOM vary by gender, age, and status of pregnancy and lactation. For example, the safety profile of a vitamin D supplement containing an overage of 20% above the label claim of 400 IUs (i.e., the adequate daily intake) is different from a product also containing a 20% overage but with a label claim of 4000 IUs (i.e., the UL).

In March 2015, the Dietary Supplement Ingredient Database (DSID) team, Nutrient Data Laboratory, Agricultural Research Service at the U.S. Department of Agriculture made available to the public regression results and research summaries on studies of adult, children's, and nonprescription prenatal multivitamin/mineral (MVM) dietary supplements (*11*) that were purchased in 2006–2007, 2008, and 2009 at mass market and natural health retail stores and from the internet. The objective of these studies was to estimate the relationship between label claims and analytical test results for vitamins and minerals, and to improve dietary intake assessments by providing analytical estimates of the ingredient content of marketed dietary supplements (*11*). Among the nutrients tested, vitamin D had mean models for overages in both children's and nonprescription prenatal at 36.3% and 13.1% above the label claim, respectively. Thiamin has a below label mean model for the nonprescription prenatal MVMs at −9.2% of the label claim, a mean model for overages for children's MVMs at 8.6% above the label claim, and a linear equation for adult MVMs predicted percent differences ranging from −6.5% to 8.6% of the label claim. At the most commonly labeled amounts, mean overages >15% above the label claim were predicted for vitamin A, vitamin B_{12}, vitamin D, folic acid, calcium, chromium, iodine, manganese, and selenium in one or more of the three MVM studies (adult, children, and/or nonprescription prenatal).

These results indicate that products labeled at or above the UL were among those analyzed in one or more of the MVM DSID studies for seven ingredients (vitamins A, vitamin B_6, folic acid, niacin, iron, magnesium, and zinc). However, even for the labeled levels at the UL, overages were still measured for some ingredients. For example, the labeled range of niacin in the adult MVMs is 5–150 mg/serving while the UL for niacin is only 35 mg/day. Using the online calculator and based on predictive models, adult MVM products labeled at 150 mg/serving of niacin were expected to contain an average of 152 mg/serving of niacin with a 95% confidence interval (CI) of 148.3–155.7 mg/serving, and for an individual adult MVM product, the 95% CI for niacin is 112.8–191.2 mg/serving [95% CI = mean ± (SE × 1.96)]. Based on the DSID findings, it was suggested that overage of nutrients was a common practice in the industry and that there were

challenges in maintaining label accuracy in some dietary supplement products being marketed. Also, consumers should be aware of any potential risks associated with excessive intakes of vitamins and minerals, especially if a product contains any vitamins or minerals above the ULs.

FACTORS AFFECTING OVERAGES

Overages for dietary ingredients in a product formulation are typically determined based on the anticipated loss of dietary ingredients due to degradation during the shelf life, as well as inherent variabilities in the manufacturing process and product testing. The chemical nature of the ingredient, the consistency in the manufacturing process, the dosage form type and/or product packaging type are factors that alone or in combination can affect the necessary overages needed to ensure the product meets 100% of the label-claimed amount of the nutrient throughout the product's shelf life. Ingredient variability does not necessarily need to affect overages in product formulation, since it can be offset by formulating a product based on the strength of the ingredient. However, ingredient variabilities likely affect the upper acceptance limit of dietary ingredients specified on the final product specifications as a product-release criterion to the market, because the manufacturers typically design the formulation based on the lower acceptance limit of ingredient purity specified on the ingredient specification release criterion.

Degradation Nature of Vitamins

Some dietary ingredients, including several vitamins in certain dosage forms or packaging conditions, may be susceptible to degradation or deterioration and may not remain in their native form over the shelf life of the product. Degradation or deterioration of dietary ingredients is one of the major factors that lead manufacturers to require overage amounts of dietary ingredients in their dietary supplements. There are several chemical reactions that can cause dietary ingredients to deteriorate over time. Oxidation is one of the major degradation pathways for some vitamins, including vitamin A, vitamin C, vitamin D, and vitamin E. Typically, oxidative degradation is accelerated under conditions of increased humidity and temperature, as well as in the presence of transition metals (e.g., iron and copper), especially in dosage forms with high moisture contents such as liquids, soft gelatin capsules, or gummies. Acidic conditions (i.e., low pH) during manufacture of the final dosage form also affect the stability of vitamins such as vitamin B_5 (pantothenic acid) and folic acid in acidic dosage forms, such as gummies. Basic conditions (i.e., high pH) can also affect the stability of vitamins; for example, thiamin becomes increasingly unstable as alkalinity increases in product matrices with high moisture content. Degradation of vitamin B_{12} (cyanocobalamin) can be accelerated in combination with vitamin B_1 and vitamin B_3 in matrices with high moisture content. Stability characteristics and degradation pathways of vitamins were summarized by Deritter (*12*). Long-term stability studies, under conditions that simulate realistic packaging and storage conditions, provide a reasonable means of determining potential losses of dietary ingredients due to degradation up to and even beyond the stated shelf life of dietary supplements. Based on an assessment of the resultant stability data, overage amounts of dietary ingredients can be added to a product formulation to compensate for degradation losses over the shelf life of the product. Supplement manufacturers are responsible for assessing the stability of all dietary ingredients in their product formulations and establishing proper overages in order to compensate for losses during the shelf life of the

dietary supplement product.

Process Variabilities

Dietary supplement GMPs emphasize, in 21 CFR §111 subpart E: Requirement to Establish a Production and Process Control System, that manufacturers should monitor critical in-process control points to ensure the consistency of product quality. The critical in-process control points should be identified, and frequency of testing should be specified in the manufacturer's written standard operating procedures. Master manufacturing records and executed batch production records should document the process variables to ascertain the production of quality products in compliance with GMPs. Poor in-process control or the failure to comply with established procedures can result in serious consequences, including batch rejection or unintentional high overages of dietary ingredients in the finished dietary supplement. A comprehensive approach should be established to ensure product consistency, including monitoring the weight variation or the content uniformity of the products at appropriate time points [see *Weight Variation of Dietary Supplements* ⟨2091⟩ (*13*)].

Analytical Testing Variabilities

Manufacturers need to consider analytical testing variability when calculating overages in dietary supplements, especially for multivitamin and multimineral supplements containing microgram levels of nutrients per serving. Micronutrients, such as vitamin B_{12}, biotin, folic acid, chromium, and iodine, at extremely low concentrations and in complex product matrices that cause interference with test responses, lead to high variability in test results, thereby affecting both test method accuracy and precision. This is an important factor for consideration when setting high overages. Dietary supplement GMPs, in 21 CFR §111.320(b): What requirements apply to laboratory methods for testing and examination?, require manufacturers to use "scientifically valid methods" that are accurate, precise, and specific for its intended purpose, for testing any incoming raw ingredients and finished products. It is the manufacturers' responsibility to establish scientifically valid methods when compendial methods, such as *USP* monograph test methods, are not available.

Validation of Compendial Procedures ⟨1225⟩ (*14*) provides manufacturers with guidance as to how to establish testing procedures that are precise, accurate, specific, and robust. Quality by design (QbD)-based experiments can facilitate method optimization in developing robust methods by identifying, reducing, and controlling sources of analytical variability. Poorly designed, poorly optimized, and non-validated test procedures result in highly variable test results. Due to high variability of assay test results, manufacturers are often compelled to increase overages to avoid the failure of products not meeting 100% of the label-claimed amount of a dietary ingredient at both the time of product release to market and throughout the product's shelf life. For minerals at trace levels, such as with microgram amounts of selenium or chromium per serving in supplements having complex matrices, the sensitive and reproducible test methodology of inductively coupled plasma mass spectrometry has helped to reduce uncertainty in test results, thereby allowing the acceptance limit range for microminerals to be reduced.

Ingredient Variabilities

Dietary ingredient preparations that are prone to degradation are often manufactured to contain high overages to compensate for any losses during transportation and storage prior to use in the manufacture of dietary supplements. Although the high overages help ensure that the ingredient preparation will comply with its specification, higher allowable overage may result in high variability of ingredient strength, which directly and negatively affects dietary supplement consistency (i.e., batch-to-batch variations in strength). This can lead to unintentional excessive intake of dietary ingredients when consumed and can be a risk to consumer health. Manufacturers often need to set high upper specification acceptance limits for dietary ingredients to encompass the variability of the content of the dietary ingredient in the component preparation, because a finished product that fails to meet the specification must be rejected, according to 21 CFR §111.123(b). Nevertheless, it is the manufacturer's responsibility to ensure that the upper limits of nutrients in a dietary supplement are below the ULs, to avoid any adverse consequences resulting from use by consumers. Variability of dietary ingredient components can be managed by setting up both a lower and upper acceptance limit for the content of the dietary ingredient rather than just a lower acceptance limit. However, if consistency of the content of the dietary ingredient in the component preparation cannot be tightly controlled, consistency in the content of the dietary ingredient in the supplement can be achieved through formulation adjustment on a batch-by-batch basis, following the determination of the content of the dietary ingredient in the batch of the component preparation to be used in product manufacturing. To maintain label accuracy, USP encourages manufacturers to implement a process of formulation adjustment for each manufactured batch of dietary supplements that will help ensure the consistency in the strength of the dietary ingredient.

DETERMINATION OF OVERAGE FACTORS

A systematic approach is needed for determining the necessary overage amount of a dietary ingredient, to ensure that the dietary supplement meets 100% of the label-claimed amount of that dietary ingredient. This systematic approach would allow dietary supplement manufacturers to not only determine the factors for overage calculations, but also to better understand variables from manufacturing processes, ingredients, and products that might be controlled to reduce the overage amount. First and foremost, scientifically validated test procedures must be in place prior to any assessment of losses due to degradation of dietary ingredients in a finished dosage form. Without reducing and minimizing variability that is attributable to test results, it will be difficult to separate that variability from any variability due to the manufacturing process and to dietary ingredient deterioration.

Determination of Degradation Losses during the Shelf Life of the Dietary Supplement

Potential losses of dietary ingredients in finished dosage forms in a package during the shelf life can be assessed by performing either long-term or accelerated stability studies under standardized conditions of temperature and humidity, such as conditions described in the International Conference on Harmonisation (ICH) Q1 guideline (*15*). The purpose of stability studies is to establish a shelf life and label storage conditions applicable to all future batches of the dietary supplement that are manufactured and packaged under similar circumstances.

Stability studies should be performed under long-term conditions [25 ± 2°/60 ± 5% relative humidity (RH)]. Stability test samples should be obtained from full scale production batches and packaged in the same or similar packaging configuration representative of the marketed product. An adequate number of commercial batches of product, preferably a minimum of three, should be tested for stability assessment to determine the rate of dietary ingredient degradation and loss. If full scale production batches are not initially available, laboratory or pilot batch samples (preferably no smaller than one tenth the size of a commercial batch) can be used to obtain an initial understanding of the stability of the dietary ingredients.

In order to quickly estimate a shelf life for the product without having to wait as long as the full shelf life of the product, stability assessment can be conducted under accelerated conditions. There are at least two different standard stability conditions typically employed, i.e., intermediate conditions (30 ± 2°/65 ± 5% RH) and accelerated conditions (40 ± 2°/75 ± 5% RH) (*15*). Although intermediate and/or accelerated stability studies are useful for making a reasonable assessment of the product's stability, long-term studies should be performed for confirmatory purposes. The primary purpose of accelerated or intermediate stability studies is to evaluate the effect of short-term excursions outside the label storage conditions that could occur during shipping.

Procedures for stability testing must be scientifically valid as well as stability indicating. Prior to the execution of a stability study, a protocol should be created specifying the batch ID, specifications, storage conditions, sample size, testing frequency, and container–closure system. A degradation trend can be assessed with an adequate number of time points (NLT three time points). A simplistic way to assess degradation losses using a confidence interval is to draw a trend line at designated time points using statistical software. The subsequent degradation loss, using the trend line, can be calculated at a specific time point against the initial amount that had been tested at the beginning of the study, rather than the theoretical values of formulation inputs.

Determination of Testing Variabilities

Variation denotes the bias and dispersion from the overall mean value for the data set. Commonly, variation is expressed as a variance or relative standard deviation (RSD). Variation can result from the analytical test procedure or the manufacturing process including sampling for a dietary supplement. In order to determine the impact of the *variability* to build further confidence levels, an appropriate number of samples (*n*) should be tested using the formula:

$$Variability = s/\sqrt{n}$$

s = standard deviation of the means
n = size of samples

Chapter ⟨1225⟩ (*14*) defines validation of an analytical procedure as the process by which it is established, by laboratory studies, that the performance characteristics of the procedure meet the requirements for the intended analytical applications. Chapter ⟨1225⟩ (*14*) and ICH Q2R1 (*16*) explain the characteristics necessary for an analytical method to be validated.

The purpose of an analytical method validation is to provide experimental evidence that the factors that impact the uncertainty associated with measurements are sufficiently controlled, such that an acceptable level of measurement uncertainty based on the method's purpose can be met with confidence. The two most important elements of analytical variation are the accuracy and precision of the test method. Accuracy is defined as the difference between the measured result and the corresponding true value (i.e., standard value). In statistical terms, accuracy consists of the true value plus systematic bias and random error. The random error is the intermediate precision of the method.

It is the manufacturer's responsibility to determine the testing variability as well as acceptance criteria to determine if the method is suitable for its intended purpose. For an example, testing variabilities can be determined through spike-and-recovery studies that are typically performed to demonstrate the accuracy of the testing method with defined acceptance criteria during the method validation. Dietary ingredients can be spiked into separate placebos at various levels. The root mean squared error at the spiked levels can be determined as a testing variability with an adequate number of replicated tests (*17*).

Determination of Process Variabilities

Process variation is the inherent variability seen in the measurements attributed to factors during the manufacturing process. Chapter ⟨2091⟩ (*13*) covers methods for testing weight variation of dietary supplements for assessing acceptability of a batch of material. Other performance tests, such as disintegration or dissolution testing [see *Disintegration and Dissolution of Dietary Supplements* ⟨2040⟩ (*18*)], provide a measure of manufacturing quality control. An extension of this would evaluate the overall process capability across multiple batches to estimate the probability of a batch or content in an individual unit being outside the specification. Process capability indices measure how close the process average is to the specification. Tolerance intervals are another tool that provides insight into the distribution of the individual values from a lot. The manufacturer should be able to determine variabilities of blending, weighing, dosage weight, and content uniformity following well-designed studies.

Determination of Overages in a Dietary Supplement

Manufacturing process and measurement variability can be utilized to model the expected distribution of any critical quality attributes of the finished dosage form. These statistical models can be simplistic whereby the process and measurement errors are independent, allowing for a summation of the errors to a more complex model where other sources are variabilities that can be incorporated in to the model. For this *Stimuli* article, as a simple model, the total variation is calculated as the sum of the measurement and process variations (*17*). In this model:

$$\sigma^2_{total} = \sigma^2_{process} + \sigma^2_{measurement}$$

Typically, process and measurement variabilities are expressed as a percent, utilizing the RSD, defined as the standard deviation divided by the mean. Since the summation of errors requires the variance, and the coefficient of variation utilizes the standard deviation (square root of the

variance), each percentage of variability must be squared and summed, and then the square root of the sum must be taken to get total uncertainty. If a process has 10% variation and the measurement system has 10% uncertainty, the total uncertainty would be

$$14.1\% = \sqrt{10^2_{process} + 10^2_{measurement}}$$

If a degradation loss, based on stability studies, shows an upper 95% confidence level of a decrease of 20% in the strength of a dietary ingredient at the end of the shelf life, the overage would be a minimum of 34.1%, by combining the 20% with the 14.1% of the total uncertainty.

Finished product or final release testing is the seminal moment when lots are either accepted or rejected based on the performance of the different assays. These results have both the assay variation and process variation. The number of units tested during final release should allow for a high probability that if a surveillance sample was taken, the product would be within the stated label claims. USP is working with industry to develop methods and sample sizes that ensure a high confidence that results seen at release can be a surrogate for the results seen during a surveillance audit. The propagation of error arises from the sum of the measurement error and manufacturing error that creates a cumulative effect on the reported result. The relative error statistic allows one to take the sum of the errors to determine the magnitude of the error. The relative error is the absolute error divided by the exact value.

STRATEGIES TO MINIMIZE OVERAGES

An understanding of the variables associated with the safety and stability of the dietary ingredients is critical to developing strategies for minimizing overages. Protection and/or stabilization of the dietary ingredients in the final dietary supplement dosage forms will help reduce overages if degradation is the major driver for overages. Microencapsulated ingredients with enhanced stability are often used to help reduce overages in dietary supplements. Various types of coating materials (e.g., gums, gelatin, resins, starch, or milk proteins) have been successfully and commercially employed to microencapsulate dietary ingredients to protect those ingredients from process damages, moisture and oxidation, and/or ingredient interaction. When encapsulated ingredients are used, release of dietary ingredients from a coated form needs to be ensured using a performance test described in ⟨2040⟩ as one of the acceptance criteria for the manufacturing process (*18*). Additionally, packaging materials with good barrier properties, product bottles with nitrogen filling, and non-vented liners would help prevent oxidative degradation of the ingredients to enhance the stability of the product. However, a careful assessment, such as stress testing to various types of packaging, is highly recommended. For example, non-vented liners may cause a paneling effect to plastic bottles during the shelf life, due to depletion of oxygen in the product bottle through product oxidation.

In addition, the QbD is a concept that quality should be built into a product from the beginning of product development based on sound understanding of product, process, and testing. QbD has gained wide-spread usage in the pharmaceutical industry (*19*), as the concept can be applied not only to product development and manufacturing operations but also to testing method development that can enhance the robustness of product quality and, consequently, reduce variabilities in manufacturing process and testing results.

CONCLUDING REMARKS

Dietary supplement manufacturers are required by federal regulations to ensure that the content of dietary ingredients meet the amount that is claimed on the label. It is the manufacturer's responsibility that the dietary ingredient content during the shelf life be NLT the claimed amount on the product label, to maintain label accuracy. In order to meet these expectations, manufacturers usually formulate products with added overage amounts of dietary ingredients so that the products, when tested, meet at least 100% of the amount claimed on the label throughout the declared shelf life. While these provisions should help consumers make purchase decisions based on accurate information provided on the label claim, there is concern that exposure to excessive amounts of dietary ingredients or their degradation products could pose safety concerns.

In order to meet the label claim over the shelf life of the product, manufacturers need to make science-based decisions when adding overage amounts of dietary ingredients to specific products, by understanding the product stability profile, manufacturing process variability, ingredient strength variability, and analytical testing variability, and how these factors can impact the quality of the finished products. This will help ensure consumer safety and build consumer trust in the quality of dietary supplements. Manufacturers should perform proper risk assessments in consultation with subject-matter experts to avoid overage amounts that exceed ULs. USP encourages the dietary supplement industry to use publically available standards to help reduce variability associated with ingredient quality and analytical test results and help set adequate overage amounts of dietary ingredients added to dietary supplements.

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Dietary Supplements Stakeholder Forum – Wrap-Up Summary

Global Expertise
Trusted Standards
Improved Health

U.S. Pharmacopeial Convention

United States Pharmacopeia: Dietary Supplements Stakeholder Forum

Wrap-Up—May 16, 2014

James Griffiths, Ph.D.

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Stakeholder Forum Purpose

Summary of Stakeholder Forum purpose…

- Provide overview of USP and its standards for dietary supplements for new participants
- Provide updates on dietary supplements topics of interest
- Receive stakeholder feedback on dietary supplements and related standards

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What We Heard

Participants made a number of comments and questions:

- Changes to reference standards may generate production backlogs and process resets; USP should include industry participation in testing in these cases.
- Evolutions in industry testing have outpaced USP method modernization.
- How can newer technologies be integrated into USP's standards-setting process?
- Better clarification on multiple testing requirements for identity is needed.

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What We Heard (cont'd)

- There is a need to increase the visibility of USP's brand and value to both retailers and consumers.
- There is a need for more discussion on the role of USP standards on shelf-life, degradants, and overages.
- There are labeling challenges when marketing a product in multiple countries; it is getting difficult to sell a single formulation in multiple countries. USP public standards help in this regard.
- Modification of USP test methods yields inconsistent findings among multiple laboratories; harmonization could help resolve this issue.

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What We Heard (cont'd)

- There is a need to confirm the absence of contaminants and adulterants using USP's identification methods. Targeted and non-targeted approaches could add to method specificity.
- There is an opportunity for shared standards and methods between AOAC and USP.
- How does USP work with other associations?
- Consider revising the limits for pesticides in General Chapter <561> *Articles of Botanical Origin.*

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How to Stay Engaged

- Participate in Stakeholder Forums
- Sign up for the Dietary Supplements e-Newsletter
- Visit the Call for Candidates page on USP.org and apply for a USP Expert Committee, Chair position, or Expert Panel
- Offer public comments on proposed methods through USP's *Pharmacopeial Forum*

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Thank You

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