The Development of USP Botanical Dietary Supplement Monographs, 1995−2005[⊥]

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The development of USP botanical dietary supplement monographs by the Subcommittee on Natural Products (1995−2000) and the Dietary Supplements−Botanicals Committee of Experts (2000−2005) of the USP is described in this review. Featured details include the USP as an organization, focusing upon its history, mission, and publication of the *United States Pharmacopeia−National Formulary* (*USP−NF*); the formulation and composition of botanical dietary supplement monographs and related general chapters, as well as appropriate admission criteria; and a summary of the accomplishments of the Committees (1995−2005).

Introduction

History of the USP.[1−3] At the time of its founding in 1820, the mission of the nongovernmental, all-volunteer United States Pharmacopeia (USP) was to develop a national formulary of the best drugs, which came to be termed "official" drugs. The first edition, published on December 15, 1820, contained monographs for 217 drugs, and the pharmacopeia's founders agreed not to make changes until the first Committee of Revision met 10 years later to publish the first revision of the *USP*. USP originally was founded primarily by medical doctors, and the Surgeons General of the U.S. Army and Navy participated in the 10-year revision process. Colleges of pharmacy were invited to participate in 1850. Beginning in 1880 *USP* changed from a book of medicinal formulas or recipes to a text of product standards. In the same decade state boards of pharmacy were formed, and *USP* was recognized in many state pharmacy board requirements. In 1888 the American Pharmaceutical Association published *The National Formulary of Unofficinal Preparations* (unofficinal indicated products prepared extemporaneously by pharmacists, in distinction to the hydroalcoholic patent medicines of dubious value that appeared in commerce after the Civil War). This title was shortened to *National Formulary* (*NF*) in response to the Federal Food and Drug act of 1906, which recognized both *USP* and *NF* as official U.S. standards of pharmaceutical strength, quality, and purity.

In 1900 USP incorporated in the District of Columbia as a not-for-profit corporation, and the United States Pharmacopeial Convention and Board of Trustees were created to support the work of the Committee of Revision, now known as the Council of Experts. USP is not a U.S. government agency, but because of references in the 1938 Federal Food, Drug, and Cosmetic Act, prescription and over-the-counter medications available in the United States must meet USP published standards for quality, purity, and strength. These published standards are enforceable by the Food and Drug Administration. The 1938 Act also established the new drug concept and mandated notification of FDA for drug safety prior to marketing. In 1942, the USP revision cycle was changed to every five years. In 1975, USP acquired *NF* in order to eliminate the publication of duplicative texts and two indices and began publication of these two official compendia in a single volume titled *USP−NF*. In 1977, the scope of the *USP* and the *NF* was redefined, with *USP* being responsible for standards for drug substances and dosage forms, and *NF* responsible for excipients. By 1980, *USP XX* and *NF XV* were published under the same cover, a practice that continued at five-year intervals until 2002, when annual publication was adopted.

Mission.[2] *USP−NF* is published annually in the continuing pursuit of the mission of the United States Pharmacopeial Convention, which is "to promote the public health and benefit practitioners and patients by disseminating authoritative standards and information developed by its volunteers for medicines, other health care technologies, and related practices used to maintain and improve health and promote optimal health care delivery".

Rules, Procedures, and Publications.[2] Standards that are published in *USP−NF* are widely recognized because they are authoritative, science-based, and are established through a transparent and credible process with a long history of integrity. These standards are recognized as representing "scientific truth" at the time of their establishment, but remain open to the process of continuous revision as science and technology inevitably evolve. All members of the governing and standard-setting bodies of USP are unpaid volunteers and, in compliance with the Constitution and Bylaws of the organization, must submit a conflict of interest statement disclosing financial interests in companies that are subject to *USP* standards or that may be influenced by *USP* information. This conflict of interest policy establishes accountability to the standard setting and revision process and, likewise, ensures its credibility. Finally, the USP Document Disclosure Policy contributes to the transparency of the standards-setting process by providing protection to manufacturers and others in the submission of confidential information.

USP 28-NF 23.[2] This text became official on January 1, 2005, and contains official substance and preparation (product) monographs. An official substance is defined as an active or inactive ingredient, a nutrient, a dietary supplement ingredient, and/or a pharmaceutical ingredient or a component of an official device. An official preparation refers to the finished dosage form, device, or dietary supplement product. The standards of a monograph for an official article include its definition; packaging, storage, and other requirements; and a specification. The specification consists of a series of universal (description, identification, impurities, assay) and specific tests, one or more analytical procedures for each test, and acceptance criteria. Ingredients are defined as either active ingredients or excipients, with an excipient being any component, inert or otherwise, other than the active substance(s), intentionally added to the formulation of a dosage form. Monographs for active ingredients and preparations, with the exception of dietary supplements, appear in the first section of *USP*. Monographs for dietary supplements appear in a separate section of *USP*, and excipient

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monographs are usually found in *NF* but may also appear in *USP*, with appropriate cross-referencing.

Botanical Monographs in the USP

History of Botanicals in the USP.[1−4] The history of the compendia of the United States Pharmacopeia is one that is rich in the inclusion of botanicals, with efforts at standardization of these substances reaching back to the first edition published in 1820. Monographs on approximately 320 botanical drug substances, as well as about 275 botanical preparations, have appeared since that time. However, by the beginning of the twentieth century, only approximately 170 botanical monographs were in existence. With advancements in organic chemistry in the latter half of the nineteenth century (including the isolation and determination of structure of many bioactive phytomedicinal compounds such as cocaine, morphine, nicotine, and quinine),[5] combined with progress in synthetic organic/medicinal chemistry and pharmacology in the twentieth century, an inevitable slow erosion of botanical monographs from official compendia occurred. By 1995, there were slightly less than 40 monographs on botanicals and their preparations in the *USP 23-NF 18*,[6] while in 2005 the *USP 28-NF 23* contained only 35 monographs.[7]

Dietary Supplement Health and Education Act (DSHEA), 1994.[2,3,8] In October, 1994, following a period of intense public debate, the United States Congress passed the Dietary Supplement Health and Education Act (DSHEA), thereby amending the Federal Food, Drug, and Cosmetic Act. DSHEA defines a dietary supplement as "A product (other than tobacco) intended to supplement the diet that bears or contains one or more of the following dietary ingredients: (A) a vitamin; (B) a mineral; (C) a herb or other botanical; (D) an amino acid; (E) a dietary substance for use by man to supplement the diet by increasing the total dietary intake; or (F) a concentrate, metabolite, constituent, extract, or combination of any ingredient described in clause (A), (B), (C), (D), or (E)" [FD&C Act § 201(ff)]. This Act affords legal recognition to *USP*−*NF* standards for dietary supplements, because the Act has stipulated that if a dietary supplement is represented as conforming to specifications found in an official compendium (*USP/NF*) but fails to conform, then the supplement is considered to be misbranded [FD&C Act § 403(s)(2)(D)]. Compliance with a USP−NF monograph is thus *voluntary* on the part of a dietary supplement manufacturer.

United States Pharmacopeial Convention: The 1995 Quinquennial Meeting.[9] The advisability of developing public standards and authoritative information concerning botanicals was a strongly debated issue at the 1995 Quinquennial Meeting of the United States Pharmacopeial Convention. After a lengthy and sometimes vigorous discussion, the Convention adopted Resolution No. 12, a resolution that "encouraged the USP to explore the feasibility and advisability of establishing standards and developing information concerning dietary supplements".

Subcommittee on Natural Products, 1995−2000.[10−12] The USP Subcommittee on Natural Products was elected at the 1995 Quinquennial Meeting of the United States Pharmacopeial Convention and began work in the autumn of 1995 to address the concerns expressed in Resolution No. 12. The Subcommittee,[11] assisted by its appointed Advisory Panel,[12] was charged with the selection of candidate botanicals and with the identification of appropriate analytical procedures for the identification and characterization of these botanicals. The following criteria were utilized by the Subcommittee in the selection process that followed: first, a presumptive belief in some therapeutic efficacy and/or beneficial pharmacological activity, as evidenced by a long history of use in traditional medicine—"apparent efficacy"; second, the absence of serious adverse effects, also as evidenced by a long history of use in traditional medicine—"apparent safety"; third, the extent of use by the public sector—"demand"; fourth, interest by a regulatory agency—"public protection"; fifth, the ability of the botanical to meet compendial criteria—"feasibility"; and sixth, the presence of existing monographs in other books and publications—"compendial presence".[10]

Dietary Supplements: Botanicals Committee of Experts (2000−2005).[13,14] At the 2000 Quinquennial Meeting of the United States Pharmacopeial Convention, the nomenclature utilized to designate the committee structures was changed from "Subcommittee" to "Committee of Experts". The new Committee of Experts[13] was also assisted by an appointed Advisory Panel.[14]

General Chapters in the *USP*−*NF*.[15,16] Before examining the individual parts of any botanical dietary supplement monograph, it is necessary to understand the definition, function, and content of general chapters within the *USP*−*NF*. General chapters include chapters that specify general requirements for tests and assays, informational chapters, and nutritional supplement chapters. Each general chapter is assigned a number that appears in brackets ⟨ ⟩ adjacent to the chapter name. The contents of general chapters are reflected in the numbering, in that those chapters documenting general requirements for tests and assays are numbered from ⟨1⟩ to ⟨999⟩, those that are informational are numbered ⟨1000⟩ to ⟨1999⟩, and those that pertain to dietary/nutritional supplements are numbered above ⟨2000⟩. The most important general chapters pertaining to botanical dietary supplements are summarized below.

Articles of Botanical Origin ⟨561⟩.[17] This long-standing general chapter describes methods of sampling (gross sample, laboratory sample, test sample); methods of analysis (foreign organic matter, total ash, acid-insoluble ash, water-soluble ash, alcohol-soluble extractives, water-soluble extractives, crude fiber, starch content, volatile oil determination, water content); aflaxotin testing; general method for pesticide residues analysis; and test for pesticides.

Identification of Articles of Botanical Origin ⟨563⟩.[18] This chapter, which details procedures that are to be used in the identification of raw materials intended for manufacture of pharmaceuticals, excipients, or dietary supplements of botanical origin, was drafted by the Committees and first appeared in *USP 26-NF 21* in 2003.[19] These procedures involve an examination of the morphological and histological features of the article under test and the performance of diagnostic chemical tests on the article. The botanical and chemical characteristics of the test article are then compared to the known botanical and chemical characteristics of the plant species. Reference articles may be specified to assist in the proper botanical and chemical identification of the plant and plant part. A reference article may be either USP Authenticated Reference Material, which may be used for both botanical and chemical identification, or a USP Reference Standard, which is used for chemical identification only. Major headings within the chapter include USP Authenticated Reference Materials; Botanical Identification (Diagnostic Plant Morphology and Anatomy, Microtechnique); and Chemical Identification (Chemotaxonomy, Active Principles and Marker Compounds, Use of USP Reference Articles).

Botanical Extracts ⟨565⟩.[20] This chapter, which describes the methods of extraction utilized in the preparation of extracts, preparations, and tinctures, was drafted by the Committees and first appeared in *USP 25-NF 20* in 2002.[21] In the extraction practice for articles of botanical origin, the constituents of interest are completely or partially separated from other components with the aid of water, alcohol, alcohol−water mixtures, or other suitable solvents. This extraction process involves the removal of the desired constituents from the plant matter with suitable menstruum, the evaporation of all or nearly all of the solvent, and the adjustment of the residual fluids, masses, or powders to the prescribed standards. Suitable inert substances may be added as carriers or diluents to improve physical characteristics, and appropriate antimicrobials and other preservatives may be added to preserve the extract integrity. Extracts may be subjected to processes that increase the content of characterized constituents, decrease the content of unwanted constituents, or both.

Extracts with no added inert substances and no processing beyond the extraction are called native extracts. In some preparations, the plant matter may be pretreated by inactivation of enzymes and microbial contaminants, grinding, defatting, or a similar procedure. Extracts may have a liquid, solid, or semisolid consistency. The products obtained by extraction are fluidextracts, powdered extracts, semisolid extracts, and tinctures. Major headings within the chapter include: Methods of Extraction (Percolation, Maceration); Preparations (Fluidextracts, Powdered Extracts, Semisolid Extracts, General Pharmaceutical Requirements [Packaging and Storage, Labeling, Residue on Evaporation, Residual Solvents, Pesticide Residues, Heavy Metals, Alcohol Content]); Tinctures (Percolation Process, Maceration Process, General Pharmacopeial Requirements [Packaging and Storage, Labeling]).

Supplemental Information for Articles of Botanical Origin ⟨2030⟩.[22] This new general chapter provides information about several aspects of botanical articles not covered in the USP standards monographs. Although the standards in the monographs address the quality issues associated with botanical plant materials, extracts, and preparations of pharmacopeial articles, there is a need to develop appropriate information to optimize the preharvesting conditions for appropriate growth and postharvesting handling to achieve consistent quality with minimum variation in the composition of chemical constituents. Toward that end, this general chapter contains information for specific botanicals about quality assurance measures for good agricultural and collection practices and other auxiliary information not covered in the monographs deemed to be important for achieving raw material of consistent quality. The following are contained in this important chapter: Contents (**Black Cohosh**, **Ginger**, and **Valerian**); General Guidances (CITES, CBD, and ESA); and Good Agricultural Practice (GAP) Protocols (Plant [Black Cohosh, Ginger, Valerian], Botanical Identification, Historical Use, Constituents, Sources, Collection and Cultivation, Drying, Storage and Shipping, Adulterants, and Global Regulatory Status).

Manufacturing Practices for Dietary Supplements ⟨2750⟩.[23] The principles elaborated in this chapter specify recommended minimum current good manufacturing practices for the methods to be used in, and the facilities and controls to be used for, the manufacture of a dietary supplement. These practices ensure that such a product meets the requirements of safety, identity, strength, quality, and purity that the product is represented to possess.

Monograph Development (1995−2005): An Introduction

The literal definition of a monograph is "one writing", with a monograph being functionally defined as a "learned treatise on a small area of learning" or "a written account of a single thing".[24] USP botanical monographs are characterized by having separate and distinct sections that provide tests critical to the identification of the botanical, as well as other tests that ensure the absence of undesirable ingredients. Each monograph is qualitatively different but is formulated to exist within the confines of a moderately uniform framework or template. A consideration of the nature and content sections of some prototypic monographs will serve to illustrate this point, as well as to highlight some of the challenges and problems that the Committees faced in the development of these monographs over the past 10 years. The botanical monographs referred to in the following pages are illustrated in tabular form as Table S1, Supporting Information.

Monograph Template − Title (Name) of the Monograph.[10,25] The title of the monograph states the identity of the botanical and generally reflects the most common name utilized in North American commerce,[10,25] as found in *Herbs of Commerce*, 2nd ed.[26] The title does *not* normally bear direct reference to the plant part(s) utilized. Examples of titles include: **Garlic**,[27] **Ginger**,[28] **Horse Chestnut**,[29] **Milk Thistle**,[30] and **Saw Palmetto**.[31] Where separate plant parts may be used for different individual monographs, these plant parts are stated in the respective titles, such as **Hawthorn Leaf with Flower**[32] (which differentiates this monograph from **Hawthorn Leaf with Berry**, the latter being a monograph not currently found in the *USP*) and **Echinacea purpurea Root**[33] (which differentiates this monograph from **Echinacea purpurea Aerial Parts**,[34] the latter monograph utilizing the fresh, aboveground parts harvested at flowering as the official article). Where different species of the same genus are used in separate monographs, the species variation is noted in the respective titles, such as **Echinacea angustifolia**,[35] **Echinacea pallida**,[36] and **Echinacea purpurea Root**[33]**/Echinacea purpurea Aerial Parts**.[34]

Monograph Template − Definition and Rubric.[10,25] The definition includes the name of the plant parts that are utilized, as well as the genus, species, authority, and family. In addition, other significant items, such as the time of collection, may be included. A rigorous definition ensures consistent quality (batch-to-batch consistency) of the pharmacopeial article, while the rubric specifies the standards of strength to which the botanical must conform.

Numerous plant parts serve as sources of the monographed botanicals, including aerial parts, flowering tops, flower heads, inflorescence (flowering branch), fruit, seeds, seed coat bark, leaves, stem bark, rhizomes, roots, stolons, and bulbs.[37] Monographs specifying the time of collection include **Black Cohosh**,[38] **Echinacea angustifolia**,[35] **Echinacea pallida**,[36] **Echinacea purpurea Aerial Parts**,[34] **Echinacea purpurea Roots**,[33] **Feverfew**,[39] **Horse Chestnut**,[29] and **St. John's Wort**.[40]

Several examples of the above variables include "**Ginger** is the rhizome of *Zingiber officinale* Roscoe (Fam. Zingiberaceae), scraped or unscraped. It is known in commerce as unbleached ginger."[28] "**St. John's Wort** consists of the dried flowering tops or aerial parts of *Hypericum perforatum* L. (Fam. Clusiaceae), gathered shortly before or during flowering. It contains not less than 0.04 percent of the combined total of hypericin ($C_{30}H_{16}O_8$) and pseudohypericin ($C_{30}H_{16}O_9$) and not less than 0.6 percent of hyperforin ($C_{35}H_{52}O_4$)."[40] Finally, a good example that illustrates most of these variables is **Echinacea pallida**: "**Echinacea pallida** consists of the dried rhizome and roots of *Echinacea pallida* (Nutt.) Nutt. (Fam. Asteraceae). It is harvested in the fall after 3 or more years of growth. It contains not less than 0.5 percent of total phenols, calculated on the dried basis as the sum of caftaric acid ($C_{13}H_{12}O_9$), chicoric acid ($C_{22}H_{18}O_{12}$), chlorogenic acid ($C_{16}H_{18}O_9$), and echinacoside ($C_{35}H_{46}O_{20}$)."[36]

An example of another variable associated with this section occurs when the botanical source may be more than one species, as found in the definition of **Licorice**: "**Licorice** consists of the roots, rhizomes, and stolons of *Glycyrrhiza glabra* L. or *Glycyrrhiza uralensis* Fisch. ex DC. (Fam. Fabaceae)."[41] Still a further example of such a variable includes the Echinacea Monographs,[33−36] where there are at least three species of the genus *Echinacea* that are popular articles of commerce: *Echinacea angustifolia* DC. (Fam. Asteraceae),[35] commonly referred to as Narrow-Leaf Echinacea, Kansas Snakeroot, or Narrow-Leaf Purple Coneflower;[26] *Echinacea pallida* (Nutt.) Nutt.[36] also known as Pale-Flower Echinacea or Pale Purple Coneflower;[26] and *Echinacea purpurea* (L.) Moench,[33,34] the commonly cultivated garden variety that is the most widely utilized species and is also known as Common Purple Coneflower.[26] A final example of a variable in this section is a plant whose nomenclature is in some state of disagreement. This occurs with the definition of **Garlic**,[27] where botanists, taxonomists, and others are not in accord with the Family designation, with some (including the USP) stipulating that the utilization of the more traditional "Liliaceae" is appropriate, while others prefer the use of the more contemporary "Alliaceae".

Monograph Template − Packaging and Storage.[3,10,15,25] This section cites the appropriate packaging and storage conditions for the botanical and is intended to ensure that the potency (strength) and integrity of the botanical within the container are preserved. These specifications are shelf-life specifications, and several

examples include **Chaste Tree** − "Preserve in a well-closed container, and store at controlled room temperature";[15,42] **Cranberry Liquid Preparation** − "Preserve in well-closed containers, and store in refrigerator";[15,43] **Garlic** − "Store in well-closed containers in a cool, dry place, protected from light";[15,27] **Ginger** − "Preserve in well-closed containers, protected from light and moisture";[15,28] **American Ginseng** − "Preserve in tight, light-resistant containers, and store protected from heat";[15,44] **St. John's Wort** − "Store in tight containers, protected from light and moisture".[15,40]

Monograph Template − Labeling.[10,15,25] This section states the requirements for the nomenclature on the label. The label of the article states the Latin binomial name and, following the official name, the part(s) of the plant contained in the article. A few examples include *Hydrastis canadensis* L., Goldenseal Roots and Rhizomes;[45] *Ginkgo biloba* L., Ginkgo Leaf;[46] *Aesculus hippocastanum* L., Horse Chestnut Seed;[29] *Silybum marianum* (L.) Gaertn., Milk Thistle Fruit;[30] and *Trifolium pratense* L., Red Clover Inflorescence.[47]

Monograph Template − USP Reference Standards ⟨11⟩.[3,10,15,25,48] USP Reference Standards ⟨11⟩ describes all of the USP−NF Reference Standards (RS), including the identity of the appropriate reference standards to be used in the analysis of botanicals.[48] USP Reference Standards are authentic specimens that are suitable for use as comparison standards in *USP* or *NF* tests and assays. These reference standards have been established and released under the authority of the USPC Board of Trustees upon recommendation of the USP Reference Standards Committee, which passes on the selection and suitability of each lot. The critical characteristics of each lot of specimen selected for the standard are usually determined independently in three or more laboratories. The USP Reference Standards Laboratory and the FDA laboratories participate in testing almost all new standards and replacements for existing standards. Academic and industrial laboratories throughout the nation also participate in the testing. The requirements for any new *USP* or *NF* standards, tests, or assays for which a new USP Reference Standard is specified are *not* in effect until the specified USP Reference Standard is available. Availability, replaceability, stability, homogeneity, and cost are important considerations with regard to Reference Standards. Some examples of different types of Reference Standards for dietary supplement botanicals monographs includes Powdered Drugs (e.g., USP **Powdered Ginger** RS,[28] USP **Powdered Valerian** RS[50]); Powdered Extracts (e.g., USP **Powdered Asian Ginseng Extract** RS,[50] USP **Powdered St. John's Wort Extract** RS[40]); Compound Mixtures (e.g., USP Ginkgo Terpene Lactones RS);[46] and Single Compounds (e.g., USP Agnuside RS [**Chaste Tree**],[42] USP Formononetin RS [**Red Clover**],[47] USP Silybin RS [**Milk Thistle**],[30] and USP Valerenic Acid RS [**Valerian**]).[49]

Monograph Template − Botanic Characteristics.[10,25] This section cites the detailed macroscopic and microscopic (histologic) characteristics of the botanical. **Ginger** serves as a good example:[28]

Ginger − Macroscopic − "... Whole rhizomes are 5 to 15 cm long, 1.5 to 6 cm wide, and up to 2 cm thick, sometimes split longitudinally ...";

Ginger − Histology − "Starch abundant in the thin-walled ground tissue, as flattened, ovate to subrectangular, transversely striated, simple granules, each with a hilum in a projection toward one end, mostly up to about 50 μm long and up to ...".

Monograph Template − Identification.[10,25] This section discusses pharmacognostic tests (color tests, precipitation tests) and chemical tests [thin-layer chromatography (TLC), high-pressure liquid chromatography (HPLC), gas−liquid chromatography (GLC)] that are useful in identification. Tests that are based on chromatographic separations tend to provide the most reliable positive identification of designated marker compounds in comparison with Reference Standards. Some examples include **Ginger** − Turbidity and color tests, TLC evaluation;[28] **Valerian** − Color tests, TLC evaluation, HPLC retention time of valerenic acid.[49]

In general, TLC identification tests are performed in a single solvent system, although multiple systems may be more appropriate in order to provide reassurance that adulteration has not occurred or to provide additional assurance of the suggested presence of the marker compound(s).

Monograph Template − Limit Tests.[10,25] The next portion of a typical monograph includes a series of tests that stipulate upper or lower limits for various substances within the botanical.

Monograph Template − Limit Tests − Total Ash ⟨561⟩.[10,17,25,51] This test measures the amount of residue that remains after the incineration of the botanical and provides an indication of the quantity of inorganic compounds present in the plant. Total ash, which has sometimes been termed "physiological ash", varies within definite limits according to the type of soil. In some cases, the figure is of importance because it tends to indicate the amount of care taken in preparation of the crude botanical. The variation in limits occurring within the currently developed monographs is within the range of from not more than 1.5% (**Maritime Pine**)[52] to not more than 13.0% (**Chamomile**)[53] with 23 of the 28 plants currently monographed having a range within the limits of 7.0−12.0%.

Monograph Template − Limit Tests − Acid-Insoluble Ash ⟨561⟩.[10,17,25,51] This test measures the residue remaining after boiling the total ash with 3 N hydrochloric acid. This residue consists mainly of sand and other silicates and is an indication of the amount of dirt, soil, clay, and related material that is present in the sample. In the past, this residue was sometimes called "foreign inorganic matter". Generally speaking, this figure is of greater value than the total ash content as a measure of quality, since the total ash varies within limits relatively far apart. The variation in limits of acid-insoluble ash occurring within the currently developed monographs is from not more than 1.0% (**Garlic**,[27] **Asian Ginseng**,[50] and **Saw Palmetto**[31]) to not more than 5.0% (**Goldenseal**[45] and **Valerian**[49]).

Monograph Template − Limit Tests − Water-Soluble Ash ⟨561⟩.[10,17,25,51] This test measures the residue remaining after boiling the total ash with water and represents that portion of the total ash that is water-soluble. It is useful in the detection of the presence of exhausted plant marc within the crude botanical, which in turn suggests adulteration. **Ginger** is the only currently developed monograph in which this limit test is found (not less than 1.9%).[28]

Monograph Template − Limit Tests − Foreign Organic Matter ⟨561⟩.[10,17,25,51] This test identifies and measures any other part of the plant except that constituting the drug, as well as any other vegetable or animal tissues or substances that may be present. These limits are determined by physically removing all parts of a sample that should not be present and weighing them. The variation in limits occurring within the currently developed monographs is from not more than 1.0% (**Ginger**)[28] to not more than 10.0% (**Feverfew**),[39] with 22 of the 28 plants currently monographed having a range within the limits of 2.0−3.0%. Two unusual examples of additional limits are found in the monographs for **Black Cohosh**[38] (dried rhizomes and roots) and **Ginkgo**[46] (dried leaves), where in the former not more than 5.0% of stem bases and not more than 2.0% of other foreign organic matter are allowed, while in the latter not more than 3.0% of stems and not more than 2.0% of other foreign organic matter are allowed.

Monograph Template − Limit Tests − Loss on Drying ⟨731⟩.[10,25,51,54] Loss on Drying ⟨731⟩ is a general chapter that describes the amount of volatile matter of any kind (such as water, volatile oils, or individual volatile chemical compounds) that is driven off under the conditions specified.[54] However, this limit test is not employed for substances that appear to contain water as the only volatile constituent. Instead, the limit test described in Water Determination ⟨921⟩ is used.[55] The variation in limits occurring

within the currently developed monographs for Loss on Drying ⟨731⟩ is from not more than 7.0% (**Cat's Claw**,[56] **Powdered Garlic**[27]) to not more than 14.0% (**Eleuthero**),[57] with 17 of the 22 plants that have prescribed limits having these values between 10 and 12.0%.

Monograph Template − Limit Tests − Water Content ⟨561⟩[10,17,25,51]**/Water Determination ⟨921⟩.**[10,17,25,51,55] Water Determination ⟨921⟩ is a general chapter that describes methods used for determination of water content.[55] Moisture is normally present to the extent of 5−10% in all dried drugs, with an excess of moisture being considered an adulterant. There are only three botanical monographs that cite limits on water content: **Garlic** (not more than 65.0% for fresh bulbs or 7.0% for dried bulbs),[27] **Maritime Pine** (not more than 35.0%),[52] and **Valerian** (not more than 12.0%).[49]

Monograph Template − Limit Tests − Alcohol-Soluble Extractives ⟨561⟩ and Water-Soluble Extractives ⟨561⟩.[10,17,25,51] These limit tests measure the amount of extractive matter obtained by treatment with alcohol, water, or aqueous alcohol and are used as a means of evaluating botanicals for constituents that are not readily estimated by other means. These extractives tend to be specific for given drugs and are usually expressed as "not less than" a stated percentage. In general, a lower figure than acceptable is an indication of adulteration with a previously extracted sample (marc) of botanical. Some examples of currently developed monographs that contain reference to extractive matter are **Feverfew** (Water-Soluble Extractives − not less than 15.0%);[39] **Ginger** (Alcohol-Soluble Extractives − not less than 4.5%; Water-Soluble Extractives − not less than 10.0%);[28] **Asian Ginseng** (Alcohol-Soluble Extractives − not less than 14.0%);[50] **Horse Chestnut**, (Aqueous Alcoholic Extractives − not less than 18.0%);[29] **Licorice** (Alcohol-Soluble Extractives − not less than 25.0%);[41] **Pygeum** (Alcohol-Extractable Matter − not less than 9.0%);[58] **Red Clover** (Water-Soluble Extractives − not less than 15.0%);[47] **Saw Palmetto** (Lipophilic Extract − not less than 7%);[31] and **Valerian** (Aqueous Alcoholic Extractives − not less than 20%).[49]

Monograph Template − Limit Tests − Volatile Oil ⟨561⟩.[10,17,25,51] This test is useful in the determination of the amount of volatile oil present in certain botanicals. Examples of currently developed monographs that contain reference to volatile oil determination are **Chamomile** (not less than 0.4%);[53] **Echinacea pallida** (between 1.0 and 2.0 mL per 100 g);[36] **Ginger** (not less than 1.8 mL per 100 g);[28] **Saw Palmetto** (not less than 2 mL per 100 g that solidifies into a white solid at room temperature);[31] **Valerian** (not less than 0.5%);[49] and **Powdered Valerian** (not less than 0.3%).[49]

Monograph Template − Limit Tests − Heavy Metals ⟨231⟩.[10,25,51,59] This general chapter describes limit tests for heavy metals.[59] These tests, which are based on a determination of the content of metallic impurities that are colored by sulfide ion, tend to be more relevant for plant parts that grow underground (rhizomes and roots), and are utilized to control the amount of heavy metals that may result from soil contamination, ground water, or milling. The variation occurring within virtually all of the currently developed monographs is from not more than 10 μg per g (0.001%, 10 ppm) (examples include **Milk Thistle**,[30] **Echinacea Angustifolia**,[35] **Red Clover**[47]) to not more than 20 μg per g (0.002%, 20 ppm) (examples include **Horse Chestnut**,[29] **Goldenseal**,[45] **Asian Ginseng**[50]). Notable exceptions are **Licorice** (not more than 30 μg per g)[41] and **Powdered Valerian** (not more than 50 μg per g).[49]

Monograph Template − Limit Tests − Organic Volatile Impurities ⟨467⟩.[10,25,51,60] This general chapter describes limit tests for organic volatile impurities present as residual solvents. Residual solvents are defined within the USP as organic volatile chemicals that are used or produced in the manufacture of drug substances or excipients, or in the preparation of drug products. Products should contain no higher levels of residual solvents than can be supported by safety data. The chapter groups residual solvents into three classes based on solvent toxicities as follows: Class 1 − Avoid unless their use can be strongly justified in a risk:benefit assessment; Class 2 − Less severely toxic, with limited exposure; Class 3 − Less toxic solvents. A complete list of solvents is found in the appendix, as well as various methods (Methods I, IV, V, and VI) for conducting the gas chromatographic analysis. Alcohol, water, or alcohol−water mixtures are commonly used to prepared powdered botanical extracts, and hence this limit test is present within the monographs of powdered plant extracts.

It was recently proposed to change the chapter title to Residual Solvents and to delete the Other Analytical Procedures section (Methods I, IV, V, and VI).[61] These proposals are consistent with revisions to individual monographs. The Organic Volatile Impurities ⟨467⟩ requirement will be deleted from all *USP*, *NF*, and *Dietary Supplements* monographs that currently contain it, and a new requirement for Residual Solvents ⟨467⟩ will be added to all appropriate drug substance, excipient, drug product, and dietary supplement monographs. These individual monograph changes will appear in *USP 29-NF 24*, with a delayed implementation date of January 1, 2007.[61]

Monograph Template − Limit Tests − Pesticide Residue ⟨561⟩.[10,17,25,51] Within the *USP−NF*, the use of the term "pesticide" applies to any substance or mixture of substances intended to prevent, destroy, or control any 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. Those botanicals that are treated as dietary supplements within the United States are subject to the statutory provisions of the Federal Food Drug and Cosmetic Act that govern *foods* but not drugs. Limits for pesticides for foods are determined by the Environmental Protection Agency (EPA), and where no limit is set, the limit is *zero* [FD&C Act § 402(a)(2)(B), 408(a)]. Since USP standards do not modify statutory requirements, pesticide limits in USP botanical monographs are not applicable in the United States when the articles are labeled for food purposes (dietary supplements). However, the limits may be applicable in other countries where the presence of pesticide residues is permitted. Generally, the *USP−NF* has adopted limits and test procedures that are in harmony with the *European Pharmacopeia*, and a limit test, appearing in Articles of Botanical Origin ⟨561⟩,[17] is intended to place strict limits on organochlorine, organophosphorus, and pyrethroid toxic residues. The challenge of limiting pesticide residues is overwhelming because of the incomplete and inconsistent control of the worldwide use of pesticides, and the best solution would be to limit the use of pesticides in cultivation on a worldwide basis.

Monograph Template − Limit Tests − Microbial Enumeration ⟨2021⟩.[10,25,51,62] There are four general chapters that are important in defining and limiting the microbial content of botanical dietary supplements. Microbial Limit Tests ⟨61⟩ provides tests for the estimation of the number of viable aerobic microorganisms present and for freedom from designated microbial species in pharmaceutical articles of all kinds, from raw materials to finished forms.[63] Microbial Enumeration Tests − Nutritional and Dietary Supplements ⟨2021⟩ provides tests for the estimation of the number of viable aerobic microorganisms present in nutritional supplements of all kinds, from raw materials to finished forms.[62] Microbiological Procedures for Absence of Specified Microorganisms − Nutritional and Dietary Supplements ⟨2022⟩[64] describes the testing of nutritional and dietary articles for specific microorganisms that are specified in the individual monographs or whose absence is recommended by guidance under Microbiological Attributes of Nonsterile Nutritional and Dietary Supplements ⟨2023⟩.[65] Good manufacturing

practices require that objectionable organisms be absent from nonsterile nutritional and dietary products. A microorganism may be considered objectionable if it represents a potential health hazard to the user who is using the product as directed or if it is capable of growing in the product. Objectionable microorganisms are defined as contaminants that, depending on the microbial species, number of organisms, dosage form, intended use, and patient population, would adversely affect product safety or if the organisms adversely affect product stability or damage the integrity of the container closure system.[64]

Microbiological Attributes of Nonsterile Nutritional and Dietary Supplements ⟨2023⟩ contains microbial enumeration tests that provide important information concerning the microbiological acceptability of excipients, active substances, and nonsterile supplement formulations.[65] If any individual monograph does not specify microbial enumeration limits, the guidance provided in this chapter is used. The chapter contains tables that describe the following: the definitions of a range of different botanical materials (chopped or powdered botanicals, botanical extracts, tinctures, infusions, decoctions, fluidextracts, and teas); the recommended microbial limits for botanical ingredients and products (dried or powdered botanicals, powdered botanical extracts, tinctures, fluidextracts, infusions/decoctions, nutritional supplements with botanicals, and teas); and the recommended microbial limits for dietary supplement ingredients and products.[65]

Botanicals may be microbiologically contaminated at any point during cultivation, harvesting, processing, packing, and distribution. Major sources of microbial contamination are associated with human or animal feces used as plant manure, contaminated irrigation water and/or process water, and poor worker hygiene and sanitation practices during harvesting, sorting, processing, packaging, and transportation. Microbial contamination needs to be minimized during the manufacture of nonsterile dietary supplements, and Good Manufacturing Practices are useful in accomplishing this goal. Since members of the family *Enterobacteriaceae* are a major component of the normal epiphytic and endophytic microflora (such as *Klebsiella*, *Enterobacter*, and *Erwinia* spp.) and have been associated with the seeds, pods, roots, leaves, and stems of plants of economic importance, coliform or Enterobacteriaceae counts are not considered to be an appropriate general microbiological criterion for botanicals. However, when considered appropriate and advantageous, coliform or Enterobacteriaceae counts may be included in the individual monographs. Bacteria tend to predominate on the microflora of new leaves, while yeast and filamentous fungi succeed bacteria and become dominant late in the growing season. With dried botanicals, the bacterial population will tend to change from Gram-negative bacteria to Gram-positive spore formers and fungi. Refinement of botanicals from chopped or powdered plant material to powdered extracts using alcoholic, alkaline, acidic hydroalcoholic, or aqueous extraction materials will reduce the likelihood of vegetative microorganisms within the botanical material. The recommended microbial limits (colony forming units/gram [cfu/g] or mL) for dried or powdered botanicals are as follows: total aerobic microbial count − not more than 10^5 cfu/g; total combined yeast and mold count − not more than 10^3 cfu/g; bile-tolerant Gram-negative bacteria (coliforms + enterobacterial organisms) − not more than 10^3 cfu/g; and the absence of *Salmonella* spp. and *Escherichia coli* in 10 g. The recommended microbial limits for powdered botanical extracts are as follows: total aerobic microbial count − not more than 10^4 cfu/g; total combined yeast and mold count − not more than 10^3 cfu/g; and the absence of *Salmonella* spp. and *Escherichia coli* in 10 g. Finally, dietary and nutritional articles containing botanical products with a history of mycotoxin contamination are also typically tested for aflatoxins, particularly if the material is obtained from rhizomes or roots.[65]

Monograph Template − Marker Substances and Content Tests.[10,25] It is generally believed that the reported pharmacological activity for a botanical dietary supplement is due to the presence of more than one constituent, and it is possible that these constituents may act in a synergistic manner. Toward this end, quantitative procedures for the determination of content of two marker substances have been developed to aid in the proper identification of the botanical. The designation of these substances as "markers" should *never* be taken as an endorsement of confirmed pharmacological activity of these compounds, but rather viewed as yet another method for ensuring appropriate identification of the botanical. Liquid chromatographic (LC) methods, particularly HPLC as well as GLC, have been the methods of choice that are utilized in content tests for markers in the current monographs, although spectrophotometric methods, particularly UV spectrophotometry, have been utilized in the absence of validated LC methods. Although most of the monographs that were developed from 1995 to 1998 specified the determination of only a single marker substance, comments from the participants at the USP Open Conference on Dietary Supplements (August 1998)[4] suggested that monographs should contain qualitative and quantitative test procedures (TLC, HPLC, GLC, or UV) for the identification and content determination of more than one marker substance. As a consequence, the Natural Products Subcommittee (December 1998) endorsed this recommendation, with the result that all existing and subsequent monographs contain two marker substances. Several examples of marker substances include **Asian Ginseng** − ginsenoside Rg_1 and ginsenoside Rb_1;[50] **Garlic** − alliin and γ-glutamyl-(*S*)-allyl-L-cysteine;[27] **Goldenseal** − berberine chloride and hydrastine hydrochloride;[45] and **St. John's Wort** − hypericin, pseudohypericin, and hyperforin.[40]

Publication of USP Monographs − *Pharmacopeial Forum*.[1,10,15,25,66] *Pharmacopeial Forum* (*PF*), the Journal of Standards Development and Official Compendia Revision of the USP, is the working vehicle of the USP Council of Experts and attendant Expert Committees. *PF*, which was first published in January 1975 as a means to publicize revision proposals prior to these proposals reaching the "proof stage", is currently published bimonthly in order to provide interested parties an opportunity to review and comment, as the Council of Experts develops or revises standards for the *United States Pharmacopeia* and the *National Formulary* (*USP−NF*). The organization of *PF* includes, but is not limited to, the following: potential revisions − entirely new standards; revision ideas, and drafts not yet targeted for official adoption (*Pharmacopeial Previews*); proposed revisions − new or revised standards targeted for official adoption (*In-Process Revision*); adopted revisions − new or revised standards that become official and binding before publication of the next *USP−NF* or *Supplement* (*Interim Revision Announcement*). Other sections of *PF* feature articles that comment upon *Stimuli to the Revision Process* (reports, statements, articles, or commentaries relating to compendial issues), *Nomenclature* (articles and announcements relevant to compendial nomenclature issues and listings of suggested and new United States Adopted Names [USAN] and International Nonproprietary Names [INN]), *Interim Revision Announcements*, and *Official Reference Standards* (catalog of current lots, with ordering information and names and addresses of worldwide suppliers).

In general, it is convenient to conceptualize the monograph development process as being fourfold: first, publication of the proposed monograph in the *Pharmacopeial Preview* stage; second, advancement of the proposed monograph to the *In-Process Revision* stage following receipt and consideration of comments; third, publication of periodic *Supplements* to official text that include text previously published in *PF*, which is ready to be made official; and fourth, publication of the official monograph, the latter remaining continually open for comment and revision.

USP welcomes comments and data on potential, proposed, or official standards and will publish these comments, along with

USP's responses, in one of the following: *PF Briefings*, the *Commentary Section* of *PF*, the *Commentary Section* of *Supplements* to *USP−NF*, or the *Commentary Section* of *USP−NF*.

Placement of Botanical Dietary Supplement Monographs within the USP−NF.[67] The difference between the "USP" and the "NF" designations on the label of a product reflects the differing admission criteria for the two official compendia. An article may appear in the *USP* if it has an FDA-approved or USP-accepted use, thereby meeting the criteria of "most fully established and best understood". An article with no FDA-approved or USP-accepted use may be included in the *NF* if it has been extensively used without a significant safety risk use, thus meeting an "extent of use criteria". Standards for botanical dietary supplements generally appeared in the *National Formulary* (*NF*) portion of the *USP−NF* until 2002. At that time, the Executive Committee of the Council of Experts voted to create a separate section entitled Dietary Supplements within the *USP* portion of the *USP−NF*, and all dietary supplement monographs and related general chapters have been placed in this new section as of *USP 27/NF 22* (2004).

Admission Criteria for Dietary Supplements.[67] Since 1995, selection and prioritization of dietary supplements for admission to the *USP−NF* were based upon several factors which continued to guide both the Expert Committee of Non-Botanicals and the Expert Committee on Botanicals during the current revision cycle. These factors are as follows: extent of use, based upon market sales or other factors; historical use; knowledge of chemical composition; existence of other pharmacopeial standards; evidence of benefit; interest from a government body; absence of significant safety risk associated with use. Because safety was a significant concern, the Scope Committee was established in 1995 to analyze safety evidence to determine whether an article should be admitted to the *USP−NF*. The Scope Committee ceased to exist with the 2000 revision cycle, and the newly formed Dietary Supplement Information Expert Committee assumed responsibility for safety evaluation. In 2002, the Dietary Supplement Information Expert Committee developed the following criteria for consideration of articles proposed for placement in the *USP−NF*: human data (safety studies, clinical studies, postmarketing surveillance, adverse events, interactions, publicly available data [taking into account issues on phytoequivalency]); pharmacological data (reproductive toxicity, experimental animal studies, pharmacokinetics, therapeutic index, presence of toxic constituents, contemporaneous extent of use globally and in the United States, including misuse and abuse, historical use); regulatory status in the United States and other countries, including regulatory actions, OTC status, GRAS status, etc.; and the existence of official pharmacopeial monographs. After evaluating the above criteria and factors, and on the basis of the information contained in the materials reviewed, it was proposed that the Committee would recommend the inclusion of an article into one of the following classes. Class 1: Articles for which the Committee is unaware of significant safety issues present when the article is used and formulated appropriately that would prohibit a monograph from being developed (**Asian Ginseng**, **Black Cohosh**, **Chamomile**, **Chaste Tree**, **Cranberry**, **Feverfew**, **Garlic**, **Ginger**, **Ginkgo**, **Hawthorn Leaf with Flower**, **Horse Chestnut**, **Milk Thistle**, **Red Clover**, **Saw Palmetto**, **Stinging Nettle**, and **Valerian**). Class 1a: Articles for which the Committee is aware of limited human scientific data concerning safety of the article, but is unaware of significant safety issues present when the article is used and formulated appropriately that would prohibit a monograph from being developed (**Cat's Claw**, **Eleuthero**, and **Goldenseal**). Class 2: Articles for which the Committee is unaware of significant safety issues present, when the article is used and formulated appropriately, that would prohibit a monograph from being developed, provided there is a warning statement in the labeling section (**Echinacea angustifolia**, **Echinacea pallida**, **Echinacea purpurea**, **Licorice**, and **St. John's Wort**). Class 3: Articles for which the Committee is aware of significant safety issues present that would prohibit a monograph from being developed (**Kava**). The Council of Experts Executive Committee approved this approach to dealing with safety issues of dietary supplements in 2003, and in 2004 the composition of the warning labels for Class 2 articles was forwarded to the Nomenclature and Labeling Expert Committee. These warnings are recommended for inclusion in the labeling of various powdered plant extract monographs as follows.

Powdered Echinacea angustifolia Extract,[68] **Powdered Echinacea pallida Extract,**[69] **Powdered Echinacea purpurea Extract.**[70] "The label bears a statement indicating that *Echinacea angustifolia* (or *pallida* or *purpurea*) may cause rare allergic reactions, rashes, or aggravate asthma."

Powdered Licorice Extract.[71] "The label bears a statement indicating that "Excessive amounts or long-term use of Licorice may cause high blood pressure or low potassium, which have been associated with irregular heartbeat and/or muscle weakness. Licorice may worsen the effects of congestive heart failure, cirrhosis, or kidney failure. Diuretic use may increase the risk. If you are pregnant or nursing a baby, seek the advice of a health professional before using this product."

Powdered St. John's Wort Extract.[72] "The label bears a statement indicating that "Rare cases of allergic reactions and photosensitivity have been reported with the use of St. John's Wort. St. John's Wort interacts with numerous medications. Check with your health care provider before using."

General Chapter ⟨2030⟩ Supplemental Information for Articles of Botanical Origin.[22] The Advisory Panel to the Dietary Supplements: Botanicals Committee of Experts was charged with the following responsibilities: first, the creation of two new general chapters, one on Good Agricultural Practices (GAP) and one on Supplemental Information for Articles of Botanical Origin; and second, the exploration of the possibility of developing Authenticated Reference Plant Materials (ARPM). These two general chapters were considered necessary to stipulate conditions important to achieve consistent quality of botanicals that meet the requirements of the USP standards monographs. The information chapter would contain specifics for each plant about other constituents not covered in the specifications, i.e., collection and cultivation practices, postharvesting handling, drying and storage, common adulterants, botanical identification, commercial sources, historical use, and global regulatory status.

Supplemental Information for Articles of Botanical Origin ⟨2030⟩[22] was recently published following extensive work by the Advisory Panel and its excellent staff liaison, Jennifer Salguero. The contents of this chapter have been previously discussed in the early portions of this Review (see **General Chapters in the *USP−NF***).

Finally, it is important to note that the work of the Advisory Panel was considered so important to the development of pharmacopeial standards for botanical dietary supplements that the status of the Panel was elevated to that of an independent Expert Committee (Dietary Supplements-General Chapters) in the 2005−2010 quinquennial cycle.

Continuing Work for the 2005−2010 Dietary Supplements: Botanicals Expert Committee − Dosage Forms Monographs and Additional Plant Monographs. For most botanical dietary supplements, the following transition of monographs is consistent: plant ⟶ powdered plant ⟶ powdered plant extract ⟶ dosage form (commonly tablet and/or capsule). There are a number of tablet/capsule monographs that either are in transition in *Pharmacopeial Forum* or have yet to be developed. The following is a brief summary detailing the existence of capsule and tablet monographs at the present time: capsule monographs (**Black Cohosh**, **Garlic**, **American Ginseng**, **Asian Ginseng**, **Goldenseal**, and **Red Clover**); tablet monographs (**Ginger**, **Pygeum**, and **Saw**

Palmetto); both capsule and tablet monographs (**Cat's Claw**, **Chaste Tree**, **Echinacea angustifolia**, **Echinacea pallida**, **Echinacea purpurea**, **Eleuthero**, **Feverfew**, **Hawthorn Leaf with Flower**, **Horse Chestnut**, **Licorice**, **St. John's Wort**, and **Stinging Nettle**).

The following plants were selected by the Committee as the next candidates for monograph development: **Bilberry**, **Green Tea**, **Grape Seed**, **Soybean**, and **Turmeric**. Work by Staff and the Expert Committee has begun in the 2000−2005 cycle and will reach fruition in the new quinquennium (2005−2010).

Summary of the Accomplishments of the 1995−2005 Committees

In the preceding 10 years, the two Committees have been responsible for the drafting and publication of 106 monographs dealing with 29 different plants within *USP−NF* compendia (Table 1). These monographs may be summarized as follows: plant − 29; powdered plant − 23; powdered plant extract − 20; capsule − 11; tablet − 10; extract − 5; fluid extract − 2; liquid preparation − 1; solution − 1; tincture − 1; fraction − 1; compounds − 2. At the current time, 83 of these monographs appear in the *USP 28/NF 23* (2005) or its Supplements, while 23 are found in *Pharmacopeial Forum* (17 monographs being in the in-process revision stage and 6 monographs in the pharmacopeial preview stage).

The second major contribution of these Committees was the drafting and publication of two new general chapters: Identification of Articles of Botanical Origin ⟨563⟩[18] and Botanical Extracts ⟨565⟩,[20] the former first appearing in *USP 26/NF 21* (2003),[19] while the latter appeared one year earlier in *USP 25/NF 22* (2002).[21] Finally, as previously stated, the Advisory Panel (2000−2005) to the Committee recently published Supplemental Information for Articles of Botanical Origin ⟨2030⟩.[22]

Supporting Information Available: Table of botanical dietary supplement monographs in the USP (1995−2005). This is available free of charge via the Internet at http://pubs.acs.org.

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(11) Elected Members of this Subcommittee included Paul J. Kucera (Chair) (Wyeth-Ayerst), Edward M. Croom (The University of Mississippi), David Katague (CDER/FDA), Edward G. Lovering (Private Consultant), Samuel W. Page (Division of Natural Products/FDA), Paul L. Schiff, Jr. (University of Pittsburgh), and E. John Staba (University of Minnesota). The USP Staff Liaison was V. Srini Srinivasan, Senior Scientist, Natural Products (NAT).

(12) Individuals who served on the appointed Advisory Panel to the Subcommittee were Dennis V. C. Awang (Mediplant), Ezio Bombardelli (Indena), Werner Busse (Schwabe Pharmaceuticals), Horace G. Cutler (Mercer University), Jonathan W. DeVries (Medallion Laboratories), Patrick Dunn (Leiner Health Products), Gary W. Elmer (University of Washington), Forouz Ertl (Technical Botanicals International), Patrick Hoffman (McCormick & Company), Charles D. Hufford (The University of Mississippi), Michael Ihrig (Zentrallaboratorium Deutscher Apotheker), A. Douglas Kinghorn (University of Illinois at Chicago), Nahid Mokhtari-Rejali (Division of OTC Products/FDA), William Popin (Nature's Herbs), Amala Raman (King's College, London), Walter Schulze (ACTA Laboratories), and Sidney J. Stohs (Creighton University).

(13) The Members of 2000−2005 Committee of Experts included Paul L. Schiff, Jr. (Chair) (University of Pittsburgh), Joseph M. Betz (2004−2005) (Office of Dietary Supplements, National Institutes of Health), Yuan-yuan Chiu (2000−2003) (Center for Drug Evaluation and Research, Food and Drug Administration), Forouz S. Ertl (2000) (Botanicals International/Hauser), Dennis Gorecki (University of Saskatchewan), Norman R. Farnsworth (University of Illinois at Chicago), Paul J. Kucera (Wyeth Pharmaceuticals), Samuel W. Page (2000−2004) (World Health Organization), William Popin (Young Living Essential Oils), Fabio Soldati (Pharmaton, Switzerland), and Otto Sticher (Swiss Federal Institute of Technology).

(14) Individuals who served on the appointed Advisory Panel to the Committee included William Popin (Chair) (Young Living Essential Oils), Rudolf Bauer (Karl Franzens University, Graz), Mark Blumenthal (American Botanical Council), Ezio Bombardelli (Indena, Italy), John Cardellina (National Cancer Institute), Edward Fletcher (Strategic Sourcing), James S. Miller (Missouri Botanical Garden), Simon Y. Mills (University of Exeter), Gregory Pennyroyal (Growin Medicine), Amala Raman (King's College London), Kathy Sharpless (NIST), and Roy Upton (American Herbal Pharmacopeia).

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