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Dietary Supplements Stakeholder Forum

Michael McGuffin, Chair
Summary Discussions
Wednesday, June 1, 2016

What We Heard

USP Updates and Discussions—Adulterants Database

- ▶ Stakeholders—consumers, marketers, regulators—will work together to solve the problem caused by adulterated products that masquerade as dietary supplements (DSs).
- ▶ USP should make more clear that tools to detect adulteration by drug spiking are not meant as standards for manufacturers, but rather as tests for regulators in enforcement/forensic actions.
- ▶ There is sensitivity in the industry about screening methods being required as regular tests for GMP compliance.
- ▶ The adulterants database was well received, but stakeholders emphasized that adulteration by ingredient substitution, dilution, and spiking with botanical chemical markers are areas more relevant for the manufacturers than adulteration by drug spiking.

What We Heard

USP Updates and Discussions—Adulterants Database

- ▶ USP must make the planned database comprehensible, segregating the drug/drug analog tainted products of interest to regulators from the economically motivated adulteration of interest to dietary supplement ingredient purchasers.
 - Confusion can arise because the adulterants database is perceived as a tool for industry, but in reality it is a tool for regulators, enforcement agencies and forensic laboratories.
 - Separate section on authentication would highlight the function of the database as a product and ingredient integrity tool manufacturers can use to protect themselves against Economically Motivated Adulteration.

Action Item: Attendees interested in participating in beta-testing the USP database will contact Mr. Anton Bzhelyansky (anb@usp.org).

What We Heard

USP Updates and Discussions—DNA-based Methods for Botanical Identification

- ▶ DNA testing is an emerging tool of indisputable value. However, it can not be used to identify different parts of the plant. RNA may be used for that purpose but it is too fragile. At the current stage of development, nucleic acids techniques are not suitable for regular quality control to determine parts of the plants.
- ▶ No single DNA method can fully define a pharmacopeial article; identity must be determined on a case-by-case basis involving orthogonal tests including physical and chemical methods.

What We Heard

USP Updates and Discussions—DNA-based Methods for Botanical Identification

- ▶ USP could take the lead in consolidating information from the various DNA libraries into a single repository targeted for dietary supplements as a reliable resource for researchers and ingredient purchasers. USP could leverage its experience in other similar library resources supplemental to public standards and explore how to apply that experience to DNA libraries.
- ▶ Industry is looking to USP to take a lead role in exploring development of a repository of authenticated plant material that could serve validation purposes in DNA procedures.
- ▶ Plants within a single species can be highly variable. Industry is looking for partnerships to ensure that if a DNA method is developed as a standard, it identifies material representative of articles in commerce.

What We Heard

USP Updates and Discussions—Residual Solvents

- ▶ Some attendees recommended that DS ingredients be excluded from General Chapter <467> Residual Solvents because of inconsistency with the scope and limitations of similar guidelines from ICH¹.
 - USP staff responded that revised language in <467> clarified previous application of residual solvents by *USP General Notices* to finished dietary supplements (not ingredients). Industry is invited to provide comments to USP on this topic and about potential exceptions to residual solvents for dietary supplements.

1. International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use

What We Heard

USP Updates and Discussions—Modernization of Monographs

- ▶ There was general support for USP up-to-date efforts. However, some attendees noted that it is important to protect existing methods that work well and to be mindful of capital expenditures that might be associated with adoption of high-tech methods.
- ▶ USP staff noted the benefit of building in flexibility in general chapters and monographs when results are equivalent so industry has options.

What We Heard

Stimuli Articles—Overages

- ▶ What can USP do to get FDA to allow shortages in dietary supplements (less than 100% label claim) that are in line with what USP allows as an industry standard?
 - USP staff responded that USP had discussed this topic with FDA officials in the past. USP could revisit the topic in future meetings with FDA officials
- ▶ CRN encouraged USP to raise the issue with FDA. In other countries, the minimum acceptance limit for dietary supplements is consistent with pharmacopeial monographs, but in US is consistent with regulations for fortified foods (NLT 100%).

What We Heard

Stimuli Articles—Pesticides

- ▶ In context of USP Pesticide stimuli article: EPA Crop Group #19 includes herbs and spices—and additional limits for Crop Groups have recently been issued. FDA action limit is 10 ppb.

What We Heard

Stimuli Articles—Nomenclature of Dietary Supplements

- ▶ AHPA intends to produce a third edition of *Herbs of Commerce* this year.
- ▶ USP Nomenclature and Labeling Expert Committee is discussing a name for “gummies”.
- ▶ The established name in dietary supplement industry is “gummies.” A concern is the dosage form is also a potential vehicle for drugs, therefore a compatible pharmacopeial name for the dosage form may be established by the Nomenclature EC.

What We Heard Standards for High-Impact Supplements— Probiotics

Standards for High-Impact Supplements

- ▶ USP invited industry comments on recent proposals for probiotics in Pharmacopeial Forum, which include USP species-level monographs listing available strains with strain-specific tests linked to the label claim.

What We Heard

Open Forum: Stakeholder Topics

USP Standards as a Resource for Industry

- ▶ It has been suggested in a USP article by USP staff that public health could be enhanced by strengthening Good Manufacturing Practices (GMPs) by requiring greater adoption and compliance with USP or other public compendial standards.
- ▶ Industry does not support such changes to the existing FDA GMPs.
- ▶ There was agreement that transparency is important for consumers, and that a minimum standard for quality should be established.
- ▶ USP staff suggested that adoption of public standards provides an opportunity to establish minimum common standards and increase transparency in communication of internal specifications that now remain private and unknown.

What We Heard

Open Forum: Stakeholder Topics

- ▶ What topics would industry stakeholders like USP to propose for future Roundtables?
 - USP is considering cranberry, modernization, contaminants, GMP quality standards Roundtables.
 - USP should consider a 2017 Roundtable on the topic of protein methodologies for authentication
 - USP should consider a 2017 Roundtable on the topic of mineral and mineral salt monograph development

What We Heard

Open Forum: Stakeholder Topics

- ▶ Work with mineral suppliers to develop new monographs for ingredients suitable for food
 - USP has numerous monographs for mineral ingredients with specific tests and defined limits. Industry sponsorship providing analytical data for the development of new monographs is needed.
 - Mineral suppliers typically do not have analytical and safety data.
 - New monographs for minerals should be developed in parallel for *FCC* and *USP*.
 - USP should consider a 2017 Roundtable on the topic of mineral and mineral salt monograph development

What We Heard

Open Forum: Stakeholder Topics

- ▶ Aggressive enforcement by regulators is needed.
- ▶ Industry is looking to USP to ensure excellent quality standards for herbal dietary supplements.
- ▶ Develop ID and testing standards for protein
 - FDA's New Nutrition Labeling Guidelines are relevant to protein discussion
- ▶ USP could explore developing allergen testing standards.

What We Heard

Open Forum: Stakeholder Topics

- ▶ What is the role of Third Party Certification?
 - Stakeholders did not support the idea that third party certification be mandated by legislation.
 - Some reports have asserted that consumers assume that marketed products are vetted by FDA
 - Educate consumers with a “Got Milk”-like campaign for DSs
 - Quality seals should indicate verification and URL for more information on the basis for the verification.
 - Separate quality assurance and excellence from drug spiking discussions.
 - Ensure all companies are using the same measuring stick for GMP compliance

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

USP Roundtable on Pesticide Residues in Dietary Supplements

December 7, 2016

Good Manufacturing Practices for Dietary Supplements in 21 CFR 111 require manufacturers to control contaminants, but do not set out specific methods or maximum residue limits. Since dietary supplements (DS) in the United States are regulated as a subset of foods, the U.S. limits for pesticides in botanical dietary supplements are set to the same levels as those for food crops by the Environmental Protection Agency (EPA). Although EPA establishes pesticide limits, the U.S. Food and Drug Administration (FDA) is responsible for enforcing them. FDA action levels are determined on a case-by-case basis. In the absence of EPA-established limits for an article, or an express exemption from the need for a limit, zero tolerance is applied when an ingredient is marketed as a food or as a dietary supplement.

USP General Chapter <561> *Articles of Botanical Origin* provides limits for common contaminants, including pesticides, aflatoxins, and elemental impurities, but compliance with USP limits is sufficient for botanical drugs, , and not when the same ingredient is labeled for use as a dietary supplement. USP published a **Stimuli article** (*Pharmacopeial Forum* 42(2) March 1, 2016) 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.

Following upon the comments for the Stimuli article, USP also organized a roundtable discussion with stakeholders on December 7, 2016, with the specific goal of exploring science-based solutions to the issue of pesticide residues in botanical dietary ingredients and dietary supplements in the majority of cases where EPA-tolerances have not been established. Stakeholder input was collected on complex issues related to the regulatory requirements, experiences with USDA's 5% of EPA tolerances for organic crops, toxicological basis for crop specific pesticide limits, non-point source pesticide contamination of wild crops, risk-based testing, analytical method challenges, and harmonization across pharmacopeias. Participants included governmental policy makers and regulators (FDA, EPA, USDA National Organic Standards Board (NOSB), Health Canada, Canadian Food Inspection Agency), independent laboratories, trade associations, botanical ingredient suppliers and manufacturers of botanical dietary supplement products and botanical drug products. The participants discussed the need for a science-based approach for establishing pesticide residue limits in botanical dietary supplements considering the challenges from the current paradigm of crop-specific limits, which have not been set by the EPA for most of the commonly used herbs of commerce.

Major outcomes from the roundtable:

- ▶ Non-point source pesticide contamination observed in organic crops as well as in wild-collected botanicals illustrates that a zero-tolerance approach is not rational, and that science-based standards could provide a framework to establish toxicologically sound limits.

- ▶ The current paradigm of crop-specific limits which have not been set by the EPA for most of the commonly used herbs in commerce should be corrected through science-based approaches such as the pharmacopoeial standards of the USP and PhEur.
- ▶ Participants highlighted the contrast between the way the exposure to contaminants, such as lead and residual solvents, are controlled on a toxicological basis, irrespective of the source of exposure, versus the crop-specific basis for pesticide residues.
- ▶ The *USP* limits for other types of contaminants (<467> *Residual Solvents*; <2232> *Elemental Impurities*; <561> *Aflatoxins*, <2023> *Microbiological Attributes*) are based on toxicological considerations. Such a science-based approach could be adopted for limiting pesticide residues in botanical dietary supplements to address the challenges posed by the current paradigm of crop-specific limits, which are lacking for most of the commonly used herbs of commerce.
- ▶ The role of compendial standards with regard to pesticide residue limits in the USP, which are applicable to botanical drugs, but not to the botanical dietary supplement ingredients.
 - ▶ It was suggested that the EPA or FDA amend their regulations to incorporate by reference the *USP* as an acceptable compendium for determining pesticide residue contaminants on all articles of botanical origin.
 - ▶ It was also suggested by an FDA attendee that pesticide residues detected on a botanical that is certified organic cultivated or wild collected could be considered to be a contaminant rather than an additive meaning that EPA tolerances are applicable to specific crops where the pesticide chemical has been intentionally applied. Regulators could view nonpoint source pesticide contamination of wild crops differently than detection of crop-specific pesticide residues within EPA-established tolerance.
- ▶ Case studies of enforcement actions based on zero tolerance illustrated the impact to the industry and international commerce. Establishing limits for pesticide residues involves consideration of analytical method challenges related to complex botanical matrices, and harmonization across pharmacopoeias to facilitate international commerce.
- ▶ General MRLs (maximum residue limits) are desirable for limiting pesticide residues in crops for which EPA or *USP* limits are not set, in way similar to how limits are set out in the Canadian and European regulations.
 - ▶ FDA Compliance Program Guidance Manual (CPG): Pesticides and Chemical Contaminants in Domestic and Imported Foods-CP7304.004, could be a place to define the general MRL. In relevant part, the CPG states “The sample containing a confirmed residue for which no tolerance or guideline in the sampled food has been established, but the residue level is such that it requires no follow-up (e.g. residue found at trace levels).”

Following the roundtable discussion, USP committed to the following activities to elevate the issue and initiate a dialogue towards finding science-based solutions:

- Collection of information on non-point source of contamination from manufacturers and testing labs
- Revision of the pesticide list, limits and methods section in General Chapter <561>
- Meetings with EPA, FDA, USDA, NOSB and others to advocate for USP standards as a part of the solution
- Development of a manuscript on the subject for publication in the [Food and Drug Law Journal](#)
- Participation in professional conferences:
 - [The Toxicology Forum](#), Washington, DC (Feb, 2017)
 - [International Conference on the Science of Botanicals](#), Oxford, MS (April, 2017).
 - [MRL Workshop](#), San Francisco, CA (May, 2017)

Stakeholder engagement is invited to develop science-based solutions to this important issue.

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 pesticide¹ 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 detection³ 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 crops⁵ 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 requirement⁷. 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:

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

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

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:

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

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:

$$\text{Limit} = A \times M \times E/100B$$

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 FFDCFA. 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 <i>USP–NF</i> Monographs	EPA Tolerances
Acacia (<i>Acacia senegal</i> or other related African species of Acacia)	No

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

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

[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 <i>cis</i> -, <i>trans</i> -, and oxychlordane)	0.05
Chlorfenvinphos	0.5
Chlorpyrifos-ethyl	0.2
Chlorpyrifos-methyl	0.1
Chlorthal-dimethyl	0.01
Cyfluthrin (sum of)	0.1
λ -Cyhalothrin	1
Cypermethrin and isomers (sum of)	1
DDT (sum of <i>o,p'</i> -DDE, <i>p,p'</i> -DDE, <i>o,p'</i> -DDT, <i>p,p'</i> -DDT, <i>o,p'</i> -TDE, and <i>p,p'</i> -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 CS ₂)	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, <i>cis</i> -heptachlorepoide, and <i>trans</i> -heptachlorepoide)	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 <i>N</i> -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 methylpentachlorophenyl 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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^a See *Appendix* for a list of Expert Committee members and USP staff.

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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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**USP Roundtable:
Incorporating Accurate, Reproducible, and Reliable DNA Methods into the USP
for the Identification of Botanical Articles and Determination of Quality
Products**

May 26, 2016

Summary of Meeting Notes

Draft for Circulation

Meeting Goals and Anticipated Outcomes

- Discuss the issues (i.e. scientific, quality, public health, etc.) related to the application of DNA technologies for identifying botanical ingredients.
- Discuss and identify criteria for determining the appropriate use of DNA methods for botanical identification purposes.
- Discuss what current DNA technologies are available to address botanical identification whether they meet the criteria determined.
- Discuss the validation parameters (i.e. accuracy, reproducibility, specificity, and others) applicable to DNA methods for botanical identification.
- Determine next steps that USP or others should take to incorporate validated DNA methods into USP standards for the identification of botanical articles and the other roles USP can play related to DNA methods for botanical identification (i.e. database coordination, sequence repository, etc.).

Current Status: Can current DNA methods fit within existing regulatory requirements for determining the identity of botanical ingredients?

This segment of the discussion was initiated by several participants providing brief introductory comments regarding important considerations for whether and how current DNA methods meet the regulatory requirements for botanical ingredients to comply with the current Good Manufacturing Practices (cGMPs) (21CFR111.75(a)(1) and 21CFR320) and how the industry is utilizing DNA methods for determining the identity of botanical ingredients. Key themes from the discussion among all participants are outlined below.

- **DNA methods can be used to comply with regulatory requirements for cGMPs for the identification of botanical ingredients and articles so long as they are appropriate for their intended use.**
 - USP held a workshop with the U.S. Department of Agriculture (USDA) in October 2014, where it was clarified that so long as the requirements under GMPs (21 CFR 111.320) are met, DNA methods can be used for botanical ingredient identification. This section requires that manufacturers verify that the laboratory examination and testing methodologies are appropriate for their intended use.
 - FDA used DNA methods for botanical identification as well as detection of adulteration.
 - DNA methods are seen as a complement to other methods and one of many tools for identifying botanical ingredients.

- The DNA method is not appropriate for its intended uses as the only method for identification of botanical ingredient, the method can be used in conjunction with chemical chromatographic and botanical morphological (macroscopic/microscopy) methods.
- **Industry use of DNA methods for determining the identity of botanical ingredients.**
 - **Impact of processing on success of DNA methods**
 - The less processed a material is the more appropriate the use of DNA methods for botanical identification.
 - The more processed the material is, the more difficult it is to extract intact DNA and the fresher the material is, the easier it is to extract DNA. Typically, processing/solvent extraction damages DNAs of plant materials.
 - Also, the type of processing done impacts the ability to extract DNA. For example, steaming affects the ability to extract DNA, while grinding up does not.
 - Questions to explore: At what points in the processing phase (i.e., from raw materials to finished product(s)) are DNA methods more or less appropriate for identifying botanical ingredients, and independently or in combination with other methods (i.e., chemical chromatographic and botanical morphological)?
 - **Impact of type of material on success of DNA methods**
 - DNA methods are used by manufacturers to identify botanical ingredients in powdered materials more often than in extracts.
 - When used on extracts, DNA methods may work well with raw material water extracts, but do not work well with organic solvent (usually ethanol) extracts.
 - DNA methods have been particularly successful for identifying fungi.
 - **Impact of plant part on success of DNA methods**
 - DNA methods are simple when the DNA is extracted from the flower, leaf, or stem of the plant, rather than the roots and bark of the plant.
 - **DNA methods as a qualitative and/or quantitative test**
 - DNA methods can be used to identify/verify the species of the botanical ingredient, but traditional chemistry and morphological methods are needed to determine what part of the plant the botanical ingredient is from.
 - Mini-barcoding which examines single nucleotide polymorphism (SNP) from multiple regions within the genome may help identify the geographic origin of an ingredient.
 - DNA method testing is a qualitative test to identify the presence of a particular botanical ingredient or adulterant, so in terms of identifying whether a specimen has been contaminated according to quantitative concentration levels, other methods should be used.
 - DNA methods are useful for determining the botanical origin of an ingredient, but do not specifically identify the botanical ingredient (i.e. DNA methods can determine if an ingredient is from an apple tree, but cannot specifically identify if the ingredient is apple fruit or apple leaves).

- DNA methods can be used in a quantitative manner by counting the frequency of a gene in a sample and calculating the fractional representation of that gene within the sample. The science of quantitative testing is in evolution.
- DNA methods are also used in a quantitative manner in metagenomics. Such as when FDA traced foodborne pathogens back to a particular produce field by measuring microbial loads in different produce fields.
- **DNA extraction methodologies**
 - Different DNA extraction methodologies are needed for different kinds of plant matrices. Research communities should share information on the effect of matrix on the extraction method.
 - Different plant parts need different DNA extraction methodologies.
 - DNA barcoding may not work for some botanical products where processing methods in manufacturing might result in degraded DNA regions which may be necessary to conduct DNA barcoding.
 - Polymerase chain reaction (PCR) methods may work well and may allow for quantification.
 - How and where DNA extraction processes are conducted is important, so that practitioners do not introduce new adulterants.
 - Different DNA extraction methods have different costs.
- **Practical realities of DNA methods**
 - Many manufacturers outsource contract labs to do the DNA method testing.
 - Botanists and taxonomists should be involved in the process.

Current Status: Scientific and quality issues related to the application of DNA technologies for identifying botanical ingredients.

Participants introducing this discussion identified and discussed important scientific and quality issues related to the application of DNA technologies for identifying botanical ingredients that should be explored. The key points that emerged from discussion among the full group are outlined below.

- **Consistency with other identification methods**
 - Manufacturers observed that DNA methods produce results that are consistent with compendial methods.
 - Manufacturers have been successful with correlating DNA, chemical testing, and physical testing methods; however, depending on how processed the natural ingredient is, the type of ingredient it is (i.e. 84% consistency rate for identifying ginkgo, as opposed to other kinds of ingredients more difficult to detect), and from where in the plant the particular botanical ingredient is derived (stem/leaf/flower vs. root/bark) it can be more difficult to align these three methods.
- **False positive or false negative results**
 - DNA methods can produce false positive and false negative results.
 - Studies have found that DNA methods have reliability rates of between 70% and 80% for identifying botanical ingredients.
- **Detection of adulterants**
 - Validated DNA methods can and should be used with other types of identification methods, such as chemical and physical testing methods. DNA methods are good for

identifying whether or not species/adulterants are present, but it is best to use with a chemical testing method for quantifying the amount of species or adulterant that is present.

- DNA methods are not suitable for identifying chemical adulterants.

Criteria for determining the applicability and suitability of DNA methods for botanical identification

Using the earlier discussions as a basis for their suggestions, participants next identified criteria that should be used for determining the applicability and suitability of DNA methods for botanical identification. Key comments are outlined below.

- **Applicability criteria for DNA methods**
 - The DNA method should be tailored to the product.
 - The DNA method should be “fit for purpose.”
 - Start with single lab validation.
 - Set standard of reference materials through a “round robin” style validation process for multiple labs.
 - Apply the method validation criteria using USP General Chapter <1225> as a reference.
- **Suitability criteria for DNA methods**
 - DNA methods may be most suitable for fresh, dried, raw, powdered, or tea bag materials.
 - The less processed a material is the more appropriate the use of DNA methods for botanical identification.
 - DNA methods may be more successful if the DNA is extracted from the flower, leaf, or stem of the plant, rather than the roots and bark of the plant.

DNA technologies available to address botanical identification

Participants next discussed what current DNA technologies are available to address botanical identification and described the pros and cons of the available technologies.

- **Appropriate DNA technology use should be determined by:**
 - The appropriate DNA extraction method or methods that should be used.
 - The portion of the botanical ingredient used (i.e., better for leaves and flowers).
 - The relative effectiveness for degree and type of processing of the botanical ingredient.
- **Technologies can perform targeted and non-targeted genome sequencing.**
 - Targeted genome sequencing
 - Use when trying to identify a specific ingredient within a product.
 - Associated with lower costs.
 - However, these methodologies do not generate as effective quantifiable information, at least with the lower cost approaches.
 - Non-targeted whole genome sequencing
 - Use when trying to identify all the ingredients within a product.
 - Generates quantifiable information.

- However, it is associated with higher costs.
- **Available DNA technologies:**
 - Next generation sequencing technologies
 - Polymerase chain reaction (PCR) technologies
 - Microarray-based technologies
- **Pros and cons of available DNA technologies:**
 - The pros and cons are specific to each technology. Several papers describe these pros and cons in detail. However, they can be generally described within the realms of:
 - Extraction method
 - Preparation method
 - Data interpretation
 - Economic burden
 - Adaptability
 - **Next generation sequencing technologies:**
 - Pros:
 - Most successful when using for diagnostics.
 - Lower rates of false positives.
 - Parts of industry use next generation sequencing.
 - Cons:
 - Next generation sequencing would be economically burdensome for some companies within the industry.
 - Next generation sequencing is not used extensively for commercial use.
 - **PCR technologies:**
 - Pros:
 - PCR barcoding is easily adaptable to plants.
 - PCR technologies produce results quickly and are easy to use.
 - PCR technologies come with a good reference library.
 - Cons:
 - PCR technology bias amplifies at different rates.
 - PCR technologies generate a higher rate of false positives than next generation technologies.
 - **Microarray based technologies:**
 - Pros:
 - Microarray based technologies build off many reference libraries.
 - Philo-chip microarray technologies are used routinely by industry so they could be easily adopted.
 - SNP-chip microarray technologies are useful for identifying SNPs which can in turn be used to identify genetic variations within a species.
 - Cons:
 - Microarray based technologies need greater investment before they are ready for wide-spread use.

Validation parameters applicable to DNA methods for botanical identification

Participants also discussed criteria for validation parameters as well as specific parameters that would be applicable to DNA methods for botanical identification. Validation of DNA methods was encouraged

to ensure the methods are accurate, repeatable and specific so that the method could be shared among interested parties.

- **Criteria for validation parameters for DNA methods**
 - There are two approaches to establishing validation:
 - **Prescriptive validation:** Prescriptive-based validation helps to align biases and results in a well-defined solution with a narrow degree of variation. However, this type of method, while increasing consistency, is not necessarily accurate.
 - Prescriptive validation should ensure the method will perform consistently when replicated.
 - **Performance validation:** Performance-based validation establishes consistency with implementation of methodologies and is done through making results transparent, so others can validate them.
 - Transparency should be built into a performance validation system.
 - In proprietary situations, a mechanism is needed to validate the results. One idea is to allow companies to send in a sample for testing, which then generates a report saying whether or not the results are acceptable.
 - USP should develop a validation process that is a blend of prescriptive and performance validations.
- **Validation parameters**
 - **Specimen/Material:** The validation process should ensure that companies and labs are testing the correct voucher specimen.
 - This process should consider and account for geographic differences in specimens.
 - Population sampling and intraspecific variation sampling within voucher specimens is critical for natural health products because in some cases, such as if the specimen is a hybrid species, the test results will not be reliable.
 - **Equipment:** The validation protocols should also describe the appropriate equipment that should be used in DNA testing processes, and including appropriate protocols for cleaning, etc.
 - **Manufacturing Considerations:** Protocols should account for manufacturing processes, and include additional constituents or ingredients added as part of the processing or production of the final product.
 - For example, rice and corn are often used in tablet production processes of pain relief and other medications, and dietary supplements, so these should not be identified as contaminants for these products.
 - **Extraction Protocols:** The validation process should account for the way in which the DNA is extracted.
 - Currently, labs are getting different results because they are unaware of how the DNA is being extracted, which can, in addition to relative success with different extraction methods, also introduce new DNA/adulterants.
 - The validation process should describe the appropriate amount of DNA extracted and type and amount of solvent that should be used.
 - The validation process should also describe the appropriate preparation steps that should be followed.

PCR Protocols: The validation process should account for the PCR process procedures with details and a fixed primer.

- **Sequencing:** The validation protocols should specify a set of practices for sequencing, but that leaves room for the use of multiple methods/technologies.
 - The validation process should specify protocols for targeted vs. non-targeted genome sequencing.
 - A challenge is that the available technologies are always changing, so when a technology changes it may no longer be valid until the parameters are updated.
- **Sensitivity:** The validation process should determine an acceptable level of sensitivity for identifying botanical ingredients, as well as contaminants and adulterants.
 - For example, is 0.1% enough to cause concern, and for which constituents?
- **Data:** The validation process should describe how data should be interpreted.
 - In the case of next generation sequencing technologies, this is an issue of bioinformatics.
 - The DNA methods community should collaborate with the chemical methods community to help with adapting and correlate validation parameters to DNA methods.
- **Account for errors:** Validation parameters for DNA should account for and prevent errors from occurring in the process. Types of errors that should be accounted for include:
 - Human error.
 - Ascertainment bias.
 - Errors specific to particular methodologies.
 - Errors specific to particular technologies (i.e. PCR error and bias).

Next steps for USP

Participants noted that USP could play a role in building transparency into the validation and standard setting process, and that these activities are important due not only because of technical and information needs, but also from policy and political standpoints, and considering state Attorney Generals are heavily involved in this issue.

Potential ideas for USP next steps are listed below.

- **USP could develop guidelines in a stimuli article or in a general chapter for industry to appropriately utilize DNA methods.** Through a public comment process, USP could work with stakeholders to identify and determine validation parameters. This is necessary because currently there is a lack of consistency in the identification results. As part of this:
 - USP should develop a broad guideline that provides flexibility for the use of multiple methods.
 - USP guidelines should coordinate with industry standards (i.e. NIH Genbank, Canada Barcode of Life, etc.).
 - China's public database (<http://tcmbbarcode.cn/en/>) could be used as an example.
- **USP could work with manufacturers, botanic gardens, testing labs, academic institutions, and others to put together a library of vouchers of plants ("safe sets") commonly used in dietary supplements** for industry and lab validation purposes and act as a clearinghouse for sharing this information. As an immediate next step, USP could facilitate a second discussion with

participants from this roundtable on how to best establish this repository and for collecting samples. It may also be important to establish a confidentiality agreement with manufacturer's so that they feel comfortable sharing their samples. As part of this agreement, if USP finds that a manufacturer's results are incorrect, USP (or another partner) will have a confidential discussion with the manufacturer to correct the problem. The library should include:

- A diversity of samples to ensure high-quality testing results (including samples from different geographic regions throughout the world and representing each continent), be well maintained (ensure that the samples are refreshed on a regular basis and retired as needed), be continually updated, be linked to industry activities, and be accessible to industries.
 - Whole genome specimens, a set of validation materials, and negative controls.
- **USP could develop pilot studies for a set of standard methods for identifying specific botanicals, such as ginseng and others, to include in the compendium.** Manufacturers, labs, and others could then use these methods to achieve the same outcomes.
 - **USP could develop guidance for where chemical methods are falling short or are problematic in terms of botanical identification and for which species and adulterants DNA methods are needed** to complement chemical methods.
 - **USP could take the lead in consolidating information from the various DNA libraries** into a single repository targeted for dietary supplements as a reliable resource for researchers and ingredient purchasers. USP could leverage its experience in other similar library resources supplemental to public standards and explore how to apply that experience to DNA libraries.

Adjourn

The meeting adjourned at 3 p.m.

VIA ELECTRONIC SUBMISSION

December 12, 2016

Division of Dockets Management (HFA-305)
Food and Drug Administration
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**Re: Draft Guidance for Industry – Dietary Supplements: New Dietary Ingredient Notifications and Related Issues; Docket No. FDA-2011-D-0376
81 Fed. Reg. 53486 (August 12, 2016)**

The United States Pharmacopeial Convention, Inc. (USP) appreciates this opportunity to submit comments on FDA's revised Draft Guidance on New Dietary Ingredient (NDI) Notifications and Related Issues (Revised Draft Guidance), issued on August 12, 2016. The following pages summarize USP's role in promoting the safety and quality of dietary supplements, through both the development of public standards and the administration of a robust verification program. In this document, we also provide comments on specific sections of the Revised Draft Guidance, highlighting ways in which USP hopes to serve as a resource to FDA, the industry, and the public in improving and maintaining the safety and integrity of the dietary supplement marketplace.

I. The Role of USP as a Standards-Setting Organization in Ensuring the Quality of Dietary Supplements

USP is a scientific nonprofit organization that sets standards for the identity, strength, quality, and purity of medicines, food ingredients, and dietary supplements that are manufactured, distributed, and consumed worldwide. USP's standards and programs are informed by global expertise from industry, academia, and regulatory authorities. USP's headquarters are in Rockville, Maryland, and we have facilities in India, China, Brazil, and Ghana, as well as offices in Switzerland, Indonesia, Nigeria, Ethiopia, and the Philippines.

Founded in 1820 with a public health mission, USP has direct experience in facilitating activities and programs that improve the safety and quality of dietary supplements in the United States. Specific to this sector, we discuss the role that USP has played in: (1) the establishment of science-based public quality standards for dietary supplements and dietary ingredients; and (2) the establishment of a verification program that helps manufacturers and distributors ensure and communicate the quality and purity of their products.

A. Development of Public Standards for Dietary Supplements & Dietary Ingredients

The enactment of the Dietary Supplement Health and Education Act of 1994 (DSHEA) and FDA's promulgation of good manufacturing practice (GMP) regulations for dietary

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supplements represented significant developments in the industry. Under DSHEA, USP standards are binding for manufacturers who label their supplements as compliant with USP specifications.¹ Additionally, because USP's science-based specifications aim to help ensure product quality and promote transparency, many parties in the dietary supplement industry voluntarily comply with our standards and use USP monographs as the basis for specifications in their contractual agreements. USP holds the view that broader use of science-based public standards – in combination with GMP compliance – can help ensure the quality and consistency of dietary supplements, as is the case for medicines.²

USP develops public standards, known as monographs, for dietary ingredients and dietary supplements that include test procedures and acceptance criteria to ascertain the quality, purity, identity, and strength of monographed articles. The monographs, associated analytical methods, and guidelines for their use are published in the *United States Pharmacopeia–National Formulary (USP–NF)*, which contains standards for drug substances, excipients, medical devices, and dietary supplements,³ and in the *Food Chemicals Codex (FCC)*, which contains standards for food ingredients.⁴ USP also publishes the *Dietary Supplements Compendium (DSC)*, a comprehensive resource for dietary supplement manufacturers and ingredient suppliers. The *DSC* is a compilation of monographs, legal and regulatory excerpts, FDA guidance documents, and reference tools relevant to the dietary supplement supply chain.⁵

USP prioritizes the development of dietary supplement monographs based on market prevalence, knowledge of chemical composition, existence of other pharmacopeial standards, interest from a government body, and potential health risks, among other factors. The admission evaluation process for introducing new dietary supplement monographs into the *USP–NF* involves the analysis of safety information from numerous sources, including adverse event reports from FDA MedWatch. This assessment is conducted for the sole purpose of determining whether or not to develop a *USP–NF* compendial monograph and is not designed to be a determination of the intrinsic safety or efficacy of the ingredient or product under review. Nevertheless, the due diligence involved in the review process is designed to exclude ingredients that present serious risks to health.⁶ Thus, USP's admission evaluation shares some objectives with the NDI Notification review process.

¹ 21 U.S.C. § 343(s)(2)(D).

² See, e.g., Schiff PL Jr., Srinivasan VS, Giancaspro GI, *et al.* The development of USP botanical dietary supplement monographs, 1995-2005. *J Nat Prod.* 2006; 69(3):464-72. See also Miller RK, Celestino C, Giancaspro GI, Williams RL, FDA's dietary supplement CGMPs: standards without standardization. *Food Drug Law J.* 2008;63(4):929-42; Sarma N, Giancaspro G, Venema J, Dietary supplements quality analysis tools from the United States Pharmacopeia. *Drug Test. Analysis* 2016; 8(3-4):418-23.

³ See <http://www.usp.org/usp-nf>.

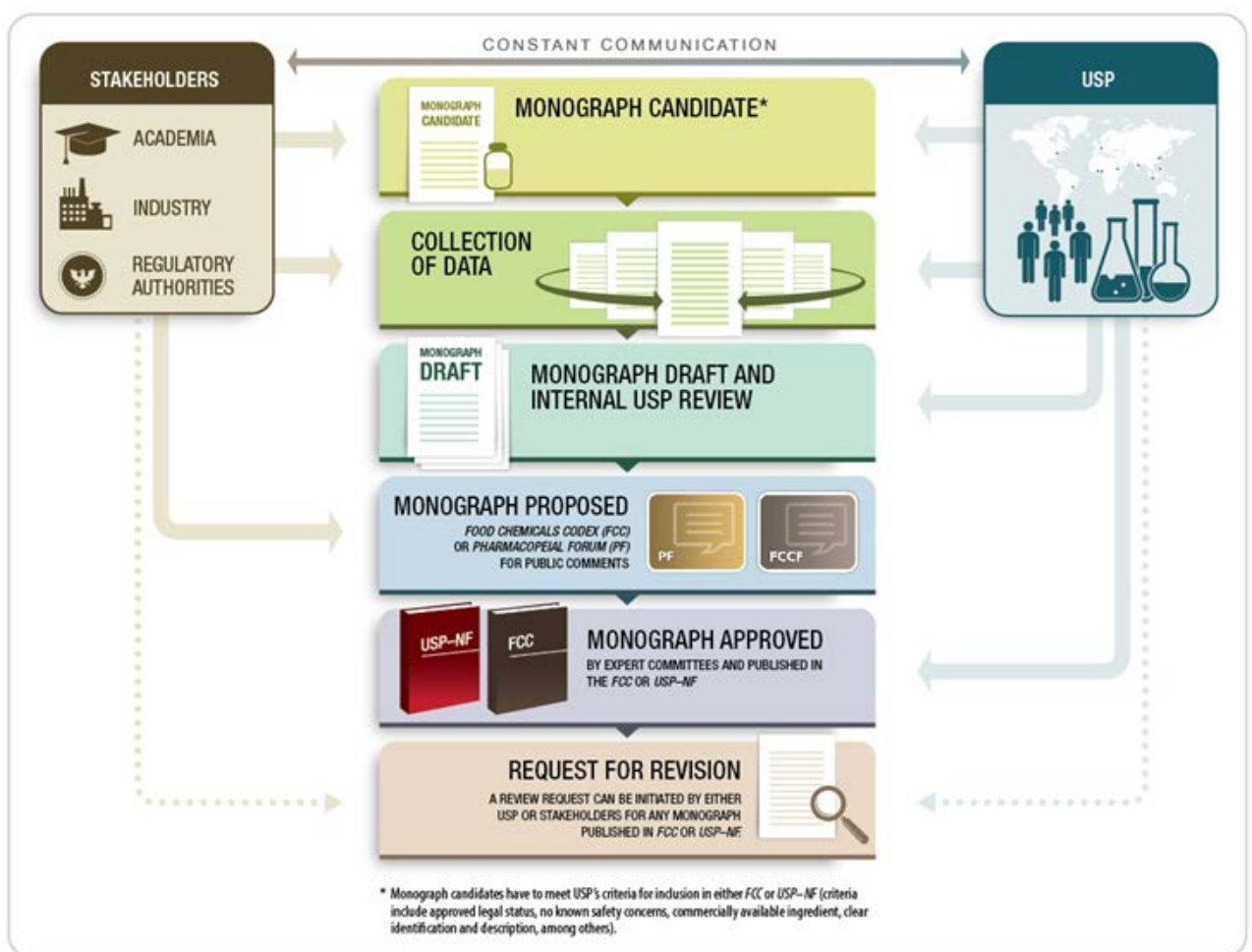
⁴ See <http://www.usp.org/store/products/food-chemicals-codex-fcc>.

⁵ See <http://www.usp.org/store/products/dietary-supplements-compendium>.

⁶ For additional detail, see USP Guideline for the Admission of Dietary Supplement Ingredients to the *USP–NF* Monograph Development Process (Effective date 03/30/2016), available at:

To develop public standards, USP works with expert volunteers from a wide cross-section of stakeholders including industry, academia, and regulatory authorities. Monographs are developed after an open and transparent public comment process in which the expert volunteers, assembled into Expert Committees, consider the existing evidence and evaluate comments and feedback from manufacturers, regulators, suppliers, and other interested parties. Ultimately, the goal of this process (shown in Figure 1) is to ensure that the outcome is based on scientific evidence and serves the public health interest.

Figure 1: USP’s Monograph Development Process for Dietary Supplements and Dietary Ingredients



In addition to developing monographs, USP leverages its scientific capabilities and its work with expert volunteers to develop broader guidelines that further promote dietary supplement safety. These guidelines are found in USP’s General Chapters, which provide

http://www.usp.org/sites/default/files/usp_pdf/EN/dietarySupp/guideline_for_the_admission_of_dietary_supplement_ingredients_to_the_usp-nf_monograph_development_process_final.pdf.

principles and analytical methods intended to assist the industry and regulators in ensuring the quality and purity of supplements.⁷

To complement the documentary standards, USP also develops and offers Reference Standards for dietary supplements and dietary ingredients. Reference Standards are highly characterized substances intended for use in monograph-prescribed analytical procedures in support of established specifications. USP's current catalog contains more than 300 Reference Standards for dietary supplements, e.g., amino acids, botanicals, vitamins, minerals, purified compounds, complex carbohydrates, and fish oils.

B. Dietary Supplement Verification Program

USP also offers and administers an innovative, voluntary Dietary Supplement Verification Program (DSVP), which complements our efforts to promote dietary supplement quality standards.⁸ Launched in 2001, the DSVP is intended to help dietary supplement manufacturers meet FDA's GMP requirements as well as USP's additional supplement manufacturing guidelines. The latter include recommendations of particular interest to retailers, such as recall procedures, expiration dates supported by stability data, and identity testing for all – not just dietary – ingredients (codified in General Chapter <2750> *Manufacturing Practices for Dietary Supplements*).

As part of the DSVP offering, USP conducts a rigorous audit – including an on-site inspection – of a supplement manufacturer's operations. USP scrutinizes documentation and examines quality management, facilities and equipment, materials, production, packaging and labeling, and laboratory control. USP also conducts follow-up surveillance auditing and product testing to ensure continuous adherence to high quality standards. Successful verification enables a manufacturer to include the official USP Verified Mark on the labels and labeling of products that have met all requirements of the verification process. To date, more than 100 dietary supplement formulas have received the USP Verified Mark, representing several major brands and retailers.⁹

II. Comments on FDA's Revised Draft Guidance

We appreciate FDA's issuance of the Revised Draft Guidance. Our comments are intended to highlight specific areas in which USP can offer support and assistance to the Agency and to the industry in the promotion of dietary supplement and dietary ingredient quality. We address these points in turn below.

⁷ See Section II.A. of these comments for references to specific General Chapters that may support the dietary supplement industry.

⁸ For additional information about the DSVP, see <http://www.usp.org/verification-services>.

⁹ See USP Verified Products Listing, available at: <http://www.quality-supplements.org/verified-products/verified-products-listings>.

A. Integration of USP Standards into Revised Draft Guidance

USP thanks FDA for recognizing the role that public standards can play in the NDI Notification process. Specifically, FDA cites the following three USP General Chapters in its example of a specification sheet or table for a dietary ingredient:

- <61> *Microbial Examination of Nonsterile Products: Microbial Enumeration Tests*: provides a series of tests designed primarily to determine whether a substance or preparation complies with an established specification for microbiological quality.
- <791> *pH*: provides guidelines for determining the pH of particular substances.
- *USP 30 <231> Heavy Metals*: provides methods to demonstrate that the content of certain elemental impurities does not exceed the limits specified in individual monographs.¹⁰ Effective January 1, 2018, <231> will be omitted, and all dietary supplements purporting to conform to USP specifications must meet the requirements in <2232> *Elemental Contaminants in Dietary Supplements*.¹¹ USP continually strives to keep monographs and General Chapters up-to-date, and standards may be omitted, replaced, or modernized over time.

USP's resources encompass significantly more than the three General Chapters highlighted above. Specifically, individual monographs for dietary ingredients include:

- An identity specification for each component;
- Component specifications necessary to ensure that specifications for the quality, purity, strength, and composition of dietary supplements manufactured with those components are met; and
- Limits on contaminants that may adulterate or may lead to adulteration of the finished product.

Also within USP's compendia, the following General Chapters may be particularly useful, as some of them are specific to dietary ingredients or dietary supplements:

- <467> *Residual Solvents*: provides guidelines detailing acceptable amounts of residual solvents in products intended for human consumption.
- <561> *Articles of Botanical Origin*: describes sampling procedures intended to reduce the effect of sampling bias on qualitative and quantitative results when analyzing botanical constituents.
- <563> *Identification of Articles of Botanical Origin*: provides guidelines for establishing the identity of botanical ingredients using orthogonal methods including macroscopic, microscopic, chromatographic, and DNA methods.

¹⁰ See Revised Draft Guidance, at page 58 (Section VI.A.5, Table 2).

¹¹ Some individual monographs for dietary ingredients will continue to specify limits for elemental contaminants using more up-to-date analytical procedures as described in <233> *Elemental Impurities—Procedures*.

- <565> *Botanical Extracts*: describes principles of extraction for articles of botanical origin.
- <2021> *Microbial Enumeration Tests—Nutritional and Dietary Supplements*: describes tests for estimating the number of viable aerobic microorganisms present in nutritional supplements, from raw materials to finished products.
- <2022> *Microbiological Procedures for Absence of Specified Microorganisms—Nutritional and Dietary Supplements*: provides tests for specific microorganisms, as specified in individual monographs or whose absence from nonsterile nutritional and dietary products is recommended in General Chapter <2023> (described immediately below).
- <2023> *Microbiological Attributes of Nonsterile Nutritional and Dietary Supplements*: describes guidelines for establishing Good Manufacturing Practices for microbiological specifications, including microbiological process control, control of the bioburden of raw materials, and control of the manufacturing process.
- <2030> *Supplemental Information for Articles of Botanical Origin*: provides additional information about several aspects of botanical articles, including optimization of pre-harvest conditions for appropriate growth and post-harvest handling to achieve consistent quality with minimum variations in the composition of chemical constituents.
- <2040> *Disintegration and Dissolution of Dietary Supplements*: provides quality-control tools to assess performance characteristics of dietary supplement finished dosage forms.
- <2251> *Screening for Undeclared Drugs and Drug Analogues*: describes analytical methodologies for screening dietary supplements to detect adulteration with synthetically derived pharmaceutical active principles.
- <2750> *Manufacturing Practices for Dietary Supplements*: provides overarching guidance that complements FDA’s GMP requirements to address quality control in dietary supplement manufacturing.

Beyond the context of NDI Notifications, USP standards can play a meaningful role in establishing the identity of any dietary ingredient for which a USP monograph exists. In the Revised Draft Guidance, FDA clarifies that an NDI Notification is not required for an NDI that: (1) is a direct food ingredient or approved food additive; (2) has been used in conventional foods; and (3) is to be used as a dietary ingredient without chemical alteration.¹² Because this exemption can result in the marketing of NDIs without notification to FDA – and in some cases, these substances may be fairly novel candidates even in the conventional food supply – USP would like to explore further with the Agency the public health significance that a compendial quality standard may have in these cases to help ensure the identity and purity of such materials. As a specific resource, *FCC* monographs and analytical methods – some of which cover ingredients that are

¹² See Revised Draft Guidance, at page 23 (Section IV.B.2). See also 21 U.S.C. § 350b(a)(1).

“generally recognized as safe” (GRAS) or that are approved food additives – may play a role in helping to ensure the safety and quality of dietary ingredients initially marketed as conventional foods.

To the extent that it is helpful, we encourage the Agency, industry, and other stakeholders to consider further and more specific integration of USP standards and similar globally recognized standards into current practice, and we stand ready to assist those who would like to do so.

B. The Role of USP Monographs in Assessing the Significance of Manufacturing Changes

USP appreciates FDA’s view that changes in the manufacturing process must be assessed to determine the appropriate regulatory classification of a dietary ingredient. In the Revised Draft Guidance, FDA indicates that certain changes to the manufacturing process for a dietary ingredient marketed in the U.S. prior to October 15, 1994 – i.e., an “old” dietary ingredient – may convert that substance into an NDI.¹³ Specifically, FDA states that “[a]ny changes in [the] manufacturing process that alter the identity of the ingredient will convert a previously marketed dietary ingredient into an NDI.”¹⁴ An exhaustive assessment of various manufacturing techniques and their potential impact on dietary ingredients is beyond the scope of these comments. However, we wish to highlight the potential utility of compendial specifications in assessing the relevance of manufacturing changes with respect to dietary ingredients for which USP monographs exist.

As indicated above, USP monographs include detailed criteria related to the identity of a particular dietary ingredient, including component specifications and limits on contaminants or impurities. From a scientific standpoint, this means that dietary ingredients that meet USP monograph specifications should be considered substantially equivalent, regardless of manufacturing method. Even where an “old” dietary ingredient is manufactured using a “new” method – i.e., a manufacturing method different from those used to produce the same ingredient prior to October 15, 1994 – USP monograph compliance may provide evidence, where applicable, that the change in the manufacturing method does not “alter the identity of the ingredient” in a manner that converts it to an NDI. This concept also applies to NDIs that are the subject of successful Notifications to FDA. Compliance with an existing USP monograph provides evidence that the dietary ingredient conserves its identity regardless of its method of manufacture or who manufactures it—subsequent NDI Notifications would not be needed.

C. The Role of USP Monographs in Assessing the Impact of Chemical Alteration

We appreciate FDA’s desire to provide guidance on which processes result in “chemical alteration” of articles of food present in the food supply. In the Revised Draft Guidance, FDA clarifies its views on the types of processes that the Agency is likely to view as

¹³ See *id.* at pages 20-21 (Section IV.A.12).

¹⁴ *Id.* at 21 (underlined emphasis added).

producing chemical alteration of an article of food present in the food supply.¹⁵ FDA also lists the “[u]se of solvents other than water or aqueous ethanol to make an extract or tincture” among its examples of processes that are likely to result in chemical alteration and affect the safety profile of a dietary ingredient.¹⁶ We appreciate the Agency’s concern that certain processes may produce chemical alteration capable of affecting the safety of a dietary ingredient. However, the use of solvents other than water or aqueous ethanol to make extracts or tinctures does not necessarily result in chemical alteration. Conversely, water extraction is not always solely a “physical step,” as extraction with hot water or steam may induce more hydrolytic reactions than extraction with an aprotic solvent such as hexane or supercritical CO₂. For reasons such as this, it is difficult to set broadly applicable guidelines outlining processes that would always result in chemical alterations of significance to FDA, i.e., alterations that adversely affect the safety profile of a substance when manufactured using an alternative method.

USP’s view is that increased reliance on science-based public standards, such as USP compendial specifications, can help alleviate this concern while eliminating the need to scrutinize individual manufacturing processes. USP monographs for dietary ingredients establish the identity of such substances with respect to the criteria relevant to safety and public health, such as quality and purity. Monographs for botanical extracts also require compliance with limits for residual solvents as specified in General Chapter <467> *Residual Solvents*. Thus, to the extent that a dietary ingredient – such as a botanical ingredient extracted with the use of supercritical CO₂ – complies with the applicable monograph, FDA and the industry can have confidence that a modification that may result from a process change does not result in a “chemical alteration” that affects the article’s safety profile when compared to its “chemically unaltered” counterpart in the food supply. We encourage FDA to adopt a broader and more flexible interpretation of the concept of “chemical alteration” that will permit the industry, where applicable, to use USP monographs or similar globally acknowledged public standards to conclude that a substance is substantially equivalent to the article present in the food supply, which is the key determination needed to protect public health.

D. The Value of USP Monographs for Synthetic Botanicals

We understand FDA’s views regarding the positioning of synthetic botanicals as dietary ingredients. We defer to FDA’s interpretation of the relevant legal provisions. From a scientific standpoint, we encourage the Agency to consider the value that USP and similar globally acknowledged public standards can provide in ensuring that nature-derived and synthetic botanicals have common specifications and standards for safety and purity. To the extent that FDA’s position may be influenced by concerns that synthetic botanicals may have different safety profiles than botanicals derived from nature, USP and other globally acknowledged compendial standards can play a role in promoting parity across sources. Where a USP monograph exists, it serves as a benchmark for quality and purity that applies generally to the substance, regardless of whether it has been naturally derived or synthesized.

¹⁵ See *id.* at pages 25-28 (Section IV.B.4-5).

¹⁶ *Id.* at 25.

E. The Role of USP Monographs in Reducing the NDI Notification Burden, Increasing Transparency, and Promoting Public Health

FDA indicates that as part of the NDI Notification process, the Agency will permit the submission of a confidential “master file” containing “manufacturing, specifications, and other identity information needed to completely describe the ingredient.”¹⁷ The submitter of the master file could then authorize other firms to reference the contents of the master file in subsequent Notifications. FDA notes its expectations that submitters will consider the contents of NDI master files and ingredient specifications to be trade secrets and thus will only discuss these data with the submitting firm.

We encourage the Agency to recognize that the existence of USP standards and similarly well-known and accepted standards may help alleviate the NDI Notification burden, as downstream submitters can easily reference public standards as the basis for identity criteria. Insofar as a dietary ingredient is described by an applicable USP (or similar globally accepted) monograph, we encourage FDA to view this as an opportunity to reduce regulatory review burden and avoid potentially unnecessary requests of the Agency. As part of USP’s ongoing education and outreach efforts toward industry stakeholders, we will encourage the continued submission of candidates for USP monograph development in the dietary supplement sector. In our view, all parties will share the public health benefits and administrative simplicity of relying on readily available, transparent public standards to supply the necessary identity specifications for NDIs.

We thank FDA for the opportunity to submit comments on the Revised Draft Guidance. We hope that these comments serve as a helpful resource to the Agency and to the industry and that they help clarify the role that USP and its compendial resources can play in promoting the safety and quality of dietary supplements.

We hope to work collaboratively with FDA and with the industry in this area, and we stand ready to provide any additional information that may be helpful to the Agency as you consider additional stakeholder comments and work to finalize the Revised Draft Guidance. Please feel free to contact Gabriel Giancaspro, Ph.D., Vice President, Science—Dietary Supplements and Herbal Medicines, at (301) 816-8343 or gig@usp.org with any inquiries related to these comments or to USP’s efforts in the dietary supplement area.

Sincerely yours,



Jaap Venema, Ph.D.
Executive Vice President and Chief Science Officer

¹⁷ *Id.* at pages 28-29 (Section IV.C.1).



**Bringing USP Dietary Supplement Standards Up-to-Date
Roundtable Discussion
Tuesday, October 25, 2016
USP–U.S., Rockville, MD**

***Co-Chairs: Paula Brown, Ph.D., Aniko Solyom, Ph.D.
Scientific Liaisons: Anton Bzhelyansky, Huy Dinh
Executive Secretariat Representative: Marie Temple***

Notes–Draft

Goals and Anticipated Outcomes

To seek industry perspectives and input on the status of compendial methodologies, documentary standards, and reference materials for dietary supplement (DS). Keeping these standards up to date is one of USP's most important responsibilities; however, including advanced methodologies should be synchronized with stakeholder capacity for adopting and conforming to modernized standards.

Attendees

Volunteer Members

1. Paula Brown, Member, Botanical Dietary Supplements and Herbal Medicines (BDSHM) Expert Committee (EC)
2. Dennis Gorecki, Chair, Non-Botanical Dietary Supplements (NBDS) EC
3. Robin Marles, Chair, BDSHM EC
4. Eike Reich, Member, BDSHM EC
5. Aniko Solyom, Member, NBDS EC

Government Liaison

Frank Switzer, FDA Liaison to BDSHM EC

Invited Guests

Silva Babajanian, Herbalife International	Hiroshi Mizoguchi, Kyowa Hakko Bio Co., Ltd.
Guillaume Blin (via teleconference), NATUREX Inc.	David Murawski, Church and Dwight Co., Inc.
Michael Blumhorst, ADM	Timothy Murray, Gaia Herbs
Larry Callahan, U.S. Food and Drug Administration	Yoko Obayashi, Ajinomoto North America
Pei Chen, U.S. Department of Agriculture	Catherine Rimmer, National Institutes of Standards and Technology
Lisa Fallon, Church & Dwight Co., Inc.	Janet Roberson, BASF Corporation
Mark Hokenson, Pharmavite	Jeremy Stewart, Gaia Herbs
Holly Johnson, Alkemist Labs	Xun Yan, Amway
Phil Koerner, Phenomenex	Jincai Yang, NBTY, Inc.
Mohamed Koroma, Pharmavite	Kurt Young, Nutra Manufacturing
	Jerry Zweigenbaum, Agilent

USP Staff

Anton Bzhelyansky, Natalia Davydova, Huy Dinh, Gabriel Giancaspro, Maria Monagas Juan, Nam-Cheol Kim, Hellen Oketch, Nandakumara Sarma, Fatkhulla Tadjimukhamedov, Marie Temple, Seong Jae Yoo

1. USP Welcome Remarks

Dr. Gabriel Giancaspro **convened the meeting at 9:00 a.m.** and welcomed attendees. He invited participants to share how they see USP's intent to update Dietary Supplement (DS) standards and share their ideas. Dr. Paula Brown and Dr. Aniko Solyom presided over the meeting.

2. Modernization Framework

Mr. Huy Dinh presented an overview of USP's plans to modernize DS monographs so that they remain current, relevant, and suitable for their intended use. He noted the following opportunities:

- Stakeholder collaborations and global expert panels can present additional avenues for updates and harmonization.
- Sourcing procedures from other compendia, literature, etc. (provided the validation data are made available)
- Use of global USP laboratory facilities to develop and validate procedures

Mr. Dinh also noted the following challenges:

- Prioritization of monographs and chapters in need of updating
- Obtaining procedures and impurity profiles from sponsors
- Formulation of adequate acceptance criteria in monographs
- Balancing the need to introduce modern methodology with the feasibility of global implementation

Discussion

Dr. Aniko Solyom wrote key points on flip charts. The following is a summary of those key points and related discussion (in sub-bullets) grouped by topic.

General Chapters and Monographs

- Provide General Chapters in a separate book, making them portable.
 - The *USP–NF* is too large; it should be separated into two books.
- Make monograph methods electronically searchable.

Monograph Considerations

- Ensure that monograph information is fit for purpose and aligned with regulatory requirements.
- Harmonize with Good Manufacturing Practices and regulatory requirements.
- Include modern methods using current science.
- Consider the impact of monograph changes on regulatory filings.

Communication

- Send automatic electronic notification of relevant *USP–NF* content changes to customers.
 - USP is improving the online product to emphasize revisions to standards.
- Provide an overview of USP's intentions to modernize monographs. This would allow companies to move forward using faster methods; those who cannot afford new methods should be allowed to continue using the older methods.

Flexible Standards

- Standards should be flexible.

- USP does not intend to remove monograph tests that fulfil important diagnostic functions (e.g., pH and melting point).

Method Equivalence, Allowable Adjustments, Alternate Methods

- USP allows alternative methods to be used when they are validated according to General Chapter <1225> *Validation of Compendial Procedures*.
 - Is USP going to re-examine its criteria for method equivalence?
- When USP moves from a packed column to new technology, it is a different chemistry and not a simple calculation to prove equivalence. The scope of changes permitted by General Chapter <621> *Chromatography* is limited.
 - For botanicals, it is frequently a challenge to produce equivalent results using two methods.
 - People are using chemical assay methods for identification purposes.
- Consider the “reverse equivalence” approach, when the advanced compendial procedure could be adapted to the company’s older hardware by conducting a confirmatory equivalence analysis.
- When a company makes a significant adjustment, more than a simple verification is required.

Omission of Old Methods

- USP needs to remove methods that are not used any more (e.g., packed GC columns).
 - Remove wet chemistry tests from the identification section of monographs.
 - Remove the organoleptic methods
 - Nuclear Magnetic Resonance (NMR) can be used for identification.
- Some companies cannot afford new technologies. It is important to retain equivalent old technologies while introducing new.
- USP should reach out to companies using other methods and ask them about the types of equipment they are using.
- It is important to work with trade organizations.
- Companies employing *USP–NF* methods generally defer to older technologies in monographs.
 - A company may still use High-Performance Liquid Chromatography (HPLC) after having purchased Ultra-High-Performance Liquid Chromatography (UHPLC) equipment. Their products may call for both types of equipment.
 - Very old methods should be removed.

Prioritization of Monographs

- How will USP prioritize monographs to be modernized?
- Prioritization criteria could include a risk of ingredient adulteration that leads to a public health issue, its prevalence in the market, and the level of consumption of in products (i.e., how much it is used).
 - USP monitors industry trends and prioritizes monographs for products that have been adulterated.
- Use the USP prioritization matrix (which was adopted by AOAC International).
- Key factors are market share, relevance, and convenience.

Address Adulteration, Consumer Protection

- Old methods frequently lack specificity, and there is the potential that adulterated or contaminated products may not be properly flagged.
- Class-based analytical procedures may be needed to address adulteration with synthetic pharmaceuticals.

- USP needs General Chapters that identify adulterants found in particular product types as well as limit contaminants (e.g., pesticides, residual solvents).
 - USP should collaborate with organizations such as AOAC International, the American Herbal Products Association (AHPA), and Health Canada that have worked on pesticides.
 - Companies should test products that have a high likelihood of adulteration.
 - USP is convening a Roundtable on pesticides on **December 7, 2016**.
- Monograph methods should be able to identify adulteration.

Adulteration Potential Database

- Assemble an adulteration potential database (a database of ingredients or products with a high propensity for being adulterated).
 - There are more data on finished product rather than ingredient adulteration; the latter is rarely disclosed.
- Data sources need to be identified and vetted.
- Chromatograms containing the most widely known contaminants should be included.

Methods

- Replace wet chemistry tests.
- Change Thin-Layer Chromatography (TLC) to High-Performance Thin-Layer Chromatography (HPTLC).
- Change HPLC to UHPLC.
- Include a Principal Component Analysis (PCA)-based identity test.
- Attenuated Total Reflectance FT-IR (ATR-FITR) for analysis of incoming powdered material
- DNA technology
 - DNA has potential, but it should not be used for identification presently.
- Mass Spectrometry (MS)
 - This technology becomes increasingly affordable and has potential of becoming the next analytical workhorse in the labs.
- NMR
 - NMR can be used for identification, and – increasingly – quantitation.
- Inductively Coupled Plasma (ICP) to analyze metals is practically a universally established technique despite the considerable expense and running costs.
- Greener chemistry (UPC Squared) – the use of supercritical mobile phases in chromatography will permit to cut on hazardous solvent use and toxic waste disposal.

Validation of Methods (e.g., DNA test kits)

Impurity Detection Methods for Multivitamin Degradation

- Toxic solvents (see Greener Chemistry above).
- MS-friendly solvents
- Impurity profiles: When USP makes revisions to monograph impurity profile, this affects the industry significantly.
 - The change can affect the approval of a product.
 - The impurity profile is a key issue in identifying the API manufacturer.

Dissolution

- General Chapter <2040> *Disintegration and Dissolution of Dietary Supplements* does not allow the use of sinkers for botanical products.

Reference Standards (RSs)

- Provide information on secondary standards and the conversion factor for their use.
 - USP methods may have preceded the use of RSs currently available.
 - Industry uses secondary RSs as a conscientious cost-cutting decision.
- Decouple the single-entity reference material from the monograph, which would allow faster modernization.
 - USP RSs are developed for use with specific documentary standards.
- Share characterization information with the public.
- Share stability information [USP monitors all RSs through its Continued Suitability for Use (CSU) program].
- Include certified concentration values, potencies, and chromatograms with peaks identified.
- Explain how RS shelf life is established. (USP does not set an expiration date for RSs. The Council of Experts, however, is revising General Chapter <11> *Reference Standards*.)
 - What is USP's process for notifying users that a Reference Standard may have degraded?

Novel Dosage Forms, "Special" Matrices

- For time-release dosage forms, other ways are needed to assess the lifespan of the product in the body.
- Probiotics
 - USP proposed probiotics standards in a PF (*monographs and general chapter*).

Overages

- Include overages in DS finished product, not ingredient, monographs.
 - . A typical DS monograph specifies upper limits of dietary ingredients. The product should contain 100% of label claim at any time.
 - For potent dietary ingredients, the impact of an overage may be very substantial, and – in some cases – even exceed the No Observed Adverse Effects Level (NOAEL).
 - A *PF Stimuli* article discussed ways to establish internal specifications based on variations in manufacturing, stability, and assay. *USP General Notices* state that when a regulatory requirement for a minimum level is different from that in *USP–NF*, a company may shift the range toward the upper limit that the U.S. Food and Drug Administration requires.
- Include science-based overage setting.
- Companies may submit overage specifications to USP, and Expert Committees will make related decisions on a case-by-case basis.

3. Modernization Practice

Discussion

The following is a summary of key points and related discussion (in sub-bullets) grouped by topic.

Continuous Improvement: User Feedback

- USP should document monograph user feedback, make it public, and send responses to commenters.
- Stakeholders may submit comments on *PF* proposals or contact the Scientific Liaison with monograph questions.
- USP captures comments and queries and shares them with the responsible Expert Committee.

- Communication: USP needs to send feedback to commenters and explain why their feedback was or was not used.
- Use modern means of communication to facilitate and stimulate discussion about USP standards.

Search and Replace

- List items (e.g., old methods) to search for in monographs and then consider replacing them.

Harmonization

- Understand the differences between *USP–NF* and *European Pharmacopoeia* monographs.

4. Modern/Emerging Technologies and Tools

Dr. Solyom asked if new technologies could generate faster results comparable to conventional technologies. Dr. Eike Reich provided a presentation on compendial quality beyond market quantitation. He proposed replacing TLC with HPTLC as described in General Chapter <203> *High-Performance Thin-Layer Chromatography Procedure for Identification of Articles of Botanical Origin*; adding HPTLC where TLC is missing; adopting a new format allowing a comparison of multiple samples in the Dietary Supplements and Herbal Medicines Compendia; collaboratively validating several methods, and creating an electronic HPTLC image database.

Discussion

The following is a summary of key points and related discussion (in sub-bullets) grouped by topic.

High-Performance Thin-Layer Chromatography

- Visual vs. numerical comparison
 - It has been traditionally challenging to compare TLC profiles.
 - TLC can be useful, but visual identification has shortcomings.
- The database should be digitized and not rely on visual images.
- When receiving ingredients, HPTLC is one of the frontline techniques for authenticity confirmation.
- HPTLC is preferred over DNA analysis, but some customers are demanding DNA testing (see below).
- Modernize HPTLC to include acceptance criteria (based on multiple samples, cumulative data).
 - HPTLC has two current dedicated General Chapters <203> and <1064> *Identification of Articles of Botanical Origin by High-Performance Thin-Layer Chromatography Procedure*, with numerous monographs referencing the former.
 - USP could use average chromatograms to establish identification acceptance criteria in two monograph families as a pilot.
- Consider automated pattern recognition for signal generation in a multi-dimensional technique.
 - A control would be needed for comparison.
- Envision something other than a monograph (e.g., a database).

Challenges to Incorporating Chemometrics

- How are chemometric models developed?
- Inclusion and exclusion criteria
 - How much variability are we willing to accept?
 - There should be a baseline with a margin of acceptance and a percentage of the internal reference.
- Validation parameters

- Underlying algorithms for determining pass/fail
 - Chemometrics can provide a quick “yes/no” answer.
 - How can we simplify the procedure to best identify positive material?
- Needs to be risk-based

DNA Analysis

- Some customers are demanding DNA testing.
 - Multiplex sequencing of DNA is needed for botanicals. There is a lot of inherent variability, and a range of RSs would be needed.
- DNA should not be used for identification in a monograph because it is not related to pharmacological activity (triggering physiological response).
 - Plants undergo complex cyclical transformations throughout lifecycle, and only at certain stages, the plant-derived product may be pharmacologically efficacious: analysis of plant DNA has no means of assessing this.
- DNA analysis can indicate presence of components that are not adulterants.
 - Full DNA sequencing has limited potential of detecting adulteration or presence of another species.
- DNA testing is used by some companies in place of RSs to identify botanicals – especially where there are no compendial standards available.
- DNA is a piece of the puzzle and eventually could be part of a series of ID tests.
- There is lack of validation, or even agreement on particular techniques, for DNA testing at this time.
- DNA testing could be part of an identification approach for USP Monographs.

New Technologies to Detect Adulteration

Dr. Solyom asked attendees if USP should include new technologies to detect adulteration. Attendees suggested the following:

- Multiple technologies for use on a case-by-case basis
 - Once the anti-adulteration procedure is published, “bad guys” tend to move to other means of adulteration.
 - USP routinely responds to publicized adulteration cases by enhancing the monograph methodologies.
- Validation challenges
- Non-targeted method to identify outliers
 - HPTLC is an example of a non-targeted approach.
 - A company used Quadrupole Time-of-Flight (QTOF), but had issues when trying to compile a database.
 - It could be difficult to transfer Liquid Chromatography-Mass Spectroscopy (LC-MS) libraries between different instruments, in particular, those with different designs and by different manufacturers.
 - More data may reduce the library’s specificity.
- Importance of sample preparation
 - Chemometric software packages exist permitting companies to do samples Class Prediction based on the MSMS profiles of complex samples.
- Limits for unintentional adulteration

Monograph Donor Submission Guidelines

- Companies want to understand the criteria for a method to be accepted for use in a monograph.
 - USP is developing Monograph Donor Submission Guidelines, which may be available after March 2017.

Challenges of Modernized Methods

Dr. Solyom asked how USP modernization would affect the use of USP methods in other countries. Attendees suggested the following:

- USP standards are rarely harmonized with standards in other countries.
 - A company that exports to China and South Korea has found that the Chinese and South Korean methods are not harmonized with *USP–NF*.
 - Ingredient suppliers selling to U.S. companies are commonly using modified USP methods.
- Challenges of complex DSs with multiple active ingredients; the point at which the monograph usefulness is limited
- Low content of chemical markers is a hallmark of botanical ingredients
- Be cautious about requiring the use of expensive technologies.
 - LC-MS provides more information to characterize material, but it is also expensive.
 - Companies do not want to be required to use expensive technologies.

5. Planning the Compendial Future for Dietary Supplements

Discussion: What should USP change about its standards?

Dr. Solyom asked attendees what USP should change about its standards, and attendees suggested the following:

Increase Transparency

- Provide a database that contains background information on USP standards and Frequently Asked Questions from common queries.
 - Share data packages and the analytical information behind monographs.
- Include validation data with a method so that a company knows how much it needs to validate (challenge: confidential proprietary information).
- Provide rationale for including and excluding parts of methods.
- More information should be made public and free of charge.

Content

- Include literature references for methods, where applicable.
- Include HPLC chromatograms (not just relative retention times) in monographs.
- Include pictures of HPTLC plates in monographs.
- Include fragmentation patterns (e.g., total ion chromatogram) for NS methods.
- Include DNA information.
- Consider upgrading units of measurement in monographs.
- Use smaller columns and make incremental changes.

Cost of Reference Standards

- Consider reducing the cost of RSs to discourage use of secondary standards.
 - Consider providing RSs in smaller quantities.
 - The quantity of a USP RS is routinely made sufficient for five complete analyses according to the monograph.

Work With Companies, Organizations

- Harmonization: companies are developing their own methods to fit specific products. USP should be the driving force to help harmonize the methods.
- Seek existing methods adopted by other organizations and trade associations.

6. Wrap-up and Next Steps

USP staff and Dr. Robin Marles noted the following ways that attendees could help USP modernize DS monographs:

- Submit alternative company-developed methods to USP.
- Submit comments on proposals through *PF*.

- Apply to serve on Expert Panels and Expert Committees to provide expertise and drive the change.
- USP would continue bringing its standards up-to-date based on the three attributes: current, relevant and suitable for their intended use
- USP would work to increase transparency in the standards revision processes.
- USP would increase effort to reach out to companies and organizations to harmonize/integrate their own methods with those of USP.
- USP would strive to provide more information about its standards to the public.

The meeting **adjourned at 5:00 p.m.**



Global Expertise
Trusted Standards
Improved Health

Probiotics Roundtable Discussion Summary

November 20, 2015
USP–U.S., Rockville, MD



Utilizing the *Food Chemicals Codex (FCC)* Model to Develop Dietary Supplement Ingredient and Finished Dosage Form Monographs

***FCC* model is to develop monographs at the strain level for the following reasons:**

- Regulatory filings are typically made at the strain level supported by information from clinical studies performed on specific strains. A monograph at the strain level would link the quality attributes to such regulatory filings.
- There is a need for validated methods to identify the specific strains claimed on the labels of articles being offered in the market according to the regulatory filings compared to the full spectrum of strains known to date. Control of consistent manufacturing would be possible at the strain level with this approach.
- The quality of specific strains used in clinical trials would be reflected in USP monographs.

Regulatory Requirements vs. Monograph Requirements

Concerns with monographs at the strain level for DS/Regulatory requirements vs. monograph requirements:

- Current regulatory requirements (GMPs) for dietary supplements include provision for 100% testing for identity of all incoming dietary ingredients.
- The need for a company to fully test by the monograph for identification of each received culture-lot was discussed.
- Participants noted that it may not be cost effective to test according to the monograph specification at strain level 100% of the time.
- Other concerns expressed with strain level: Insufficient strain-specific research, potential loss of the ability to make general non-strain-specific claims on finished dietary supplement serving forms, tests at the strain level not available for every strain, and specificity of the ID tests.
- USP staff mentioned that monographs could be developed at the strain level for ingredients and to the species level for dosage forms.



USP Verification Program for Probiotics

- Attendees asked about the implications of the USP Dietary Supplement Verification Program for probiotics.
- For USP-verified products, the manufacturer has to test 100% of the incoming lots of probiotic ingredients for identity.
- The USP Verification Program verifies the products according to label claims and related manufacturing/control practices; verification would be performed at the level claimed on the label: genus, species or strain.
- Higher testing costs are usually associated with highly specific tests. Testing costs may be reduced as technology evolves. Verification of a dietary supplement containing a single ingredient is more affordable than verification of products containing blends. Verification of specific strain enumeration claims could be costly with current technology.

Developing Two Types of Monographs: Strain and Species Level

- ▶ USP staff asked if it would be useful to have both type of monographs: species and strains.
- ▶ There is virtue in having species protocols to differentiate at that level (i.e.: *L. acidophilus* vs *L. rhamnosus*).
- ▶ It is understood that a strain level monograph is needed to link to specific clinical trials, claims, and regulatory filings.
- ▶ There were proposals to address species level in guidelines, general chapters, or appendices, and keep monographs for specific strains.

- Tests for species could be included in an appendix or general chapter, and strain level specific tests could be included in a monograph. The strain will pass the general tests described in the appendix or general chapter while the specifications remain in the monograph.
- General Chapter <1113> *Microbial Characterization, Identification, and Strain Typing* gives information on testing to genus and species. However, limiting to species level does not mean you can distinguish between different biotypes.
- A strain or species monograph could be developed depending on the type of article in *USP–NF* (ingredients defined at the strain level vs. finished dosage forms defined at the species level, naming suitable strains linked to labeling requirements).

DS Industry Needs—Monograph Standards With or Without Reference Standards?

What is the benefit of getting RSs from USP when thinking of the complexity and specificity of my strains? What is the added value of USP material?

- Considering the PCR primers used for Identification, a company that does not have the knowledge and capabilities may need to source the primers and/or strains for comparison from an independent source.
- USP RSs are collaboratively tested and could be used to ensure primers are correctly validated.
- There was interest from the attendees in USP verifying the primer sets. The RS development process is rigorous and expensive. The sales of RSs need to cover the cost of developing them.
- USP will ask sponsors to consider this as well as the possibility of supplying materials so that users can verify primer sets or PCR system suitability. USP will need industry help with this.

Tests for Pathogens/Contaminant Microorganisms

- These tests are needed for consumer protection because viable microorganisms are derived from fermentation.
- Regulators ask manufacturers to identify appropriate tests.
- Molds should be included.
- Guidance documents exist from Australia Therapeutic Goods Administration (TGA), Health Canada, and National Sanitation Foundation (NSF).
- Listeria testing is not uniform; some consider it a low risk of contamination.
- The Hazard Analysis Critical Control Point (HACCP) approach for contamination testing is followed by some in industry, while others test 100% of production lots.
- Consider that probiotics with a high count may interfere with detection of pathogens.

Quality Control of Finished Dosage Forms (continued)

Mycotoxins

- Mycotoxin contamination is not a common risk factor in the industry. The fermentation broth is heat-treated before inoculation, which makes mycotoxin growth unlikely (along with pH lowering from lactic acid production).
- Contamination could arise from cross-contamination in the fermentation broth. Industry usually relies on information from raw material suppliers.

Strain-specific Enumeration

- Enumeration methods are usually provided by probiotic suppliers. Enumeration tests are designed/validated for a specific strain, but others may grow and compete.
- Identification is made on colonies growing on the medium used for enumeration. Therefore, both identification and enumeration are strain-specific.
- In the case of probiotic blends, enumeration is a challenge and total counts are usually reported. New genomic science will provide methods for the proper enumeration of different strains in a blend.

Enumeration Methodology and Feasibility for Blends (continued)

Current Practices in Blends

- GMPs ensure that the proper strains were used in a blend; this is traceable by production batch records. Strain identification is not usually carried out in blends.
- For every lot released, the total count and contaminants are tested. This is done for raw materials and finished products.
- In the case of mixtures of bacteria of different species, differentiated media could be used.
- Probiotics have unique challenges, so even after packaging some manufacturers will retest again to ensure counts are viable.
- Skip lot testing is not a current practice for probiotics because viable counts are critical. Multiple microbiologists conduct the testing in triplicate.
- In the case of dosage forms, testing for enumeration is more complex because excipients or other polymeric material may need to be removed.

Enumeration Methodology and Feasibility for Blends

Viable but not cultivable bacteria:

- Viability, quantity, and specificity are critical.
 - Flow cytometry is being used for enumeration and new methods are being developed. Not all bacteria can grow on plates; this population can be as high as 50%. Also, flow cytometry is more reproducible for single strains.
 - Deviants may not be seen in plate counts but could have an influence on humans; non-viable and cell fractions may stimulate the immune system.
 - In addition, when using selective media, complete recovery is not always achieved. MRS agar supplemented with cysteine is the standard in industry for total count.
 - Some companies are using both Colony Forming Unit (CFU) and flow cytometry data in their Certificates of Analysis (CoAs). However, industry is not there yet. Everything is currently defined in terms of viable microorganisms (CFUs): a probiotic is viable by definition.

Label Claims and Overages

- Overages vary according to the manufacturer, but could be as high as 50%. It should be considered that method variability for plating can be also be as high as 50%.
- All probiotics lose viability over time, except BC30 which has longer shelf life, and you need to manage with overages.
- Different strains have different stability; this also depends on how they were processed and on the particular manufacturer.
- Some companies require compliance with 100% enumeration (CFU) for label claims. Other companies allow 80-90%. FDA commented that they expect 100% of CFU for label claims, as required for other ingredients. Some attendees think 80% rule for quantity in natural ingredients applies, like content of DHA in fish oil.
- It was discussed that an upper cap for overages should not be placed for probiotics because of the decrease in bacteria viability during storage. However, FDA commented that this is necessary because of safety concerns.

- It was also commented that it is necessary to consider that bacteria do not grow in linear progression. Log-count may be more appropriate for limit setting.

Label Claims may be misleading:

- There is a lack of clear and uniform requirements for labeling. Current labeling practices are not always consistent and in some instances could be misleading. For example, some products report a viable count on the front label and a much lower amount on the back label with an asterisk that will indicate the amount of capsules to be taken to achieve the CFU stated in the front label.
- The Council for Responsible Nutrition (CRN) is currently working on guidelines for the consistent labeling of probiotics. They are expected to be published in 2016.

Other Topics for Best Practices

- Allergen labeling and testing
- Appropriateness of accelerated stability testing
- Sample selection, total count, and shelf life
- Expiration dating at the end of shelf life versus at time of manufacturing
- Storage, handling and shipping – The supply chain (retailers, including warehousing, and shippers) could dramatically affect the shelf life of probiotics.

Use in Infant Formula

- ▶ USP monographs typically cover specifications for ingredients with multiple applications. The ingredient may be used exclusively in a particular application (i.e., infant formula products), in which case the specifications reflect the quality for that sole intended use. The Expert Committee may decide to develop monographs based on a single application (i.e., skim milk powder) and consider different testing parameters for vulnerable populations.

Path forward

- USP is interested in contributing public standards for probiotics with new *FCC* monographs as well as corresponding *USP-NF* dietary supplement monographs.
- USP values the input received from the stakeholders during this round table. This input will be used to draft proposals for new probiotic monographs as dietary ingredients and dietary supplements based on information already available to USP.
- Proposals are to be published in *Pharmacopeial Forum* to invite additional public comment from the stakeholders.
- USP will welcome proposals from interested parties. Those interested in contributing to these proposals are encouraged to submit the following:
 - Recommended tests to evaluate quality parameters – identification, purity, strength, contaminants and labeling requirements.
 - Specification sheets, certificate of analysis of different commercial batches, validation data for identification, enumeration and contaminants tests
- The public review process will further solidify a path forward to public standards for probiotics.



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Thank You

USP Cranberry Standards Development Roundtable
June 22, 2017
USP-U.S., Rockville, Maryland

On June 22nd 2017, USP is hosting a **Cranberry Standards Development Roundtable** at the headquarters in Rockville, MD. This event is intended to foster discussion among the attendees and USP staff with the specific goal of defining key quality attributes and embarking on development of standards for cranberry ingredients and finished products.

Cranberry comprises a major category of botanical dietary supplements, representing 3 out of the 10 ten selling herbals with sales of \$76MM as per A.C. Nielsen for the 52 week period ending June 4th, 2016. According to the NIH Labels Database, there are more than 1000 dietary supplements in the US market containing cranberry ingredients. The large and widespread use of Cranberry Dietary Supplements among the female population to alleviate symptoms associated with urinary tract infection demands the creation of robust public standards to assure the quality of these products.

Proanthocyanidins, one of the main classes of bioactive compounds in cranberry, are complex oligomers and polymers which are very difficult to characterize. Defining the various types of cranberry ingredients existing in the market (i.e., juice-derived, skin-based and whole berry powders) and establishing appropriate specifications based on the content and distribution of proanthocyanidins has been a challenge for the industry.

USP is interested in convening stakeholders from industry and regulatory agencies to assist in the development of cranberry standards. These standards comprise test procedures and acceptance criteria for the correct identification, measurement of strength, level of contaminants, and chemical/microbiological impurities. Through this roundtable discussion, USP would like to assess stakeholder needs for quality standards for cranberry ingredients as well as finished products, including discussions on technical and quality challenges in testing cranberry ingredients in compliance with cGMP regulations for Dietary Supplements.

In general, USP would like to seek and discuss stakeholder inputs on the following topics:

1. Different types of cranberry ingredients and their manufacturing processes
2. Specific tests and reference standards needed for the correct identification of cranberry ingredients based on characteristic marker compounds
3. Specific tests and reference standards needed for the measurement of the content and distribution of cranberry proanthocyanidins
4. Possible adulteration concerns with other botanicals or chemical contaminants
5. Challenges in dosage form formulations, testing and compliance

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Dietary Supplements Standards Up-to-Date

Huy Dinh, MS.
Senior Scientific Liaison
Dietary Supplements

Dietary Supplements Standards Up-to-Date— A background

USP Convention Resolution 2:

USP will meet the needs of U.S. Food and Drug Administration (FDA), industry, and other stakeholders for modern monographs within USP–NF.

USP will work to:

- **eliminate the existing backlog of monographs in need of modernization, and**
- **proactively evaluate and update monographs to maintain their relevance given scientific advances and evolving manufacturing and regulatory approaches.**

USP will work with industry and FDA to explore new strategies for sharing analytical methods and specifications needed to modernize monographs.

USP-NF UP to Date Program aligns with:

USP Corporate Strategy
Winning Ambitions
FY 17 Objectives
USP Core Values

Dietary Supplements Standards Up-to-Date

What is “Standards Up-to-Date”?

Current:

- Add new monographs and general chapters in timely manner.
- Omit monographs and general chapters that are no longer needed

Relevant:

- Update monographs and general chapters to reflect “state of the industry” practices.
- Ensure availability of relevant Reference Standards

Suitable for the intended use:

- All components clear, complete and correct.
- Remove unnecessary tests.
- Appropriate selection of reference standards

Dietary Supplements Up-to-date

Replace

- Non-Specific Assay
 - Titrations
 - Spectrophotometry
 - Microbial Assay Procedures
- Outdated Technology
 - TLC Impurity procedures
 - Packed-Column GC
- Hazardous Tests
 - Toxic Solvents
 - Odor Tests

Add/Delete

- Add missing Impurity Procedures
- Add second Identification Procedures (preferably two orthogonal procedures)
- Delete non value-added procedures (melting point, pH)

Update

- Old Chromatographic Reagents
- Use Common Assay and Impurity Procedures
- Reference Standards information
- Include Multidimensional Detectors

Dietary Supplements Up-to-Date Strategies

- **Traditional donor model ('externally sourced')**
 - Engage sponsors
- **USP laboratories ('internally sourced')**
 - Procedure development and validation in US, India, China and Brazil
- **Trade organizations**
- **Expert panels to leverage industry expertise**
 - Gain stakeholder input and buy-in early in the process
- **Other Pharmacopeias**
 - Acquire validation data to support procedures from other pharmacopeias

Dietary Supplements Up-to-Date Opportunities and Challenges

➤ Opportunities:

- Stakeholder collaborations and global expert panels can stimulate additional avenues for updates and harmonization.
- Sourcing procedures from other compendia, literature, etc. (validation data required)
- Use of global USP laboratory facilities to develop and validate procedures.

➤ Challenges:

- Prioritization of monographs and chapters in need of updating
- Obtaining procedures, impurity profiles and acceptance criteria from sponsors
- Balancing the need to introduce modern methodology with the feasibility of global implementation

Dietary Supplements Standards Up-to-Date

RoundTable's Objectives

- Foster discussion among the participants to ensure that USP standards for dietary supplements are up-to-date, using current analytical procedures that are affordable, relevant, and can be effectively carried out by dietary supplement stakeholders in the next five years and beyond.
- Address the challenges outlined in the Slide# 6:
 - Prioritization of monographs and chapters in need of updating
 - Obtaining procedures, impurity profiles and acceptance criteria from sponsors
 - Balancing the need to introduce modern methodology with the feasibility of global implementation

Quality Leadership

Roundtable on USP Dietary Supplements Up-to-Date Standards

October 25, 2016

Stakeholders from academia, regulatory agencies, ingredient manufacturers, finished product manufacturers, and trade associations participated in the discussion of how USP standards for dietary supplements need to be up to date, using current analytical procedures, and at the same time be affordable and relevant. The discussion topics at the meeting were (1) Prioritization of Monographs and Chapters in Need of Updating, (2) Up-to-Date Practices for USP Standards, (3) Up-to-Date Process and Communication, (4) Modern/Emerging Technologies and Tools, and (5) Planning the Compendial Future for Dietary Supplements.

Below is a summary of the feedback stakeholders provided at the roundtable:

- Prioritization criteria could include a risk of ingredient adulteration that leads to a public health issue, its prevalence in the market, and the level of consumption of it in products (i.e., how much it is used).
 - Consider factors such as market share, relevance, and convenience.
 - Omit monographs and general chapters that are no longer needed.
 - Properly flag methods that lack specificity, so that potential for adulteration or contamination is understood.
 - Omit methods that are outdated and no longer used (e.g., GC packed columns).
 - Some companies cannot afford new technologies. It is important to retain equivalent old technologies while introducing new ones.
 - Replace wet chemistry methods with instrumental methods. Change Thin-Layer Chromatography (TLC) to High-Performance Thin-Layer Chromatography (HPTLC). Change HPLC to UHPLC; NMR can be used for identification and quantitation. Inductively Coupled Plasma (ICP) to analyze metals is practically a universally established technique despite the considerable expense and running costs. Change to greener methods; for example, the use of supercritical mobile phases in chromatography will permit to cut on hazardous solvent use and toxic waste disposal.
 - Send automatic electronic notification of relevant *USP–NF* content changes to customers.
 - Provide an overview of USP's intentions to modernize monographs. This would allow companies to move forward using faster methods; those who cannot afford new methods could still use the older methods.
- The following are other topics for which USP received feedback from participants:
- Adding HPTLC where TLC is missing; Adopting a new format allowing a comparison of multiple samples in the Dietary Supplements and Herbal Medicines Compendia; collaboratively validating several methods, and creating an electronic HPTLC image database Challenges to incorporating chemometrics
 - New technologies to detect adulteration
 - Use of a non-targeted method to identify outliers such as HPTLC, Quadrupole Time of Flight (QTOF), HPLC-MS
 - Planning the compendial future for dietary supplements:
 - Share data packages and the analytical information behind monographs. Provide

rationale for including and excluding parts of methods.

- Include validation data with a method so that a company knows how much it needs to validate.
- Consider upgrading units of measurement in monographs.
- Consider reducing the cost of Reference Standards to discourage use of secondary standards.
- Companies are developing their own methods to fit specific products. USP should be the driving force to help harmonize the methods.
- Seek existing methods adopted by other organizations and trade associations.



**Bringing USP Dietary Supplement Standards Up-to-Date
Roundtable Discussion
Tuesday, October 25, 2016
USP–U.S., Rockville, MD**

***Co-Chairs: Paula Brown, Ph.D., Aniko Solyom, Ph.D.
Scientific Liaisons: Anton Bzhelyansky, Huy Dinh
Executive Secretariat Representative: Marie Temple***

Notes–Draft

Goals and Anticipated Outcomes

To seek industry perspectives and input on the status of compendial methodologies, documentary standards, and reference materials for dietary supplement (DS). Keeping these standards up to date is one of USP's most important responsibilities; however, including advanced methodologies should be synchronized with stakeholder capacity for adopting and conforming to modernized standards.

Attendees

Volunteer Members

1. Paula Brown, Member, Botanical Dietary Supplements and Herbal Medicines (BDSHM) Expert Committee (EC)
2. Dennis Gorecki, Chair, Non-Botanical Dietary Supplements (NBDS) EC
3. Robin Marles, Chair, BDSHM EC
4. Eike Reich, Member, BDSHM EC
5. Aniko Solyom, Member, NBDS EC

Government Liaison

Frank Switzer, FDA Liaison to BDSHM EC

Invited Guests

Silva Babajanian, Herbalife International	Hiroshi Mizoguchi, Kyowa Hakko Bio Co., Ltd.
Guillaume Blin (via teleconference), NATUREX Inc.	David Murawski, Church and Dwight Co., Inc.
Michael Blumhorst, ADM	Timothy Murray, Gaia Herbs
Larry Callahan, U.S. Food and Drug Administration	Yoko Obayashi, Ajinomoto North America
Pei Chen, U.S. Department of Agriculture	Catherine Rimmer, National Institutes of Standards and Technology
Lisa Fallon, Church & Dwight Co., Inc.	Janet Roberson, BASF Corporation
Mark Hokenson, Pharmavite	Jeremy Stewart, Gaia Herbs
Holly Johnson, Alkemist Labs	Xun Yan, Amway
Phil Koerner, Phenomenex	Jincai Yang, NBTY, Inc.
Mohamed Koroma, Pharmavite	Kurt Young, Nutra Manufacturing
	Jerry Zweigenbaum, Agilent

USP Staff

Anton Bzhelyansky, Natalia Davydova, Huy Dinh, Gabriel Giancaspro, Maria Monagas Juan, Nam-Cheol Kim, Hellen Oketch, Nandakumara Sarma, Fatkhulla Tadjimukhamedov, Marie Temple, Seong Jae Yoo

1. USP Welcome Remarks

Dr. Gabriel Giancaspro **convened the meeting at 9:00 a.m.** and welcomed attendees. He invited participants to share how they see USP's intent to update Dietary Supplement (DS) standards and share their ideas. Dr. Paula Brown and Dr. Aniko Solyom presided over the meeting.

2. Modernization Framework

Mr. Huy Dinh presented an overview of USP's plans to modernize DS monographs so that they remain current, relevant, and suitable for their intended use. He noted the following opportunities:

- Stakeholder collaborations and global expert panels can present additional avenues for updates and harmonization.
- Sourcing procedures from other compendia, literature, etc. (provided the validation data are made available)
- Use of global USP laboratory facilities to develop and validate procedures

Mr. Dinh also noted the following challenges:

- Prioritization of monographs and chapters in need of updating
- Obtaining procedures and impurity profiles from sponsors
- Formulation of adequate acceptance criteria in monographs
- Balancing the need to introduce modern methodology with the feasibility of global implementation

Discussion

Dr. Aniko Solyom wrote key points on flip charts. The following is a summary of those key points and related discussion (in sub-bullets) grouped by topic.

General Chapters and Monographs

- Provide General Chapters in a separate book, making them portable.
 - The *USP–NF* is too large; it should be separated into two books.
- Make monograph methods electronically searchable.

Monograph Considerations

- Ensure that monograph information is fit for purpose and aligned with regulatory requirements.
- Harmonize with Good Manufacturing Practices and regulatory requirements.
- Include modern methods using current science.
- Consider the impact of monograph changes on regulatory filings.

Communication

- Send automatic electronic notification of relevant *USP–NF* content changes to customers.
 - USP is improving the online product to emphasize revisions to standards.
- Provide an overview of USP's intentions to modernize monographs. This would allow companies to move forward using faster methods; those who cannot afford new methods should be allowed to continue using the older methods.

Flexible Standards

- Standards should be flexible.

- USP does not intend to remove monograph tests that fulfil important diagnostic functions (e.g., pH and melting point).

Method Equivalence, Allowable Adjustments, Alternate Methods

- USP allows alternative methods to be used when they are validated according to General Chapter <1225> *Validation of Compendial Procedures*.
 - Is USP going to re-examine its criteria for method equivalence?
- When USP moves from a packed column to new technology, it is a different chemistry and not a simple calculation to prove equivalence. The scope of changes permitted by General Chapter <621> *Chromatography* is limited.
 - For botanicals, it is frequently a challenge to produce equivalent results using two methods.
 - People are using chemical assay methods for identification purposes.
- Consider the “reverse equivalence” approach, when the advanced compendial procedure could be adapted to the company’s older hardware by conducting a confirmatory equivalence analysis.
- When a company makes a significant adjustment, more than a simple verification is required.

Omission of Old Methods

- USP needs to remove methods that are not used any more (e.g., packed GC columns).
 - Remove wet chemistry tests from the identification section of monographs.
 - Remove the organoleptic methods
 - Nuclear Magnetic Resonance (NMR) can be used for identification.
- Some companies cannot afford new technologies. It is important to retain equivalent old technologies while introducing new.
- USP should reach out to companies using other methods and ask them about the types of equipment they are using.
- It is important to work with trade organizations.
- Companies employing *USP–NF* methods generally defer to older technologies in monographs.
 - A company may still use High-Performance Liquid Chromatography (HPLC) after having purchased Ultra-High-Performance Liquid Chromatography (UHPLC) equipment. Their products may call for both types of equipment.
 - Very old methods should be removed.

Prioritization of Monographs

- How will USP prioritize monographs to be modernized?
- Prioritization criteria could include a risk of ingredient adulteration that leads to a public health issue, its prevalence in the market, and the level of consumption of in products (i.e., how much it is used).
 - USP monitors industry trends and prioritizes monographs for products that have been adulterated.
- Use the USP prioritization matrix (which was adopted by AOAC International).
- Key factors are market share, relevance, and convenience.

Address Adulteration, Consumer Protection

- Old methods frequently lack specificity, and there is the potential that adulterated or contaminated products may not be properly flagged.
- Class-based analytical procedures may be needed to address adulteration with synthetic pharmaceuticals.

- USP needs General Chapters that identify adulterants found in particular product types as well as limit contaminants (e.g., pesticides, residual solvents).
 - USP should collaborate with organizations such as AOAC International, the American Herbal Products Association (AHPA), and Health Canada that have worked on pesticides.
 - Companies should test products that have a high likelihood of adulteration.
 - USP is convening a Roundtable on pesticides on **December 7, 2016**.
- Monograph methods should be able to identify adulteration.

Adulteration Potential Database

- Assemble an adulteration potential database (a database of ingredients or products with a high propensity for being adulterated).
 - There are more data on finished product rather than ingredient adulteration; the latter is rarely disclosed.
- Data sources need to be identified and vetted.
- Chromatograms containing the most widely known contaminants should be included.

Methods

- Replace wet chemistry tests.
- Change Thin-Layer Chromatography (TLC) to High-Performance Thin-Layer Chromatography (HPTLC).
- Change HPLC to UHPLC.
- Include a Principal Component Analysis (PCA)-based identity test.
- Attenuated Total Reflectance FT-IR (ATR-FITR) for analysis of incoming powdered material
- DNA technology
 - DNA has potential, but it should not be used for identification presently.
- Mass Spectrometry (MS)
 - This technology becomes increasingly affordable and has potential of becoming the next analytical workhorse in the labs.
- NMR
 - NMR can be used for identification, and – increasingly – quantitation.
- Inductively Coupled Plasma (ICP) to analyze metals is practically a universally established technique despite the considerable expense and running costs.
- Greener chemistry (UPC Squared) – the use of supercritical mobile phases in chromatography will permit to cut on hazardous solvent use and toxic waste disposal.

Validation of Methods (e.g., DNA test kits)

Impurity Detection Methods for Multivitamin Degradation

- Toxic solvents (see Greener Chemistry above).
- MS-friendly solvents
- Impurity profiles: When USP makes revisions to monograph impurity profile, this affects the industry significantly.
 - The change can affect the approval of a product.
 - The impurity profile is a key issue in identifying the API manufacturer.

Dissolution

- General Chapter <2040> *Disintegration and Dissolution of Dietary Supplements* does not allow the use of sinkers for botanical products.

Reference Standards (RSs)

- Provide information on secondary standards and the conversion factor for their use.
 - USP methods may have preceded the use of RSs currently available.
 - Industry uses secondary RSs as a conscientious cost-cutting decision.
- Decouple the single-entity reference material from the monograph, which would allow faster modernization.
 - USP RSs are developed for use with specific documentary standards.
- Share characterization information with the public.
- Share stability information [USP monitors all RSs through its Continued Suitability for Use (CSU) program].
- Include certified concentration values, potencies, and chromatograms with peaks identified.
- Explain how RS shelf life is established. (USP does not set an expiration date for RSs. The Council of Experts, however, is revising General Chapter <11> *Reference Standards*.)
 - What is USP's process for notifying users that a Reference Standard may have degraded?

Novel Dosage Forms, "Special" Matrices

- For time-release dosage forms, other ways are needed to assess the lifespan of the product in the body.
- Probiotics
 - USP proposed probiotics standards in a PF (*monographs and general chapter*).

Overages

- Include overages in DS finished product, not ingredient, monographs.
 - . A typical DS monograph specifies upper limits of dietary ingredients. The product should contain 100% of label claim at any time.
 - For potent dietary ingredients, the impact of an overage may be very substantial, and – in some cases – even exceed the No Observed Adverse Effects Level (NOAEL).
 - A *PF Stimuli* article discussed ways to establish internal specifications based on variations in manufacturing, stability, and assay. USP *General Notices* state that when a regulatory requirement for a minimum level is different from that in *USP–NF*, a company may shift the range toward the upper limit that the U.S. Food and Drug Administration requires.
- Include science-based overage setting.
- Companies may submit overage specifications to USP, and Expert Committees will make related decisions on a case-by-case basis.

3. Modernization Practice

Discussion

The following is a summary of key points and related discussion (in sub-bullets) grouped by topic.

Continuous Improvement: User Feedback

- USP should document monograph user feedback, make it public, and send responses to commenters.
- Stakeholders may submit comments on *PF* proposals or contact the Scientific Liaison with monograph questions.
- USP captures comments and queries and shares them with the responsible Expert Committee.

- Communication: USP needs to send feedback to commenters and explain why their feedback was or was not used.
- Use modern means of communication to facilitate and stimulate discussion about USP standards.

Search and Replace

- List items (e.g., old methods) to search for in monographs and then consider replacing them.

Harmonization

- Understand the differences between *USP–NF* and *European Pharmacopoeia* monographs.

4. Modern/Emerging Technologies and Tools

Dr. Solyom asked if new technologies could generate faster results comparable to conventional technologies. Dr. Eike Reich provided a presentation on compendial quality beyond market quantitation. He proposed replacing TLC with HPTLC as described in General Chapter <203> *High-Performance Thin-Layer Chromatography Procedure for Identification of Articles of Botanical Origin*; adding HPTLC where TLC is missing; adopting a new format allowing a comparison of multiple samples in the Dietary Supplements and Herbal Medicines Compendia; collaboratively validating several methods, and creating an electronic HPTLC image database.

Discussion

The following is a summary of key points and related discussion (in sub-bullets) grouped by topic.

High-Performance Thin-Layer Chromatography

- Visual vs. numerical comparison
 - It has been traditionally challenging to compare TLC profiles.
 - TLC can be useful, but visual identification has shortcomings.
- The database should be digitized and not rely on visual images.
- When receiving ingredients, HPTLC is one of the frontline techniques for authenticity confirmation.
- HPTLC is preferred over DNA analysis, but some customers are demanding DNA testing (see below).
- Modernize HPTLC to include acceptance criteria (based on multiple samples, cumulative data).
 - HPTLC has two current dedicated General Chapters <203> and <1064> *Identification of Articles of Botanical Origin by High-Performance Thin-Layer Chromatography Procedure*, with numerous monographs referencing the former.
 - USP could use average chromatograms to establish identification acceptance criteria in two monograph families as a pilot.
- Consider automated pattern recognition for signal generation in a multi-dimensional technique.
 - A control would be needed for comparison.
- Envision something other than a monograph (e.g., a database).

Challenges to Incorporating Chemometrics

- How are chemometric models developed?
- Inclusion and exclusion criteria
 - How much variability are we willing to accept?
 - There should be a baseline with a margin of acceptance and a percentage of the internal reference.
- Validation parameters

- Underlying algorithms for determining pass/fail
 - Chemometrics can provide a quick “yes/no” answer.
 - How can we simplify the procedure to best identify positive material?
- Needs to be risk-based

DNA Analysis

- Some customers are demanding DNA testing.
 - Multiplex sequencing of DNA is needed for botanicals. There is a lot of inherent variability, and a range of RSs would be needed.
- DNA should not be used for identification in a monograph because it is not related to pharmacological activity (triggering physiological response).
 - Plants undergo complex cyclical transformations throughout lifecycle, and only at certain stages, the plant-derived product may be pharmacologically efficacious: analysis of plant DNA has no means of assessing this.
- DNA analysis can indicate presence of components that are not adulterants.
 - Full DNA sequencing has limited potential of detecting adulteration or presence of another species.
- DNA testing is used by some companies in place of RSs to identify botanicals – especially where there are no compendial standards available.
- DNA is a piece of the puzzle and eventually could be part of a series of ID tests.
- There is lack of validation, or even agreement on particular techniques, for DNA testing at this time.
- DNA testing could be part of an identification approach for USP Monographs.

New Technologies to Detect Adulteration

Dr. Solyom asked attendees if USP should include new technologies to detect adulteration. Attendees suggested the following:

- Multiple technologies for use on a case-by-case basis
 - Once the anti-adulteration procedure is published, “bad guys” tend to move to other means of adulteration.
 - USP routinely responds to publicized adulteration cases by enhancing the monograph methodologies.
- Validation challenges
- Non-targeted method to identify outliers
 - HPTLC is an example of a non-targeted approach.
 - A company used Quadrupole Time-of-Flight (QTOF), but had issues when trying to compile a database.
 - It could be difficult to transfer Liquid Chromatography-Mass Spectroscopy (LC-MS) libraries between different instruments, in particular, those with different designs and by different manufacturers.
 - More data may reduce the library’s specificity.
- Importance of sample preparation
 - Chemometric software packages exist permitting companies to do samples Class Prediction based on the MSMS profiles of complex samples.
- Limits for unintentional adulteration

Monograph Donor Submission Guidelines

- Companies want to understand the criteria for a method to be accepted for use in a monograph.
 - USP is developing Monograph Donor Submission Guidelines, which may be available after March 2017.

Challenges of Modernized Methods

Dr. Solyom asked how USP modernization would affect the use of USP methods in other countries. Attendees suggested the following:

- USP standards are rarely harmonized with standards in other countries.
 - A company that exports to China and South Korea has found that the Chinese and South Korean methods are not harmonized with *USP–NF*.
 - Ingredient suppliers selling to U.S. companies are commonly using modified USP methods.
- Challenges of complex DSs with multiple active ingredients; the point at which the monograph usefulness is limited
- Low content of chemical markers is a hallmark of botanical ingredients
- Be cautious about requiring the use of expensive technologies.
 - LC-MS provides more information to characterize material, but it is also expensive.
 - Companies do not want to be required to use expensive technologies.

5. Planning the Compendial Future for Dietary Supplements

Discussion: What should USP change about its standards?

Dr. Solyom asked attendees what USP should change about its standards, and attendees suggested the following:

Increase Transparency

- Provide a database that contains background information on USP standards and Frequently Asked Questions from common queries.
 - Share data packages and the analytical information behind monographs.
- Include validation data with a method so that a company knows how much it needs to validate (challenge: confidential proprietary information).
- Provide rationale for including and excluding parts of methods.
- More information should be made public and free of charge.

Content

- Include literature references for methods, where applicable.
- Include HPLC chromatograms (not just relative retention times) in monographs.
- Include pictures of HPTLC plates in monographs.
- Include fragmentation patterns (e.g., total ion chromatogram) for NS methods.
- Include DNA information.
- Consider upgrading units of measurement in monographs.
- Use smaller columns and make incremental changes.

Cost of Reference Standards

- Consider reducing the cost of RSs to discourage use of secondary standards.
 - Consider providing RSs in smaller quantities.
 - The quantity of a USP RS is routinely made sufficient for five complete analyses according to the monograph.

Work With Companies, Organizations

- Harmonization: companies are developing their own methods to fit specific products. USP should be the driving force to help harmonize the methods.
- Seek existing methods adopted by other organizations and trade associations.

6. Wrap-up and Next Steps

USP staff and Dr. Robin Marles noted the following ways that attendees could help USP modernize DS monographs:

- Submit alternative company-developed methods to USP.
- Submit comments on proposals through *PF*.

- Apply to serve on Expert Panels and Expert Committees to provide expertise and drive the change.
- USP would continue bringing its standards up-to-date based on the three attributes: current, relevant and suitable for their intended use
- USP would work to increase transparency in the standards revision processes.
- USP would increase effort to reach out to companies and organizations to harmonize/integrate their own methods with those of USP.
- USP would strive to provide more information about its standards to the public.

The meeting **adjourned at 5:00 p.m.**

Roundtable Discussion on Pesticide Residues in Dietary Supplements
December 07, 2016
USP–U.S., Rockville, Maryland

Meeting Notes

Goals and Anticipated Outcomes

The goals of the roundtable were to foster discussion and understanding of different perspectives on pesticide residues in botanical dietary ingredients and dietary supplements (DS). The anticipated outcome was to explore science-based solutions.

Background

Good Manufacturing Practices for Dietary Supplements in 21 Code of Federal Regulations (CFR) Part 111 *Current Good Manufacturing Practice in Manufacturing, Packaging, Labeling, or Holding Operations for Dietary Supplements* require manufacturers to control contaminants, but do not set specific methods or maximum residue limits (MRLs). Since DS in the U.S. are regulated as a subset of foods, U.S. limits for pesticide residues in botanical DS are set by the U.S. Environmental Protection Agency (EPA) to the same levels as for food crops. Although EPA establishes pesticide limits, the U.S. Food and Drug Administration (FDA) is responsible for enforcing them. FDA action levels are determined on a case-by-case basis. In the absence of EPA-established limits for an article, or an express exemption from the need for a limit, an ingredient marketed as a food or DS could be considered adulterated (“zero tolerance”) if presence of a pesticide residue is detected, even if the pesticide is legally allowed in other crops at much higher levels.

USP–NF General Chapter <561> *Articles of Botanical Origin* provides limits for common contaminants, including pesticides, aflatoxins, and elemental impurities, but compliance with *USP–NF* limits is mandatory only for botanical drugs, not when the ingredient is labeled for use as a DS. USP published a *Stimuli* article ([Pharmacopeial Forum](#) 42(2) [Mar.–Apr. 2016]) to provide background about the need for rational limits for pesticide residues, ensure the quality of articles of botanical origin, and engage stakeholders to strengthen *USP–NF* contaminant standards. Public comments were reviewed and considered by USP’s Botanical Dietary Supplements and Herbal Medicines Expert Committee (BDSHM EC).

Following up on the *Stimuli* article comments, USP organized this roundtable with stakeholders to explore science-based solutions to address pesticide residues in botanical dietary ingredients and DS (for which, in the majority of cases, EPA has not established tolerances). Dr. Robin Marles, BDSHM EC Chair, and Mr. Josef Brinckmann, a BDSHM EC member, led the roundtable discussions. Stakeholder input was collected on complex issues related to regulatory requirements, experiences with U.S. Department of Agriculture’s (USDA’s) 5% of EPA tolerances for organic crops, the toxicological basis for crop-specific pesticide limits, non-point source pesticide contamination of wild crops, risk-based testing, analytical method challenges, and harmonization across pharmacopeias. Participants included governmental policy makers and regulators [FDA, EPA, USDA National Organic Standards Board (NOSB), Health Canada, Canadian Food Inspection Agency], independent laboratories, trade associations, botanical ingredient suppliers, and manufacturers of botanical DS products and botanical drug products. Participants discussed the need for a science-based approach to establish pesticide residue limits in botanical DS, considering the challenges of the current paradigm of crop-specific limits (which have not been set by EPA for most of the commonly used herbs of commerce). The major themes from the roundtable follow:

Regulatory and compendial framework

Mr. Brinckmann reviewed the current U.S. regulatory framework (40 CFR Part 180 *Tolerances and Exemptions from Tolerances for Pesticide Chemicals in Food*; 21 CFR Part 111 *Current Good Manufacturing Practice in Manufacturing, Packaging, Labeling, or Holding Operations for Dietary Supplements*; 7 CFR Part 205 *National Organic Program* Section §205.671 *Exclusion from organic sale*) and the following problem statements:

- Articles from an estimated 3,000 botanical species are in commerce, yet the majority of species have no EPA-established tolerances.
- Occurrence of non-point source pesticide residues is a problem, even with certified organically grown and/or wild-collected botanicals. Long-range transport of pesticides is reported in the literature.
- In the absence of EPA-tolerances (i.e., zero tolerance), residues of “allowed pesticides” intentionally applied to conventional herb crops in other countries are “unlawful pesticides” as per U.S. regulations.
- EPA has not specified limits for most dietary supplement botanical raw materials, which will typically be ingested at lower levels than most botanical crop commodities for which MRLs have been set by EPA.
- Recent technological advancements in pesticide analysis have substantially improved the sensitivity of detection, identification, and quantitation of pesticide residues.

As discussed in the *Stimuli* article, pesticide residue limits in *USP–NF*, the Official Compendium, apply to botanical drugs, but not to botanical DS ingredients (even when the same botanical can be a drug or DS). In the absence of EPA-established limits for an article, compliance with *USP–NF* limits is permitted for drugs, but zero tolerance is applied when the same ingredient is labeled as a food or supplement. Dr. Nandakumara Sarma, USP staff, reviewed the limits for 70 pesticides in General Chapter <561> and noted that the *Contaminants* section of *USP–NF* botanical quality monographs requires compliance with these standards. <561> refers to EPA limits when an article is used in the U.S. as a food or DS. However, this creates a gap because EPA did not establish tolerances for most of the commonly used botanical dietary ingredients or their extracts. He noted that USP limits are harmonized with the *European Pharmacopoeia (Ph.Eur.)* (chapter 2.8.13) limits.

Participants noted that the Food Safety Modernization Act and 21 CFR 117 require preventive control of pesticide residues based on hazard analysis. An FDA participant noted that the EPA review process for approval of limits for crops requires submission of a safety data package (typically submitted by pesticide manufacturers for selected high-value crops). Multiple industry participants noted the challenges and high costs associated with this review and approval process, considering that a botanical may be sourced from multiple geographical locations. Furthermore, a pesticide manufacturer would probably not submit a limit-setting request for each pesticide for each botanical ingredient (especially if the crop is not grown in the U.S. and there are no U.S. customers for the pesticide). Multiple industry participants provided examples of the rejection of containers at the port of entry due to the detection of pesticide residues for which there were no established EPA tolerances.

An FDA participant noted that the pre-market approval system is used for pesticides because they are intentionally applied, in the same way that food additives and colors are added to foods. The non-point source of exposure complicates the approach based on crop-specific limits. Pesticide residues from such an exposure would be contaminants rather than intentional additions. Although the law does not provide a remedy for the situation, an administrative fix that categorizes foods with action levels may provide a solution. Such a measure would require EPA to declassify the non-point source pesticides to be regulated by other provisions based on safety assessments. A participant from Health Canada noted that pre-market approval of natural health products coupled with general MRLs helps Canada address cases where no MRLs have been established.

Attendees discussed ways that USP compendial standards could address the concern. They suggested that FDA amend its regulations to incorporate, by reference, *USP–NF* as an acceptable compendium for determining pesticide residue limits for all articles of botanical origin. Because Table 4 in General Chapter <561> refers to the EPA tolerances (in the event that a specific pesticide chemical is not listed in Table 4), this could be acceptable to EPA given that they will not establish crop-specific tolerances for the thousands of articles of botanical origin in U.S. commerce.

Non-point source pesticide contamination in organic botanical crops and in wild harvested botanicals

Dr. Pilar Pais, a BDSHM EC member, shared the following observations:

- Botanical raw materials and extracts are considered herbal medicinal products for traditional use in Europe, while they are considered DSs in the U.S. Suppliers should control and ensure the quality of raw materials through quality contracts, audits, and specifications.
- Good agricultural and collection practices (GACPs) are important to ensure the quality of raw materials. Buyers and sellers consult *USP–NF* and *Ph.Eur.* for pesticide lists and limits.
- Responsible growers who follow GACPs keep records of the identity and use of pesticides in their crops during cultivation and harvesting. However, non-point source contamination is a serious concern despite GACPs.
- Analysis of the same sample in different laboratories yielded different results. Good control of recovery, a validated method, and trained laboratory personnel are important to ensure reliable results. In some cases, the pesticide residue levels in an article comply with European regulations, but the article cannot be used as a U.S. DS.

As a case example, no pesticides were detected in linden flower (*Tiliae flos*), a non-industrialized rural wild crop which is widely used as traditional medicine in Europe. On the other hand, St. John's Wort herb (aerial parts) may be either cultivated or collected from wild sources from remote non-industrialized areas. Although pesticides were not detected in the dried herb, some residues were detected from time to time in St. John's Wort extracts or nettle root. In the case of Milk Thistle fruit, pesticide residues were observed as contaminants in organically grown crops, but were not detected in highly purified Milk Thistle extracts.

Ms. Zea Sonnabend, an NOSB member, noted that NOSB does not have control over pesticide residues from a non-point source, nor can NOSB make a recommendation about how to address the issue. The organic regulations allow organic food to contain 5% of EPA's pesticide residue tolerance. There is no particular exemption for something that does not have an EPA-established pesticide residue tolerance, which is the case for most herbs and botanical extracts. It is not clear how that rule could be changed, but it is probably not in the purview of NOSB. However, a meeting with NOSB or EPA on tolerance issues could lead to a path forward.

Representatives of botanical raw material suppliers and DS manufacturers noted that a zero tolerance limit for non-point source contamination is impractical and unreasonable. Instead of crop-specific controls, one participant suggested that pesticide manufacturers register and label new pesticides on the market for any crop. The following case studies presented by Mr. Ed Fletcher, a BDSHM EC member, to illustrate the issues:

- Cultivated products: *Echinacea purpurea* was grown on organic land in Canada with a 17 year field/farm history. The soil was tested years prior to planting and had no residues. However, it tested positive for DDT, aldrin, and dieldrin when the soil was tested again. The problem is that these residues have a long half-life and remain in the soil for a very long time (decades for DDT). Accordingly, organically grown crops with low levels of DDT have been rejected. Considering that the residues may have been in the soil for over 40 years (DDT was banned in the U.S. and Canada in 1972, and dieldrin was banned in 1974), and their presence was due to contamination (not intentional application), the pesticide registration process comes into question. A 2008 FDA monitoring study also found DDT residues in *Echinacea*, indicating that the issue was noticed for quite some time. Participants suggested that the premarket approval process may need more scrutiny when pesticide residues show up in soil five times past the half-life that is on the pesticide manufacturer's label.
- Wild collected crop: *Cascara sagrada* bark. Low DDT residue levels were found, although the material was collected in the forest and many miles from population centers or downstream contamination.

An FDA participant noted that legacy pesticides like DDT deserve special mention because they are in their own category. Chlorinated pesticides were used widely from the 1940s and 1950s until they were

banned and phased out in the 1970s and 1980s. Residues in the environment are persistent. At the time that these pesticides were banned, both FDA and EPA recognized that the lack of tolerances would be an ongoing problem. In the absence of a legal route to address this issue, EPA established an administrative fix in the form of “action levels” (which are not tolerances)—administrative numbers to account for the persistence of unavoidable residues for a long period of time. FDA agreed to utilize them in the absence of tolerances. Without legal provisions or this administrative fix, common food articles such as carrots would probably be banned. The 1996 update of the pesticide laws, known as the Food Quality Protection Act (FQPA), includes a provision whereby EPA could establish tolerances for unregistered persistent pesticides. Environmentally persistent residues that may not have been used for decades have been found in source countries. Industry may approach EPA and explore the applicability of an administrative remedy to establish tolerances for unregistered persistent pesticides, utilizing FQPA approaches. Participants acknowledged that the presence of persistent pesticides is a significant issue. FDA may agree to recognize EPA tolerances.

Participants noted that the current regulations do not recognize several of the pesticides that are used in Europe for crops grown in the region and imported into the U.S. This leaves gaps in the regulation, resulting in import alerts. A trade association representative noted challenging efforts to enlarge the list of crops with established FDA action levels for persistent pesticides (*Compliance Policy Guide* 7141.01; <https://www.fda.gov/downloads/iceci/compliancemanuals/compliancepolicyguidancemanual/ucm186872.pdf>). FDA has received comments from consumer advocates that even 10 ppb tolerance levels may be excessive. Other participants noted that education of all interested parties is needed. Although there are persistent contaminants in the environment, regulations have not kept pace with reality. A rational approach would be to develop maximum allowable limits with default levels based on toxicological considerations, recognizing that we live on a polluted planet where pesticide residues may occur not necessarily from intentional application but also from non-point source contamination.

Sharing Canadian perspectives, a participant noted that approximately 15% of the fresh fruit and vegetable samples tested were labeled “organic”, and 35% to 50% of these had detectable pesticide residue levels. When Canada applied the 5% rule to the general MRL of 0.1 ppm for those crop-pesticide combinations without a specific Canadian MRL, there were very few MRL violations in domestic or imported organic products (greater than 97% compliance). Often there is no explanation for these pesticide residues (aside from non-point source pesticide contamination). Therefore, the cultivators would not lose their organic certification. Canada aims to publish a longitudinal analysis of its program based on the pesticide analysis of organic products since about 2010.

The participants emphasized that glyphosate was recently detected in organic products, especially in products from the U.S. Regulatory monitoring of glyphosate is expected to begin after some analytical method challenges are resolved.

Regarding the list of pesticides that are tested, participants suggested including the chemicals that are permitted in the ecosystem by the ministry of agriculture of the country of origin.

Toxicological basis for pesticide limits

European Pharmacopoeia's approach

Dr. Bernhard Klier shared his perspectives on European regulations and his experiences with sample analysis over 20 years. He noted that the lists and limits in *Ph.Eur.* (chapter 2.8.13) and *USP–NF* (General Chapter <561>) are identical [except for the limit for inorganic bromide]. The limits are based on the maximum acceptable daily intake (ADI) of pesticide (mg/kg of body weight) established by the Food and Agriculture Organization of the United Nations. The MRLs for the 70 pesticides in *Ph.Eur.* and *USP–NF* are based on more than 11,000 findings in medicinal herbs, 90th percentile levels, and quantitation limits [analysis published in *Pharmeuropa*, 17(1), 2005]. These MRLs assume 6 g/day consumption of the whole botanical material (dried or fresh plant material) and were calculated based on 70 kg adult body weight. Most of the tolerances are stricter than the calculated value based on the ADI (less than 10% of the ADI). The speaker noted that the exposure data is from 14,900 samples that were analyzed over the years.

Health Canada approach

Mr. Yadvinder Bhuller from Canada's Pest Management Regulatory Agency (PMRA) provided information in advance of the roundtable about the Canadian regulatory situation. While *USP–NF* general chapters and specific monograph requirements for pesticide residues apply to licensed natural health products (NHPs) in Canada, the Canadian regulatory framework for the control of pesticide residues in botanical food ingredients is different from the way residues in NHP ingredients are controlled. Many raw material ingredients received by a broker in a single shipment (different aliquots) could become components of a food, an NHP, or a cosmetic. PMRA sets the MRLs for foods to protect the health and safety of Canadians. As part of the assessment process prior to the registration of a pesticide, Health Canada determines whether the consumption of the maximum amount of residues that are expected to remain on food products (when a pesticide is used according to labeled directions) will not be a human health concern for any segment of the population, including vulnerable subpopulations (such as infants and toddlers, pregnant women and nursing mothers, and the elderly). The maximum amount of expected residues is established as an MRL, regulated under the Canada Pest Control products Act, and listed in the online MRL database (<http://www.hc-sc.gc.ca/cps-spc/pest/part/protect-proteger/food-nourriture/mrl-lmr-eng.php>). MRLs for each pesticide/crop combination and any related processed food products are set well below the amounts that could pose a health concern. If an unacceptable risk is determined, the product will not be permitted for sale or use in Canada.

Following a consultation with stakeholders who supported increasing the number of specific MRLs, Health Canada specified over 19,000 MRLs, which streamlined the process and facilitated international trade. Registrants and growers have used this opportunity to engage in consultative processes with organizations such as Codex Alimentarius with a strong interest in harmonizing these internationally "to further minimize trade irritants."

The Canadian Food Inspection Agency enforces PMRA regulations for pesticide residues in foods, such as eggs, dairy, fresh fruit and vegetables, processed fruits and vegetables, honey, and fish. The Canadian National Chemical Residue Monitoring Program detects chemical residues and contaminants based on Codex principles, and publishes its results within two years of the testing fiscal year.

General MRL

Mr. Bhuller noted that Canada's general MRL of 0.1 ppm for pesticide residues that are not covered by a specific MRL is established in the Food and Drugs Act, which states, "A food is adulterated if a pest control product as defined in the Pest Control Products Act for which no maximum residue limit has been specified under sections 9 or 10 of the act, are present in or on the food, singly or in any combination in an amount exceeding 0.1 ppm." It applies to Canada's domestically grown and imported foods unless a specific MRL is established. He noted that "a key consideration in making these MRLs arose in the late 1970s, and at that time the analytical methodologies were not sufficiently sensitive to detect most pesticides below 0.5 ppm in a general food monitoring and surveillance food program for pesticide residues. For this reason, Health Canada relied on the general MRL more frequently when pesticide residues were at or below 0.1 ppm." Therefore, there was a pragmatic, analytical aspect to it, in addition to a toxicological basis. "Over the past several years, PMRA has taken steps to continue to establish science-based, specific MRLs, thereby allowing the department to reduce its reliance on the general MRL." Initial work was conducted by the department to identify pesticide/crop combinations where the general MRL was not protective (risk-based prioritization) and to establish MRLs for those combinations based on the data from other jurisdictions (which incorporated an international context).

Regarding the question of whether the default general MRL of 0.1 ppm is too stringent or not applicable for some pesticides because of safety issues, Dr. Bhullar noted that Health Canada reevaluates MRLs on a case-by-case basis to determine if the levels are valid and adequately protective. If a reevaluation indicates unacceptable health risks, Health Canada may propose the revocation of the existing MRLs. An exception would occur when revocation of the existing MRL resulted in an increase in the actual MRL value because the general MRL of 0.1 ppm was greater than the current, established MRL. In such instances, revocation would not be advisable. A recent example of this situation occurred with the

reevaluation of the active amitrole, which was discontinued for use in Canada. For importation purposes, the Canadian MRL of 0.01 ppm for amitrole currently established for wheat, barley, canola (rapeseed) and peas was maintained (not revoked). Revocation of the established MRL of 0.01 ppm for these commodities would have resulted in residues being regulated by the higher general MRL of 0.1 ppm. Details of the related dietary risk assessment can be found in the *Science Evaluation* section of [PRVD2012-01](#).

European Regulation 396/2005 provides the basis for MRLs for food and feed raw materials. For the fresh products for which no specific MRLs are set or for pesticides not listed in EU regulations, a default MRL value of 0.01 mg/kg is applied. Considering the drying and processing of the fresh botanicals and the analytical variability, participants noted the challenges with the 0.01 ppm limits and suggested a general MRL of 0.1 ppm.

Participants contrasted the toxicological basis for controlling exposure to contaminants such as lead and residual solvents (irrespective of the exposure source) with the crop-specific basis for controlling pesticide residue exposure. A participant presented an example of an EPA crop-specific limit of 3.0 ppm for rice for tricyclazole (40CFR180.678), while the limit for the same pesticide was held at zero tolerance for botanicals (which may be consumed at much lower levels) for which crop-specific limits were not established.

Participants suggested the adoption of a general MRL to limit pesticide residues in crops for which there were no EPA or *USP-NF* limits (similar to how limits are set in Canadian and European regulations). A general MRL could be defined in the *FDA Compliance Program Guidance Manual (CPG): Pesticides and Chemical Contaminants in Domestic and Imported Foods-CP7304.004*. In the relevant section, *CPG* states, "The sample containing a confirmed residue for which no tolerance or guideline in the sampled food has been established, but the residue level is such that it requires no follow-up (e.g. residue found at trace levels)." Depending on the safety profile of specific pesticides, the general MRL may not be applicable and a specific limit should be established to protect consumers.

Analytical challenges

USP staff noted that General Chapter <561> refers to the EPA or European Commission Directorate-General for Health and Consumers (DG-SANCO) methods for pesticide analysis. Participants discussed the challenges around ion suppression when using mass spectrometry (MS) methods for botanical matrices. Dr. Jon Wang of FDA noted that there are over 1000 pesticides (not including metabolites whose analysis is also important to obtain the total pesticide concentration). There are challenges with different matrices (such as roots, leaves, barks, nuts and flowers), fresh and dried products, and sample size. Instrumentation requires sensitivity. The most common techniques are MS methods. Gas chromatography (GC) and liquid chromatography–mass spectrometry (LC-MS) methods are often used because GC detects legacy pesticides such as DDT and endosulfan. QECHERS-based sample preparation and triple quadrupole MS are frequently used. Recently, high-resolution MS has also been used to try to expand that scope. FDA publications (Wong et al.) describe the test methods. Botanical analysis is a significant challenge because many pesticides originate in natural products (such as pyrethrins), which are natural pesticides and are the basis of some man-made pesticides (such as pyrethroids). Other pesticides such as DDT are based on a structure/activity relationship with these pyrethroids. Cleaning these extracts would be difficult because it would involve separating chemicals with structures similar to plant components.

Participants noted that the level of instrument sophistication used by the FDA and by industry may be very different. This could lead to Agency detection of pesticide residues in botanicals that may have passed the tests using other methods. The National Organic Program (NOP) list of about 200 pesticides could be used for multi-residue analysis methods and to assure compliance. An FDA representative suggested a review of FDA annual reports to understand FDA's testing of about 100 pesticides, with the caveat that the list was not representative of the universe of pesticides tested.

Participants suggested that better GC or LC-MS data could be obtained using the matrix match standard calibration. It could be very challenging for a contract laboratory to test different sample types and provide a matrix that is free of pesticides for use in matrix matching. While many analytical methods exist, they

should be used correctly in the laboratory. This is the basis of the DG-SANCO document that describes quality, acceptance criteria, recovery, and precision, among others. FDA bases enforcement action on the limit of quantitation, even if it is the enforcement confidence limit of 0.01 ppm.

Participants suggested that USP expand the list of 70 pesticide residues in General Chapter <561> to cover approximately 200 pesticides that are tested by regulators. They encouraged USP to consider providing Reference Standards for pesticide residue testing to help strengthen inter-laboratory qualification of data. Laboratories often obtain different results because they are constantly updating their instrumentation and methods. For consistency and to facilitate international commerce, participants suggested harmonization of *USP–NF* compendial standards with other pharmacopeias.

A recent Government Accountability Office (GAO) report recommended that FDA improve its methodology, and that FDA and USDA disclose limitations in their monitoring and data collection efforts (<https://www.gao.gov/products/GAO-15-38>). FDA said it will consider methodological changes and will disclose limitations. USDA agreed with GAO's recommendations.

For Investigative New Drug and New Drug Application review of botanical drug candidates, the Agency reviews exposure based on the suggested dose. The U.S. Center for Drug Evaluation and Research (CDER) may rely on inputs from the U.S. Center for Food Safety and Applied Nutrition. CDER may also consider a case-by-case safety evaluation of these particular products, similar to that used by China, the European Union, and Canada.

Major outcomes and potential solutions from the roundtable

Participants noted that the problem of non-point source contamination exists, and that *USP–NF* standards could help provide potential solutions and build transparency into the validation and standard-setting process.

- ▶ Non-point source pesticide contamination observed in organic crops and wild-collected botanicals demonstrates that a zero tolerance approach is not rational. Science-based standards could provide a framework for toxicologically sound limits.
- ▶ A survey could be conducted to determine the magnitude of concern from non-point source pesticides. The observations could be published to increase regulators' awareness of the issues.
- ▶ The current paradigm of crop-specific limits (which have not been set by EPA for most of the commonly used herbs in commerce) should be corrected through science-based approaches, such as *USP–NF* and *Ph.Eur.* pharmacopeial standards
- ▶ *USP–NF* limits for other types of contaminants (in General Chapters <467> *Residual Solvents*, <2232> *Elemental Impurities*, <561> *Aflatoxins*, and <2023> *Microbiological Attributes*) are based on toxicological considerations. A similar science-based approach could be adopted to limit pesticide residues in botanical DS and address the challenges posed by the current paradigm of crop-specific limits.
- ▶ Currently, *USP–NF* pesticide residue limits apply to botanical drugs, but not to botanical DS ingredients.
 - ▶ Participants suggested that EPA or FDA incorporate *USP–NF* by reference into regulations as an acceptable compendium for determining pesticide residue contaminants on all articles of botanical origin. Understanding the challenges of regulatory amendments and in the absence of a specific MRL, FDA guidance could include *USP–NF* pesticide residue limits as action levels. This could also help assure ingredient quality.
 - ▶ An FDA attendee suggested that a pesticide residue detected on a botanical that is certified organically cultivated or wild-collected could be considered a contaminant rather than an additive. EPA tolerances could be applicable to specific crops where a pesticide chemical had been intentionally applied. Regulators could view non-point source pesticide contamination of wild crops differently than the detection of crop-specific

pesticide residues within EPA-established tolerances.

- ▶ Case studies of enforcement actions based on zero tolerance illustrated impacts on industry and international commerce. Analytical method challenges related to complex botanical matrices need to be considered when establishing pesticide residue limits. Harmonization across pharmacopeias could facilitate international commerce.
- ▶ Participants suggested the adoption of a general MRL for limiting pesticide residues in crops for which there are no EPA or *USP–NF* limits, similar to how such limits are set in the Canadian (0.1 ppm) or European (0.01 ppm) regulations. A general MRL could be defined in the FDA *CPG: Pesticides and Chemical Contaminants in Domestic and Imported Foods-CP7304.004*. It is worth exploring whether the “trace levels” in class 2 results of the CPG could provide a regulatory relief. If so, they could be defined as administrative MRL levels.

Post-roundtable developments

After the roundtable, USP committed to the following activities to elevate the issue, initiate dialogue, and explore science-based solutions:

- ▶ Collect information on non-point source contamination from manufacturers and testing laboratories
- ▶ Meet with representatives of EPA, FDA, USDA, NOSB, and others to advocate for USP standards as a part of the solution
- ▶ Develop a manuscript on the subject for publication in the [Food and Drug Law Journal](#)
- ▶ Consider revising the pesticide list, limits, and methods section in General Chapter <561>
- ▶ Participate in professional conferences, including the following:
 - ▶ [The Toxicology Forum](#), Washington, DC (February, 2017)
 - ▶ [International Conference on the Science of Botanicals](#), Oxford, MS (April, 2017).
 - ▶ [MRL Workshop](#), San Francisco, CA (May, 2017)