

Above: Cover of the *Pharmacopoeia of the United States of America*, published in 1820.
Below: Current 2020 *USP-NF* website.



QUALITY STANDARDS FOR BOTANICALS THE LEGACY OF USP'S 200 YEARS OF CONTRIBUTIONS

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The *Pharmacopoeia of the United States of America (USP)*,[†] first published in 1820, was intended to bring nationwide uniformity to the quality of drugs, most of which at the time were based on botanical and mineral ingredients. Over the last 200 years, the United States Pharmacopeial Convention (USP) has adapted to evolving technologies and products and has continued to provide public quality standards for botanical, chemical, and biological medicines. This article examines the history of the evolution of botanical quality standards, as well as the current status of botanical monographs for drugs, herbal medicines, dietary supplements, and excipients (i.e., antioxidants, binders, bulking agents, coloring agents, flavoring agents, pharmaceutical bases, sweetening agents). It also provides an outlook for the future, in which USP anticipates adapting to rapid changes in technologies. This article is an abbreviated version of a more detailed paper by the authors and has been revised for *HerbalGram*. The full-length paper, as referenced in this article, can be accessed at: <http://abc.herbalgram.org/site/DocServer/HG126-USP-Legacy-FullPaper-5-1-20.pdf/>.

HISTORICAL CONTEXT

As the settlements of European colonists expanded through the 16th to 18th centuries, native American botanical species and their uses in the indigenous systems of medicine were observed, documented, classified in a European context, and initially monographed in pharmacopoeias of the colonial powers. The American War of Independence (1775-1783) created an urgent need for pharmacopoeias that could serve the needs of military hospitals. William Brown (1748-1792), Physician-

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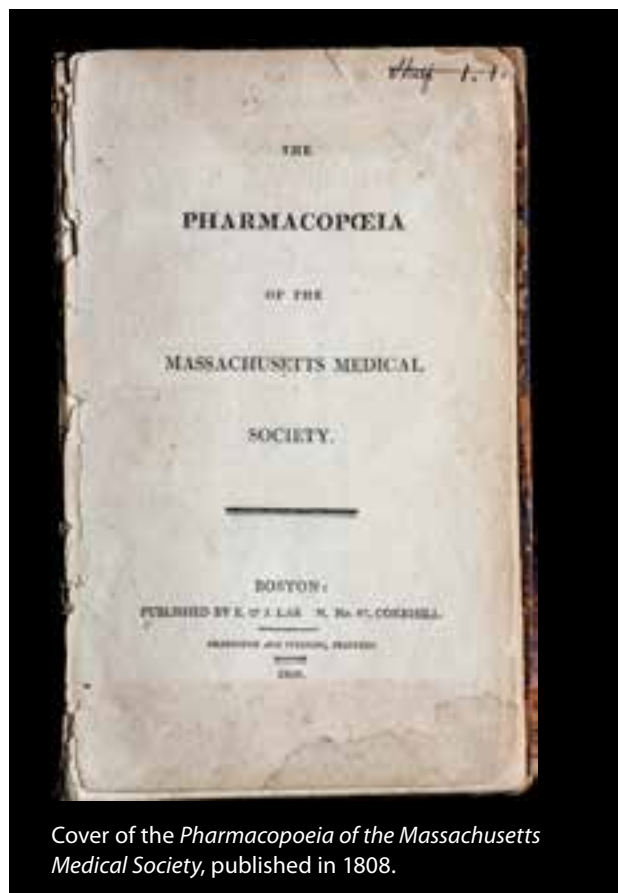
† The abbreviation USP (without italics) is used in this article to refer to the United States Pharmacopeial Convention, and the abbreviation *USP* (in italics) is used to refer to the pharmacopeial compendium.

General of the Middle Department of the Continental Army, while stationed at the army hospital in Lititz, Pennsylvania, compiled a work now known as the *Lititz Pharmacopoeia*, published in 1778. (The full title, translated from Latin, is *Pharmacopoeia of simple and efficacious remedies for use of the military hospital, belonging to the army of the Federated States of America; especially adapted to our present poverty and straitened circumstances, caused by the ferocious inhumanity of the enemy, and the cruel war unexpectedly brought upon our fatherland.*)¹ Much of the traditional knowledge of the indigenous peoples was adopted more formally into American medical practice and, by the late 18th century, codified in the first pharmacopoeias and dispensatories of the new country, the United States of America.² Examples of plants native to North America that were of medicinal importance to indigenous peoples and were also published in Scottish physician William Cullen's (1710-1790) 1769 handbook on medicines included capsicum (*Capsicum annuum*, Solanaceae), sarsaparilla (then *Smilax sarsaparilla*, now *S. glauca*, Smilacaceae), sassafras (*Sassafras albidum*, Lauraceae), and Seneca snakeroot (*Polygala senega*, Polygalaceae).³

Publishing in English, another factor in the development of a truly American pharmacopoeia, was championed by physicians James Jackson (1777-1867) and John Collins Warren (1778-1856), who formed the committee for the 1808 *Pharmacopoeia of the Massachusetts Medical Society*.⁴ Dr. Samuel Latham Mitchill (1764-1831; misspelled "Mitchell" in the 1820 and 1831 editions of the *USP*) and Dr. Valentine Seaman (1770-1817) followed a similar approach in their *Pharmacopoeia of the New York Hospital*, published in 1816.⁵ They wanted their work to be written in English and mutually convenient to the physician and pharmacist. Most European pharmacopoeias at that time were written in Latin.

The United States Pharmacopoeial Convention was founded on January 1, 1820, by 11 forward-thinking physicians, three of whom were responsible for leading the effort. The idea to form a national pharmacopoeia originated with Dr. Lyman Spalding (1775-1821), a passionate physician and masterful organizer from New York; the previously mentioned Mitchill, a charismatic statesman and former senator from New York as well as a physician who was president of the USP Convention and helped promote the creation of the first national pharmacopoeia; and Dr. Jacob Bigelow (1787-1879), from Harvard University in Massachusetts, an expert in plant drugs and an experienced editor, who oversaw its publication. Physicians at the time wanted "to recognize the full range of truly American medicinal plants that patriotic medical gentlemen expected."⁶

Building on the pharmacopoeias of the Massachusetts Medical Society and the New York Hospital and under the direction of Mitchill, the first national *Pharmacopoeia of the United States of America* was published in 1820.⁷ It was divided into sections, beginning with the front matter, historical introduction, and preface, followed by the *materia medica* (a primary list of 217 drugs, including 145 botanicals); most of the entries were botanicals or botanically derived ingredients.⁸ This section was followed by a secondary list of 71 drugs with ingredients of "doubtful efficacy" and whose use was uncertain, including 67 botanicals; a section on weights and measures; and an



Cover of the *Pharmacopoeia of the Massachusetts Medical Society*, published in 1808.

GLOSSARY OF IMPORTANT TERMS

Compendium	A compendium (plural: compendia) is a compilation of knowledge about a particular subject (e.g., articles of botanical, algal, or fungal origin).
Pharmacopoeia	A pharmacopoeia (also spelled "pharmacopoeia") is a compendium of standards and quality specifications, providing tests to confirm the composition, identity, quality, purity, and strength of defined articles used in medicines and foods.
Dispensatory	A dispensatory is a compendium that supplements the pharmacopoeia, providing commentary on the pharmacopoeial articles, posology (dosing), and indications for their therapeutic, nutritional, or other uses.
Formulary	A formulary, in the strict sense, is a compendium of formulations currently in use, although the current <i>National Formulary (NF)</i> also includes standards for excipients of botanical origin as well as other articles and preparations that do not appear in the <i>USP</i> . The <i>USP</i> and the <i>NF</i> are official compendia of the United States of America.
Materia medica	<i>Materia medica</i> is the Latin term for substances used in medicine.
Monograph	A pharmacopoeial monograph provides a specification with acceptance criteria and tests to verify the composition, identity, quality, purity, and strength of the defined article.
Official	Official means stocked by apothecaries and standardly used in medicine. Although the title <i>National Formulary of Unofficial Preparations</i> replaced the term "Unofficial" in the 1896 revision, the two terms are not exactly synonymous.

untitled section of 329 preparations and compositions.⁹ In the section that included formulae for the preparation and compositions of medicines, all articles that were presented by the District Conventions (that held regional meetings prior to the National Convention) were included, except in cases where two preparations were considered similar, in which case only one formula was included. A visual representation of the botanicals in the *USP 1820* is available at www.usp.org/trustXI.

Some native North American plants included in *USP 1820* were substitutes for European plants of the same genus with similar qualities. The pharmacopeia reflected the therapeutics of the time, including tonics, strong laxatives, diuretics, and flavoring herbs. The preparations included cerates (waxy preparations for external use), confections, decoctions, extracts, honeys, infusions, liniments, mixtures, ointments, pills, plasters, powders, spirits, syrups, tinctures, troches (lozenges), vinegars, washes, waters, and wines. Recipes and compounding techniques were included, but no analytical methods appeared in the monographs.⁹ The USP also recognized that new medical discoveries would lead to many new articles that would expand the *materia medica* to an unmanageable size. The USP therefore planned for the “retrenchment of superfluities,” creating what became known as the process of “omission” of articles from the pharmacopeia in the later years.

There were two second editions of the *USP*, the New York version of 1830¹⁰ and the Philadelphia version of 1831¹¹; the latter was more accurate and actually became the first decennial revision of the *USP*, also called *USP I*. From these versions onward, the monographs included brief botanical descriptions, macroscopic, and organoleptic properties to be verified for identification of the articles. The complexity of this information increased with subsequent editions. However, to address the need for standards of identity, purity, and strength, additional detailed information on each *USP* article was included in *The Dispensatory of the United States of America*, which was published from 1833 to 1973.

Figure 1. A black cohosh tincture product (“Tincture Cimicifuga N. F. IV.”) illustrating raw material quality in compliance with Black Cohosh *USP IX* (1910). Photo courtesy of Scott Jordan, PhD

AS *PHARMACOPOEIA OF THE MASSACHUSETTS MEDICAL SOCIETY* AUTHORS JACKSON AND WARREN NOTED IN 1808:

“In this, as in former ages, men are creating confusion by creating names. The object of the reforms in scientific language is to obviate this evil and to establish nomenclature upon solid grounds.”

As *USP* evolved into an authoritative compendium for drugs of first choice, other efforts for “standardization of names and formulas for dosage forms of drugs not described elsewhere” were in development.¹² One such publication was the *National Formulary (NF)*, which was intended to provide formulas that could be “compounded on a small scale that physicians and self-medicating public wanted.” The first issue of the *National Formulary of Unofficial Preparations* was published in 1888 by the American Pharmaceutical Association (APhA), now called the American Pharmacists Association.¹³ The first editions of the *USP* and the *US Dispensatory* were authoritative but not official; the *USP* and the *NF* achieved legal recognition with the passage of the

Food and Drug Act of 1906.

Botanicals have always been prone to intentional economically motivated adulteration or unintentional substitution with closely resembling species that may share the same common name. Collaboration between pharmacists and physicians improved the quality of standards in the early years. The role and importance of pharmacy and public trust in medicines grew with the increase in quality standards made available in the *USP*. Gregory J. Higby, PhD, pharmacy historian and former executive director of the American Institute of the History of Pharmacy, described the methods used by Dr. William Procter, Jr. (1817-1874) in examining the adulteration of aloe (*Aloe* spp., Xanthorrhoeaceae) latex.¹⁴ Procter used an intelligent combination of organoleptic sensory tests (color, appearance, odor) coupled with comparison of observations of authentic material for solubility in different solvents and the ash values to distinguish the “original” material from the adulterated aloe.

Standardization of botanical and chemical nomenclature for pharmacopeial articles was another goal of the *USP*. As *Pharmacopoeia of the Massachusetts Medical Society* authors Jackson and Warren noted in 1808: “In this, as in former ages, men are creating confusion by creating names. The object of the reforms in scientific language is to obviate this evil and to establish nomenclature upon solid grounds.”⁴

Botanicals and botanically derived medicines were considered critical for the US Army Medical Department during the Civil War.¹⁵ These included South American cinchona (*Cinchona* spp., Rubiaceae) tree bark extract; quinine (obtained from cinchona tree bark extract); opium (*Papaver*



somniferum, Papaveraceae) capsule exudate; camphor (a monoterpene ketone obtained by distillation of the bark and wood of the East Asian camphor tree [*Cinnamomum camphora*, Lauraceae]); and ginger (*Zingiber officinale*, Zingiberaceae) rhizome. Issues of quality and adulteration concerned the pharmacists and physicians of the mid-19th century. In addition, the need for larger-scale manufacturers to adopt and use the pharmacopeia was highlighted during the 1870-1900 revisions. *USP* came to be valued increasingly as a source of industry-wide standards for nomenclature, strength, and purity, while the role of the compounding guide was assumed by the *US Dispensatory*.¹⁵

BOTANICALS IN *USP 1820* AND THEIR CONTINUED USE IN 2020

The first issue of the *USP*, published on December 15, 1820, contained monographs for 217 drugs in its Primary List,¹⁶ of which about 130 listed substances were herbal drugs used by Native Americans.⁸ For example, pharmacist John Uri Lloyd (1849-1936) wrote that the medical uses of black cohosh (Figure 1), then called “black snake root” (then *Cimicifuga serpentaria*, now *Actaea racemosa*, Ranunculaceae), were introduced “by the Indians” to “early domestic American medicine.” An aqueous decoction preparation of black cohosh was indicated for “diseases of women, for debility, to promote perspiration, as a gargle for sore throat, and especially for rheumatism.”¹⁷ While most of the botanicals in *USP 1820* were native plant species, by 1820 many European species had become naturalized in North America and adopted for use in indigenous medicine as well.

Several botanicals described in *USP 1820* have remained relevant for health care and appear in the *USP–NF 2020* edition. These include many native American species such as black cohosh root, capsicum fruit, ipecac (then *Calli-cocca ipecacuanha*, now in the *USP* as *Cephaëlis acuminata* or *Cephaëlis ipecacuanha*, both of which are subsumed under the currently accepted name *Carapichea ipecacuanha*, Rubiaceae) rhizome and root, podophyllum (*Podophyllum peltatum*, Berberidaceae) rhizome and root, and slippery elm (*Ulmus rubra*, Ulmaceae) inner bark, among others.

USP also included imported botanicals that still appear in *USP–NF* as of 2020. Some of these are African plants such as aloe (*Aloe spicata*) latex; myrrh (*Commiphora molmol* syn. *C. myrrha*, Burseraceae) oleo-gum resin; and senna (then *Cassia senna*, now *Senna alexandrina*, Fabaceae) leaflet. Asian species include garlic (*Allium sativum*, Amaryllidaceae) bulb; ginger rhizome; opium capsule exudate; turmeric (*Curcuma longa*, Zingiberaceae) rhizome; and the European species include valerian (*Valeriana officinalis*, Caprifoliaceae syn. Valerianaceae) root. Many of the aforementioned botanicals that appeared in *USP* in both 1820 and 2020 are top-selling herbs in the US market today as dietary supplement ingredients, especially aloe, black cohosh, garlic, ginger, senna, and turmeric.¹⁸



Figure 2. Dr. Charles Rice at his desk in the Bellevue Hospital library in New York City. Source: American Institute of the History of Pharmacy

BOTANICALS IN THE *NATIONAL FORMULARY* AND THEIR MIGRATION TO *USP*

The *National Formulary of Unofficial Preparations* was first published by the authority of APhA in 1888. The title of this compendium changed to *National Formulary* from the fourth edition in 1916 onward. The immediate predecessor and basis for the *NF* that today accompanies the *USP* was the *New York and Brooklyn Formulary of Unofficial Preparations*, published in 1884, edited by Dr. Charles Rice (1841-1901) (Figure 2), a pharmacist and chair of the Committee of Revision for the 1880 edition of the *USP*. The *National Formulary of Unofficial Preparations* published in 1888 was based on those unofficial (preparations not included) articles of the *USP 1880* that were in the most frequent demand, to

Figure 3. Documentation of the revision history of *USP VII*, 1890. Source: *USP*





Figure 4. An 1882 record of the ballot for approval of a standard. Source: USP



Figure 5. A comparative picture of the USP Committee of Revision and the officers of the Convention in 1910 (upper right) and the corresponding Council of Experts in 2017 (lower right). Source: USP

provide formulas that would enable pharmacists to prepare them to a uniform standard.¹⁹

Rice also established the first subcommittees and pioneered the use of revision circulars (Figure 3). This gave each member of the USP's Committee of Revision equal influence in the revision process by implementing a voting and commenting system, the framework of which is still in use today (Figures 4 and 5).

Joseph P. Remington (1847-1918) (Figure 6) was a distinguished Philadelphia pharmacist who succeeded Rice as the chair of the USP's Committee of Revision. Rice served as chair from 1880 to 1901 and Remington from 1901 to 1918. Remington was a member of the APhA Pharmacopeial Committee that was appointed specifically to provide APhA's input for the pharmacopeia. By the start of the 20th century, pharmacists began to dominate the revision of the pharmacopeia and make it more relevant to the times.

Admission of articles to the *NF* was based on extent of use rather than therapeutic value. The *NF* did not include monographs of botanical raw materials until 1916. "In listing a botanical drug, for example, the *NF IV* (1916) provided specifications of the species and part of the plant to be utilized, permissible percentage of foreign matter, odor, taste, and color, a description of the macroscopic and microscopic appearance, in addition to other characteristics," wrote Higby.²⁰ There was a dramatic increase with two-thirds more articles than the previous revision of the *NF*, resulting from increasing recognition of uncompounded botanical and chemical ingredients for the first time. Depending on the *USP*'s admission criteria, a mono-

graph developed for the *NF* could appear in the *USP*, and those dropped from the *USP* could be admitted into the *NF* if there was widespread usage, even if the therapeutic value had not been proven.

As shown in Table 1 on page 58, the two compendia borrowed from each other in terms of organization, and thus monographs in the two became similar. According to Higby:

The general thrust was to harmonize the *NF* with the activities and the character of the *USP*, while preserving the traditional conceptual difference between the two books — the *USP* setting specifications for drugs of first choice therapeutically, the *NF* for other drugs whose extent of use justified development of a monograph.... Of equally durable interest was a question about which drugs should be recognized by the *NF* and dealt with in the monographs. The [*USP*] had stuck by its original concept of scope, recognizing only drugs of first choice in each therapeutic category, as determined by representatives of organized medicine. This left a majority of the medicaments open for selection by the *NF*, and left ample room for differences of opinion. The pharmacist's journals reflected this interest at least until industrialization removed drug manufacture and most compounding from the local pharmacy.²⁰

In the *NF V* (1926), at the end of a botanical monograph, a list of preparations that included it as an essential ingredient was published. Many botanical drugs were deleted (omitted) in the *NF IX* (1950).

Federal Recognition

Long before the Federal Food and Drug Act of 1906, the 1848 Drug Importation Act was enacted to control the number of spurious and adulterated articles coming into the United States. New York City was the major port of entry for drugs, and since the 1830s, inspectors were seeing imports that were not of consistent quality. In an article titled “Good Enough for America,” Professor Dennis B. Worthen wrote: “Six articles dealing with adulteration or questionable identity of calomel, rhubarb,** morphine, colocynth, and quinine were published in 1835, four by NYCCoP [New York City College of Pharmacy].”²¹ The NYCCoP and many others, including Dr. Montgomery J. Bailey, an examiner in the NY Customs House, had also cataloged adulterated and counterfeit drugs coming through New York City. The bill passed quickly through the House of Representatives and Senate and was signed into law by President James K. Polk. In the Act, *USP* was mentioned along with other pharmacopeias and it was stipulated that articles that originated from England, Scotland, France, and Germany had to adhere to their respective pharmacopeias, and any others had to comply with the *USP*.

** Regarding the adulteration and identity of the laxative drug rhubarb (*Rheum palmatum*, Polygonaceae) root, while it was included in the *materia medica* of *USP 1* (1830), along with several monographs for preparations made from it (Rhubarb Pills, Infusions, Syrups, Tinctures, and Wines), the *US Dispensatory* (1833, p. 528) monograph dedicated pages of discussion on the uncertainty of the origin and botanical identity of rhubarb articles of commerce at that time, noting that “the question yet remains unsettled from what precise plant it is derived. The remoteness of the region where it is collected, and the jealous care with which the monopoly of the trade in this drug is guarded, have prevented any accurate information on the subject.” They did not know then that the medicinal rhubarb of commerce was, and still is for the most part, wild-collected in the high-altitude Qinghai-Tibet Plateau and Hengduan Mountains of China.

USP and *NF* standards were recognized in the Food and Drug Act of 1906, which provided a definition for drugs and misbranding and established the importance of standards. During the same time period, the chemical industry was growing, while the use of medicines derived from natural products was declining. This changed the pharmacopeial structure, with the inclusion of many more chemical medicines than botanicals. The Federal Food, Drug, and Cosmetic Act (FD&C Act), first enacted in 1938, defined the term “official compendium” as the official *USP*, the official *NF*, the official *Homeopathic Pharmacopoeia of the United States*, or any supplement to these publications.

To eliminate duplication of the same standards in different publications, the *USP* acquired the *NF* in 1975, and the combined volumes then became *USP–NF*.¹⁶ In the United States, compliance with a *USP–NF* monograph, if one exists, is mandatory for botanical drugs for the drug’s nonproprietary name, identity, strength, quality, purity, packaging, and labeling. Thus, *USP–NF* standards play a role in the prevention of adulteration and misbranding provisions of the FD&C Act.

Figure 6. Dr. Joseph P. Remington at his library; note the innovative use of the pool table for document review.
Source: American Institute of the History of Pharmacy



In 1994, the Dietary Supplement Health and Education Act (DSHEA) amendment to the FD&C Act recognized voluntary compliance with the “official compendia of United States” for dietary supplements. The amendment provided that a dietary supplement may be deemed misbranded if it is covered by a monograph in an official compendium, and is represented as conforming to this monograph, but fails to so conform. The dietary supplement must be represented as conforming to a *USP–NF* dietary supplement monograph for the compendial standards to apply. This contrasts with pharmaceutical products,

for which conformance to the monograph is mandatory whether or not the product claims to conform.²² This means that a dietary supplement is not required to meet *USP* standards unless the label includes a *USP* quality claim. Many dietary supplement products do not claim to conform to *USP* standards. When public standards are not mandatory, as in the case of dietary supplements, products that may be traded under identical names may possess vastly dissimilar attributes, and thus may be dissimilar in quality, benefits, and safety for consumers.

In 1995, a resolution at the *USP* Convention passed by its member delegates recognized the need for standards for dietary supplements and provided the mandate to *USP* to contribute in this area. Consistent with the regulatory recognition, the structure of the *USP–NF* publication introduced a separate section for dietary supplements.

Notable Inclusions and Omissions since *USP 1820*

The preface to the first edition of *USP* stated: “It is the object of a Pharmacopoeia to select from among substances which possess medicinal power, those, the utility of which is most fully established and best understood.” Faithful to this principle, and also in association with the rise in government regulation of both drugs and new drug claims, *USP* has evolved over time. Starting out as a compendium of complex botanicals whose pharmacology and composition were not well established or understood, *USP* has evolved in favor of including more of the simple small molecules for which the pharmacological mechanisms and composition were much clearer. In the early 20th century, analytical technology was not sufficient to enable a clear understanding of the composition of the complex mixtures used in traditional medicines, much less the underlying pharmacological mechanisms that involve multiple synergies and compensating interactions among constituents. Fortunately, this situation is changing rapidly, as new knowledge and analytical technologies emerge that can appropriately characterize botanicals.

American ginseng (*Panax quinquefolius*) plate from the 1818 *American Medical Botany* by Jacob M. Bigelow, one of the authors of *USP 1820*. (*American Medical Botany*, vol. 2, 1818, pl. XXIX)

THE PREFACE TO THE FIRST EDITION OF *USP* STATED:

“It is the object of a Pharmacopoeia to select from among substances which possess medicinal power, those, the utility of which is most fully established and best understood.”

Examples of important botanicals that were published in the pharmacopoeia after *USP 1820* and omitted in subsequent revisions, but later reintroduced or are presently in the process of being included, are American ginseng (*Panax quinquefolius*, Araliaceae) root and cannabis (*Cannabis sativa*, Cannabaceae) female (pistillate) inflorescence.

The American ginseng trade began in Québec, New France, in the early 18th century, and the article was initially defined in the *Dictionnaire de l'Académie Française*. Later, it entered the 1827 edition of *Pharmacopée française, ou Code des médicaments*, which

included the Iroquois common name “*Garent-Oguen*” (meaning “resembles man” or “a man’s thigh”) among others under the entry “Panax De La Chine.”²³ While initially appearing only on the Secondary List of *materia medica* of the second revision of the *USP 1840*, “Panax” (described as the root of *Panax quinquefolium*, now *P. quinquefolius*) had a short pharmacopoeial life. Secondary



List drugs were articles deemed to be of secondary importance; they were on probation toward dismissal or toward promotion to the Primary List, but were not for use in official preparations.²⁴ *Panax* root was dismissed 40 years later from the *USP VI* (1880). After a 122-year hiatus, American ginseng root reentered the *USP*, published in the *USP 26* in 2002,²³ this time as a dietary ingredient along with monographs for processed forms, such as powder and dry extract, and in dietary supplement dosage forms, namely capsules and tablets.

Cannabis, under the entry “Extractum Cannabis. *Extract of Hemp*. An alcoholic extract of the dried tops of *Cannabis sativa*—variety *Indica*,” first appeared in the Secondary List of *USP III* (1850). It was subsequently elevated to the Primary List in *USP IV* (1860). Interestingly, *USP V* (1870) included monographs for both “*Cannabis Americanae*” (flowering tops of *C. sativa* cultivated in North America) and “*Cannabis Indicae*” (flowering tops of female *C. sativa* var. *indica* from India), as well as monographs for their respective preparations, “*Extractum Cannabis Americanae*” and “*Extractum Cannabis Indicae*.” In 1888, both “*Extract of Indian Cannabis*” and “*Tincture of Indian Cannabis*” were included as components of several multi-ingredient preparations monographed in the first issue of *NF*.^{13,25} Cannabis extract remained in *USP* until the twelfth decennial revision (*USP XII*, 1940), published in 1942.

In recent years, there has been active and growing interest in cannabis inflorescence for medical purposes. In light of the unique regulatory status of cannabis, *USP* published a Stimuli Article for public comment in 2016 on the topic of

the advisability and feasibility of developing new *USP* quality standards for medical cannabis. As a result of legalization of the medical use of cannabis in numerous US states and in other countries, and in the absence of modernized quality standards such as monographs (i.e., other than the extensive but unofficial *Cannabis* monograph published by the American Herbal Pharmacopoeia in 2014), *USP* was asked to develop such standards.²⁶ The *USP Cannabis Expert Panel* was established, comprising scientific experts in areas of cannabis testing, procedure development and validation, and compendial procedures. The *USP Cannabis Expert Panel* has recommended specifications for fit-for-purpose analytical methods and to limit contaminants such as toxic elemental impurities, pesticides, microorganisms, and fungal toxins. Multiple complementary tests are included to provide an exhaustive quality characterization. The Expert Panel also highlighted the importance of naming, definition of chemotypes based on the cannabinoid profile, use of reference materials, and packaging/storage conditions. In April 2020, the *USP Cannabis Expert Panel* published a peer-reviewed article in the *Journal of Natural Products* describing quality attributes for cannabis inflorescence.²⁷ *USP* also submitted public comments to the US Food and Drug Administration (FDA) and US Department of Agriculture (USDA) regarding the need for quality standards for cannabis and cannabis-related compounds.

While *USP 1820* listed 145 botanical drugs in its Primary List, many more were admitted in the subsequent decennial revisions throughout the remainder of the 19th century. *NF* provided for the continuance of official standards for drugs

Illustration of cannabis (*Cannabis sativa*) from *American Medicinal Plants: An Illustrated and Descriptive Guide to the American Plants Used as Homeopathic Remedies: Their History, Preparation, Chemistry and Physiological Effects* by Charles F. Millsbaugh (1887). Image courtesy of Steven Foster



deleted from the *USP* during periodic revisions. Table 1 provides a list of selected notable articles of botanical origin admitted through *USP VIII* (1900), along with their year of dismissal and eventual readmission (including those that are expected to be readmitted). Additional information on the regional types and geographic origins of each botanical species is included in the table, although such data were generally not included in the *USP*. Inclusion in the table indicates significant current use in herbal foods, herbal

dietary supplements, botanical drugs, and other natural health products in North America. In the 20th century, when an article was dismissed from the *USP*, it was generally admitted to the next edition of the *NF*. Furthermore, most botanicals were eventually dismissed from the *NF* as well. Thus, the Dismissed column of Table 1 shows dismissals from the *USP* and, in most cases, subsequent dismissal from the *NF*. Many of the dismissed botanicals in Table 1 that subsequently entered the *NF* and left the *NF* eventually

TABLE 1. NOTABLE ADMISSIONS AND DISMISSALS OF *USP* ARTICLES OF BOTANICAL ORIGIN

Admitted	Article	Native	Dismissed	Readmitted
<i>USP</i> (1820)	Black cohosh [then black snake root] (then <i>Cimicifuga serpentaria</i> , now <i>Actaea racemosa</i>) root	Canada and USA	<i>USP XI</i> (1930); <i>NF IX</i> (1950)	<i>USP 31</i> (2008)
<i>USP</i> (1820)	(Ceylon) Cinnamon (then <i>Laurus cinnamomum</i> , now <i>Cinnamomum verum</i>) bark	Asia (Sri Lanka)	<i>USP X</i> (1920); <i>NF XII</i> (1965)	In process
<i>USP</i> (1820)	(Chinese) Cassia (then <i>Laurus cassia</i> , now <i>Cinnamomum cassia</i>) bark	Asia (China)	<i>USP VIII</i> (1900)	In process
<i>USP</i> (1820)	Garlic (<i>Allium sativum</i>) bulb	Asia	<i>USP VIII</i> (1900); <i>NF VI</i> (1936)	<i>USP 23–NF 18</i> , 8th Suppl. (1998)
<i>USP</i> (1820)	Ginger (<i>Zingiber officinale</i>) root	Asia	<i>USP XIV</i> (1950); <i>NF XIII</i> (1970)	<i>USP 23–NF 18</i> , 7th Suppl. (1997)
<i>USP</i> (1820)	Licorice (<i>Glycyrrhiza glabra</i>) root	Europe and Asia	<i>USP XXII–NF XVII</i> (1990)	<i>USP 25</i> (2001)
<i>USP</i> (1820)	Saffron (<i>Crocus sativus</i>) stigma	Europe	<i>USP VIII</i> (1900); <i>NF VIII</i> (1946)	Not yet planned
<i>USP</i> (1820)	Slippery elm (then <i>Ulmus fulva</i> , now <i>Ulmus rubra</i>) inner bark	Canada and USA	<i>USP XI</i> (1930); <i>NF XI</i> (1960)	<i>USP 23–NF 18</i> (1995)
<i>USP</i> (1820)	Turmeric (<i>Curcuma longa</i>) root	S. Asia (India)	<i>USP VI</i> (1880)	<i>USP 32</i> (2009)
<i>USP</i> (1820)	Valerian (<i>Valeriana officinalis</i>) root	Europe	<i>USP XII</i> (1940); <i>NF IX</i> (1950)	<i>USP 23–NF 18</i> , 8th Suppl. (1998)
<i>USP 1</i> (1830)	Dandelion (then <i>Leontodon taraxacum</i> , now <i>Taraxacum officinale</i>) root	Europe	<i>USP X</i> (1920); <i>NF XII</i> (1965)	In process
<i>USP 2</i> (1840)	(American) ginseng (then <i>Panax quinquefolium</i> , now <i>P. quinquefolius</i>)	Canada and USA	<i>USP VI</i> (1880)	<i>USP 26</i> (2002)
<i>USP 2</i> (1840)	(German) chamomile (<i>Matricaria chamomilla</i>) flower	Europe	<i>USP X</i> (1920); <i>NF IX</i> (1950)	<i>USP 23–NF 18</i> , 9th Suppl. (1998)
<i>USP 2</i> (1840)	(Lemon) balm (<i>Melissa officinalis</i>) leaf	Europe, W. Asia	<i>USP VIII</i> (1900)	Not yet planned
<i>USP 3</i> (1850)	Cannabis extract (alcoholic liquid extract of the dried flowering tops of <i>Cannabis sativa</i> var. <i>indica</i>)	S. Asia	<i>USP XII</i> (1940)	Work in progress ²⁷
<i>USP 4</i> (1860)	Goldenseal [then hydrastis] (<i>Hydrastis canadensis</i>) root	Canada and USA	<i>USP XI</i> (1930); <i>NF XI</i> (1960)	<i>USP 27</i> (2003)
<i>USP 4</i> (1860)	Skullcap (<i>Scutellaria lateriflora</i>) herb	Canada and USA	<i>USP IX</i> (1910); <i>NF VIII</i> (1946)	Not yet planned
<i>USP 4</i> (1860)	Yarrow (<i>Achillea millefolium</i>) leaves & flowering tops	Europe, W. and C. Asia	<i>USP VI</i> (1880)	In process
<i>USP 5</i> (1870)	American hemp (<i>Cannabis sativa</i> cultivated in North America) flowering tops	N. America	<i>USP VII</i> (1890)	In process
<i>USP 5</i> (1870)	American hemp (alcoholic liquid) extract	N. America	<i>USP VI</i> (1880)	In process
<i>USP 5</i> (1870)	Indian hemp (female plant of <i>Cannabis sativa</i> var. <i>indica</i>) flowering tops	S. Asia (India)	<i>USP XII</i> (1940)	In process
<i>USP 5</i> (1870)	Oregano (<i>Origanum vulgare</i>) herb	Europe, N. Africa, Asia	<i>USP VII</i> (1890)	In process
<i>USP 6</i> (1880)	Calendula (<i>Calendula officinalis</i>) ligulate flowers	Europe	<i>USP IX</i> (1910); <i>NF VIII</i> (1946)	Not yet planned
<i>USP 6</i> (1880)	Guarana (then <i>Paullinia sorbilis</i> , now <i>P. cupana</i>) dried paste prepared from the crushed or ground seeds	S. America (Brazil)	<i>USP X</i> (1920); <i>NF VIII</i> (1946)	<i>USP 43–NF 38</i> , 1st Suppl. (2020)
<i>USP 7</i> (1890)	Saigon cinnamon (then an undetermined species of <i>Cinnamomum</i> , now <i>Cinnamomum loureiroi</i>) bark	Vietnam	<i>USP XV</i> (1955); <i>NF XVII</i> (1990)	Not yet planned
<i>USP 8</i> (1900)	Saw palmetto [then sabal] (<i>Serenoa repens</i>) fruit	USA	<i>USP X</i> (1920); <i>NF IX</i> (1950)	<i>USP 23–NF 18</i> , 9th Suppl. (1998)

reentered the merged *USP–NF* in the late 20th century, or are again prioritized for readmission in the early 21st century. In 1995, the use of Roman numerals ceased, replaced with Arabic numerals starting with *USP 23–NF 18*.

Introduction of bioassays in *USP IX* (1910) marked a notable method for testing the potency of some botanicals. Optional bioassay methods were introduced for digitalis (*Digitalis purpurea*, then Scrophulariaceae, since moved to Plantaginaceae) leaf, squill (then *Urginea maritima*, now *Drimia maritima*, Asparagaceae) bulb inner scales, strophanthus (*Strophanthus kombe* or *S. hispidus*, Apocynaceae) ripe seed, and aconite (*Aconitum napellus*, Ranunculaceae) tuberous root. A bioassay requirement was also introduced for cannabis and its preparations. The bioassay for cannabis is based on the symptoms of incoordination in dogs and then adjusting the strength by comparison with a standard preparation. This requirement was omitted by *USP XI* (1930), possibly due to the challenges with bioassays (large variability) and a preference for replacing bioassays with chemical assays, as evidenced by a paragraph in Anderson & Higby's (1995) *Spirit of Voluntarism* stating concerns with bioassay reliability and reproducibility.²⁸

Current Status of *USP* Botanical Standards

Over the last two centuries, the Pharmacopeia's content has evolved dramatically, from simple descriptions to comprehensive monographs with specifications for identity, assays, impurities, and characterization of quality, as well as detailed requirements for storage, packaging, and labeling. An elaborate description of the current monograph specifications has been published^{16,29} with examples by both Schiff et al.

Over the last two centuries, the Pharmacopeia's content has evolved dramatically, from simple descriptions to comprehensive monographs with specifications for identity, assays, impurities, and characterization of quality, as well as detailed requirements for storage, packaging, and labeling.

(2006) and Ma et al. (2018) (see also the section *A Walk Through a USP Monograph*, available in the full-length paper). The number of monographs has increased substantially from a few hundred in 1820, which consisted mostly of botanicals and minerals, to nearly 5,000 in 2020, which are mostly chemical medicines but also include about 300 botanical ingredients, botanically derived compounds, and their dosage forms (see Table 2 in the full-length paper).

Depending on the manufacturer's claims and intended use(s), botanical articles described in the *USP* can be considered drugs, dietary ingredients, or excipients. The monographs in the *USP–NF* compendium are organized into

different sections. When an article of botanical origin can be legally used as a drug, the monograph that describes the article's quality attributes would appear in the main section of the *USP*. When the article is used to supplement

the diet, not intended to diagnose, prevent, treat, or cure a disease, it would appear in the dietary supplements section of the *USP*. If the botanical article is intended as an excipient, it would appear in the *NF*. Some articles may be used legally across these categories, thus their monographs may appear in multiple sections of the compendium, at times with different names pursuant to the nomenclature guidelines of the *USP*³⁰ or as cross references.

USP botanical drugs.

The current edition of the *USP* includes 60 botanical drugs (see Table 3 in the full-length paper), most of which are legacy articles included in early editions of the *USP* (e.g., belladonna [*Atropa belladonna*, Solanaceae], digitalis, and podophyllum) and botanical drugs of more frequent use that are available over the counter (OTC), such as senna, psyllium (*Plantago ovata*



Belladonna *Atropa belladonna*
Photo ©2020 Steven Foster

or *P. arenaria*, Plantaginaceae) husk, and capsicum oleoresin. Botanical drugs that are developed according to the recent FDA guidance for “botanical drugs,” such as sinecatchins, a partially purified extract of green tea (*Camellia sinensis*, Theaceae) leaf, and crofelemer, a preparation of dragon’s blood croton (*Croton lechleri*, Euphorbiaceae) latex, could be admitted to *USP* as botanical drugs, but are not yet listed.

Herbal Medicines Compendium (HMC). Recognizing the need for and the gap in standards for herbal medicines, USP published a Stimuli

Article in 2012 to seek comments on the development of a specialized compendium of herbal medicines.³¹ The Stimuli Article reviewed regulatory approaches in the United States and other countries, as well as the rationale for USP’s development of standards for traditional medicines. After the public comments were received and considered, the *HMC* was developed as an online resource that provides standards for herbal ingredients used in herbal medicines.³² Articles that are approved by a national authority for use as ingredients of herbal medicines, or are included in a national pharmacopeia, and are also deemed appropriate for inclusion in the *HMC* by a USP Expert Committee, are admitted into the compendium.

Through the *HMC*, USP created a forum for advancing standards for herbal ingredients used in traditional medicines around the world. The *HMC* publication, which is available in electronic form, contains only articles that are recognized as ingredients of herbal medicines in other countries and jurisdictions. Given that a botanical may be used as both a traditional medicine and a dietary ingredient, some of the *HMC* monographs overlap with the USP’s dietary supplement monographs, although their nomenclature would be different because of the different nomenclature guidelines for the two compendia. Currently, more than 45 monographs in the *HMC* are at the Final Authorized stage, and 25 monograph proposals are open for public comment. The expert volunteers of regional Expert Panels, for example the South Asia Expert Panel and East Asia Expert Panel, prioritize and recommend the standards for adoption. *HMC* provides the avenue to set standards for botanicals such as *Polygonum multiflorum* (syn. *Reynoutria multiflora*, Polygonaceae) and *Cullen corylifolium* (Fabaceae) that do not qualify for admission into the *USP*. In these two cases, the USP Dietary Supplements Admission Evaluations Joint Standard-Setting Subcommittee decided not to proceed with monograph development due to safety concerns if used as dietary supplements. However, the *HMC* is an appropriate home for such botanicals when used within their traditional medicine contexts with specific indications and posology.

Botanical dietary ingredients. A major advance toward including botanicals in *USP–NF* came after the 1994 passage of DSHEA, which defined dietary supplements as including herbs and other botanicals and extracts thereof, among other substances. The USP adopted a resolution in 1995 that

“The value of the Pharmacopoeia depends upon the fidelity with which it conforms to the best state of medical knowledge of the day.”

— JACOB BIGELOW, MD (1820)

“encouraged the USP to explore the feasibility and advisability of establishing standards and developing information concerning dietary supplements.” This resolution enabled USP to develop new monographs for this category of articles, including botanicals within the *NF* section until 2002, after which a separate section for dietary supplements was created in the *USP*. Since then, USP has steadily added new monographs of plant materials used as dietary ingredients with due diligence in the prioritization and admission of

the ingredients for standards development.¹⁶

Dietary Supplements Compendium (DSC). In 2009, USP published a separate compendium dedicated to dietary supplements named the *Dietary Supplements Compendium (DSC)*. By 2019, the *DSC* transitioned to an online-only publication with annual updates. The *DSC* includes all the monographs for dietary supplements and dietary ingredients published in *USP–NF*, plus other monographs for dietary ingredients that are included in the *Food Chemicals Codex (FCC)* and monographs for other non-dietary ingredients published in the *NF* that can be used to formulate dietary supplements. The *DSC* also includes supplemental information of interest to the dietary supplements industry, such as FDA guidance documents pertaining to dietary supplements (e.g., dietary intake tables) and supporting material for the monographs, such as sample chromatograms and micrographs.

Botanical excipients. Botanicals and botanically derived excipients have always been included in the *NF*, but if an excipient is also used as a pharmaceutical active ingredient in an FDA-approved product sold in the United States, its monograph will appear in the *USP* section instead. That is because some botanicals may function as excipients at non-therapeutic dosage levels but as active ingredients when used at therapeutic dosage levels. The criterion for inclusion of botanical excipients in *NF* is based on whether the article is used as an ingredient in one or more FDA-approved drugs or legally marketed as an excipient in the United States. The article must be included in the FDA Inactive Ingredient Database, referenced in the FDA approved drug label, or included in a drug awaiting approval by the FDA.^{33,34} Thus, USP works closely with the FDA to prioritize new monographs to be developed for excipients.³⁵

Reference Standards (RSs). *USP* monograph tests for identification and quantitation of active principles or marker compounds require well-characterized materials. The USP RSs for botanicals are thoroughly characterized for use in qualitative tests (such as identification by fingerprint tests, system suitability tests, or chromatographic peak markers) and quantitative tests (such as assays for ingredients and formulations, assays for composition of major constituents, limit tests, or control tests). These RS are intended for use in specific analytical tests in monographs in which properties of the product under examination are compared with those of the relevant RS. Depending on the intended purpose, the botani-

cal RSs may be represented by a powdered plant material (e.g., USP Powdered Ginger RS), a dry extract (e.g., USP Powdered Asian Ginseng [*Panax ginseng*] Extract RS), a purified fraction (e.g., USP Ginkgo [*Ginkgo biloba*, Ginkgoaceae] Terpene Lactones RS), or a pure compound (e.g., USP Valeric Acid RS). USP RSs are authentic specimens that have been collaboratively tested and approved for use as comparison standards in *USP–NF* or *HMC* tests and assays. USP RSs are provided for legal metrology purposes (the practice and process of applying regulatory structure and enforcement to metrology, which is the science of measurement) and can help ensure the comparability of results and traceability to the SI or metric units. Additional information regarding USP RSs is presented in the general chapter *USP Reference Standards* <11> (“chapter 11”). These RSs help to determine whether an article meets the monograph acceptance criteria to be deemed a USP-grade material.³⁶

USP guidance documents. USP has developed several guidance documents that explain aspects of the monograph development process. The Admission Evaluation guidance describes the prioritization, selection, and evaluation of information in admitting a monograph to the *USP* monograph development process.³⁷ The Nomenclature guidance explains how monograph titles and article names are constructed.^{30,38} Additional guidance documents, available on the USP website, address how to define the quality parameters for submission of monograph proposals.³⁹

General chapters. General chapters (found in every *USP* revision) are documentary standards that cover general requirements for tests and assays, and general information on analytical procedures. The most relevant general chapters pertaining to herbal medicine ingredients and botanical dietary supplements are:

- *Articles of Botanical Origin* <561>
- *Identification of Articles of Botanical Origin* <563>
- *Botanical Extracts* <565>
- *High-Performance Thin-Layer Chromatography Procedure for Identification of Articles of Botanical Origin* <203>
- *Residual Solvents* <467>
- *Chromatography* <621>
- *Water Determination* <921>
- *Identification of Articles of Botanical Origin Using High-Performance Thin-Layer Chromatography Procedure* <1064>
- *Microbial Enumeration Tests-Nutritional and Dietary Supplements* <2021>
- *Microbial Procedures for Absence of Specified Microorganisms-Nutritional and Dietary Supplements* <2022>
- *Elemental Contaminants in Dietary Supplements* <2232>

EVOLUTION OF BOTANICAL MONOGRAPHS

“The value of the Pharmacopoeia depends upon the fidelity with which it conforms to the best state of medical knowledge of the day.”—Jacob Bigelow, MD (1820)

The monographs in *USP–NF* undergo periodic revision to ensure that the pharmacopeial standards remain state-of-the-art in terms of the methods and technologies they describe, so they help meet the regulatory requirements. While the

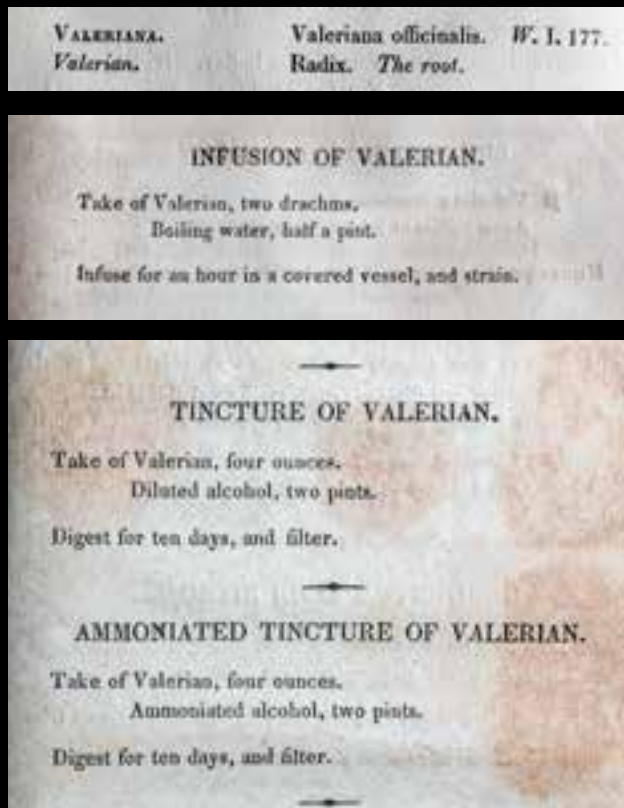
publications in the early 19th century did not include quality parameters to address the purity of chemicals (i.e., chemical formula, identifications, or assays, which are hallmarks of a modern pharmacopeia), the monographs were periodically revised and modernized in the 20th century to update the standards in line with the state of the science.

The revision history of the valerian monographs is presented here to illustrate the major changes over time. The first edition of *USP* in 1820 included monographs for Valerian, Infusion of Valerian, Tincture of Valerian, and Ammoniated Tincture of Valerian (Figure 7). The monograph for the plant material provided a compendial name for the botanical and defined the part of the plant. The monographs for the tea infusion and tincture provided a method to compound the plant mate-

Valerian *Valeriana officinalis*
Photo ©2020 Steven Foster



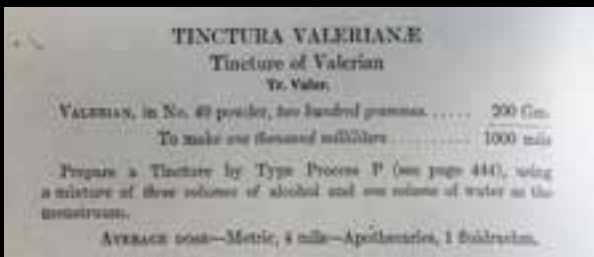
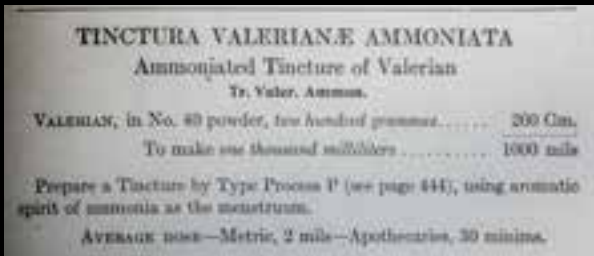
Figure 7. Valerian monographs in *USP 1820*.



rial into a standardized form. These monographs did not include methods to analyze the active principles or marker compounds or limits for contaminants.

Revisions of valerian monographs over time expanded the description of the morphological characteristics and included detailed methods for preparing the extract and tinctures. Shown in Figure 8 are the valerian monographs in *USP IX*, 1910.

Figure 8. Valerian monographs in *USP IX*, 1910.



Monographs for the valerian family were omitted from *USP XII* (1940) and *NF IX* (1950), apparently due to the decreased use of botanical remedies in the 1940s. The passage of DSHEA in 1994 provided a framework for botanical dietary supplements, and thereafter the standards for botanical dietary supplements were introduced in the *NF* portion of the *USP-NF* where they resided until 2002. Accordingly, the monographs for valerian were reintroduced in the *USP 23-NF 18*, 8th Suppl. (1998) as *NF* monographs. With the creation of a separate Dietary Supplements section within the *USP* portion of the *USP-NF*, all dietary supplement monographs and related general chapters were migrated to this new section as of *USP 27-NF 22* (2004). As of January 2020, these monographs for *Valeriana officinalis* are official in *USP 43*:

- Valerian
- Powdered Valerian
- Valerian Tablets
- Valerian Tincture
- Valerian Root Powdered Capsules
- Powdered Valerian Extract
- Valerian Root Dry Extract Capsules

The current monographs for valerian provide detailed descriptions of quality parameters in alignment with the state of the science and regulations (see *A Walk Through a USP Monograph* in the full-length paper). Modern monographs in the *Dietary Supplements Compendium* include illustrations of macro- and microscopic features with photographic material to aid the analysts. Identification tests are based on characteristic chromatographic fingerprints using high-performance thin-layer chromatography (HPTLC) and high-performance liquid chromatography (HPLC). The content of relevant constituents is typically determined by chromatographic methods such as HPLC. Detection of adulterants and contaminants is a major concern, and modern monographs now typically include provisions in the identification tests to rule out potential confounders, as well as modern purity tests to detect contaminants such as heavy metals by inductively coupled plasma (ICP) or pesticides by advanced chromatography.

Figure 15. Current USP valerian monograph.

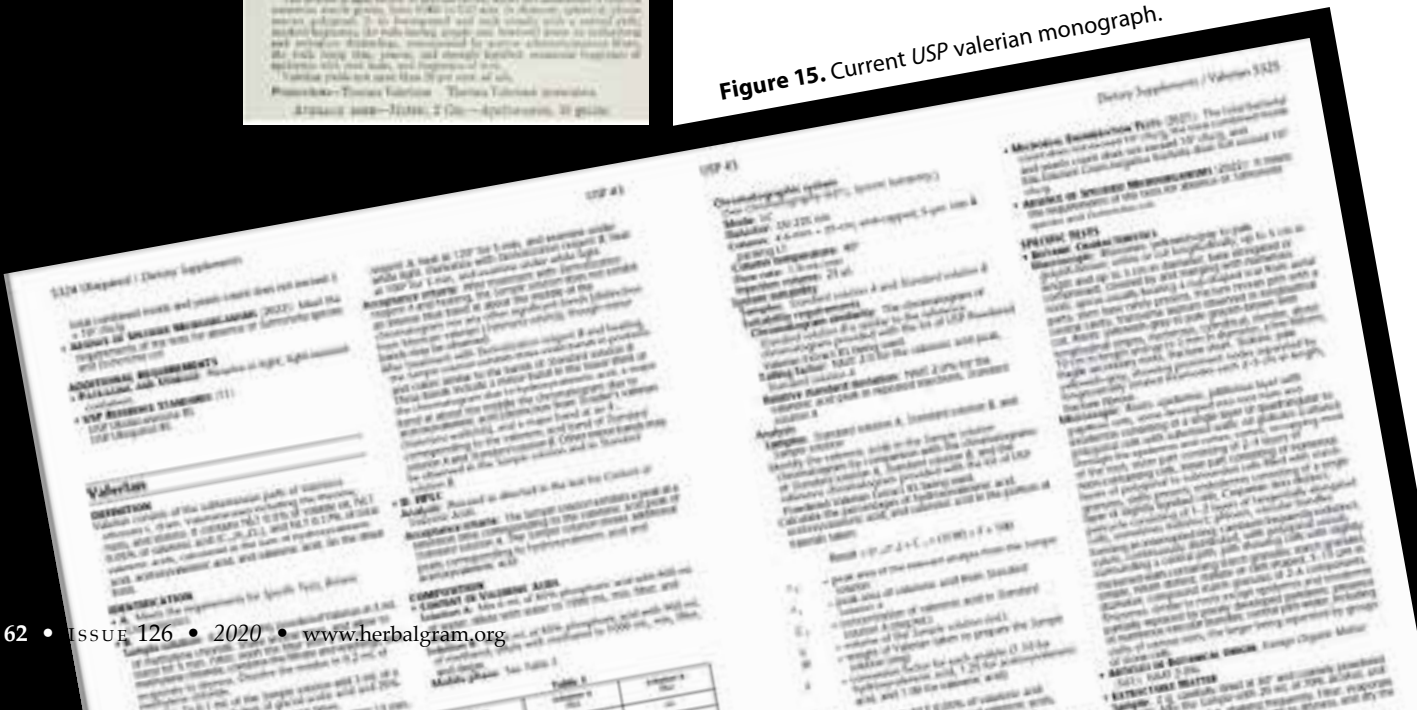




Figure 9. Subterranean parts of valerian.

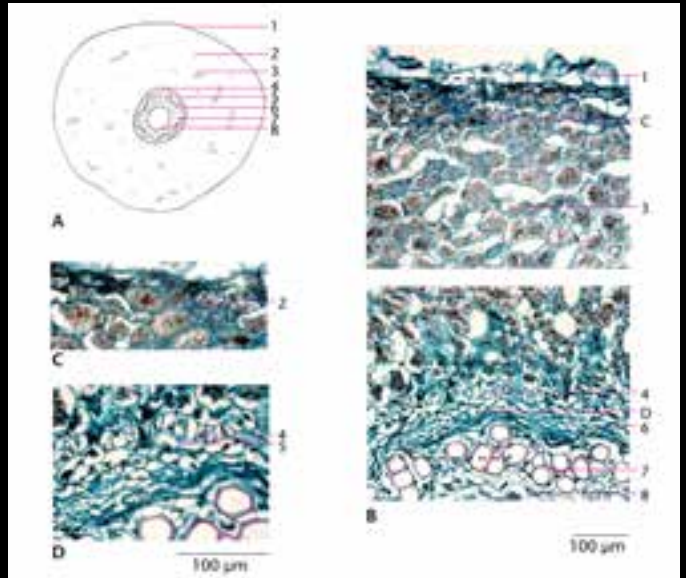


Figure 10. Microscopic characteristics of valerian.

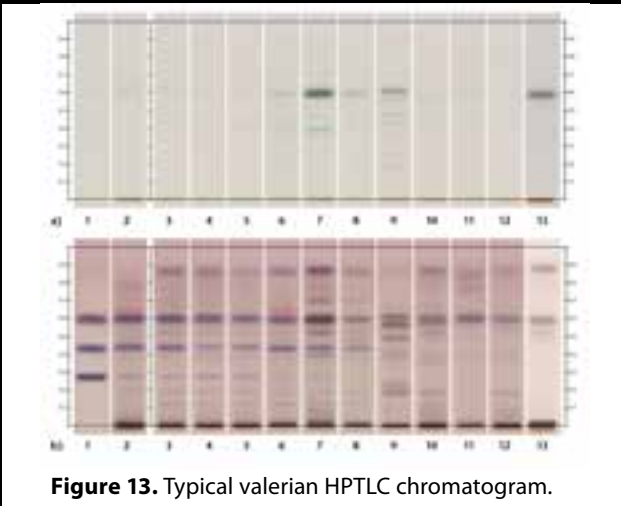


Figure 13. Typical valerian HPTLC chromatogram.

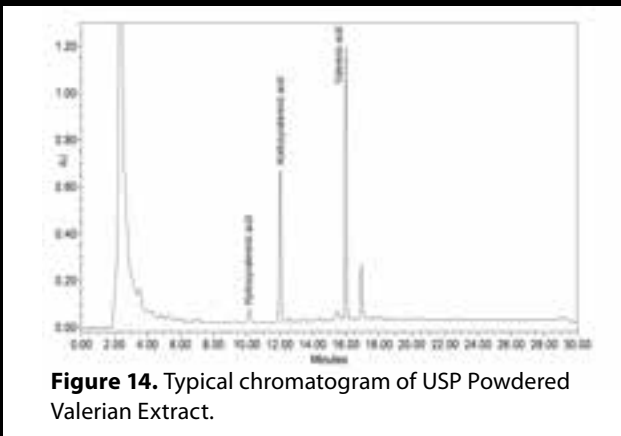


Figure 14. Typical chromatogram of USP Powdered Valerian Extract.

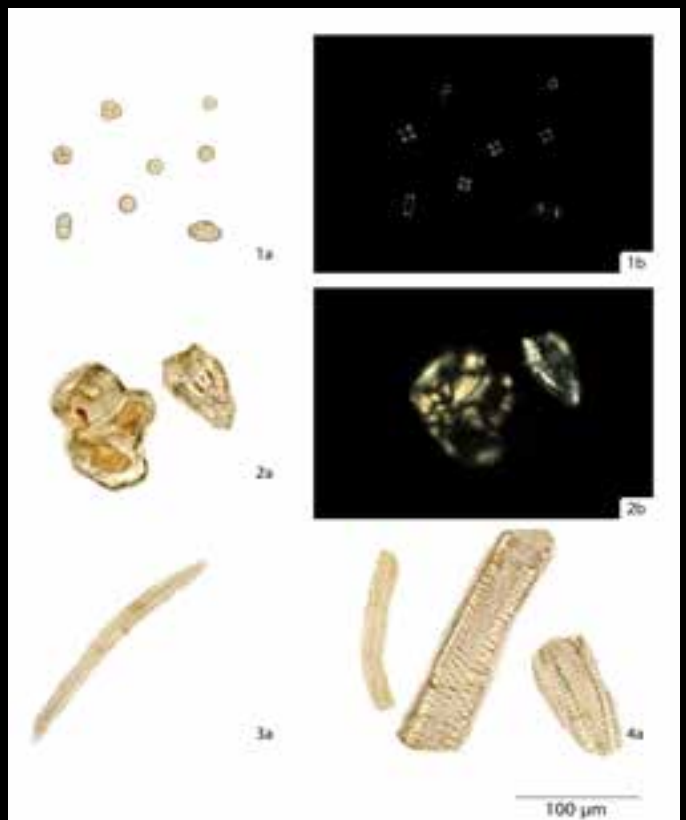


Figure 11. Microscopic characteristics of valerian root powder.



Valerian *Valeriana officinalis*
Photo ©2020 Steven Foster

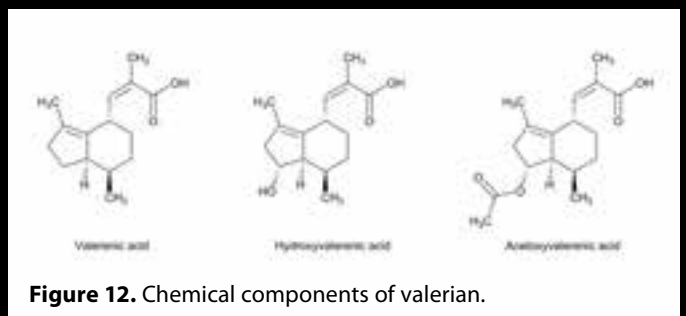


Figure 12. Chemical components of valerian.

Figures 9-15 illustrate the comprehensive requirements of current *USP* monographs for valerian, reflecting the current state of science.

AN OUTLOOK FOR THE FUTURE

Up-to-date and modernized standards. *USP* is committed to keeping its monographs up to date by following the principles articulated for the valerian monographs. Another aspect of the evolution is reflected in the fact that print editions of *USP–NF* are being phased out. *USP* is moving from print media in the form of published books to digital and visual media in the form of databases of standards and knowledge accessible electronically. This new format creates opportunities for users of the pharmacopeia to access a reference repository of data linked to monographs for comparison. For example, chemometric approaches to identification of botanicals could be introduced in the modernized monographs with links to digital databases to provide an avenue to compare the phytochemical profile of a test sample with that of several samples from multiple locations and growing conditions. This approach could further refine the monograph acceptance criteria.

New technologies. *USP* recognizes the value of new technologies with greatly improved analytical sensitivity, but also knows they are likely to pose an undue burden on users familiar with older methods. To address this dilemma, *USP* formed a Modern Analytical Methods Joint Subcommittee to evaluate the full breadth of available approaches for including modern technologies in both the development of monographs and the establishment of reference materials. The subcommittee is a collaborative effort led by the Botanical Dietary Supplements and Herbal Medicines Expert Committee (EC) in conjunction with the Non-Botanical Dietary Supplements EC and the Food Ingredients EC. New research and innovation projects related to botanicals include DNA analysis for the identification of herbal/botanical articles and the use of quantitative nuclear magnetic resonance (qNMR) spectroscopy and liquid chromatography-mass spectrometry (LC-MS) procedures in dietary supplement monographs. As an example, it may be possible to use qNMR as a simultaneously selective and universal screening tool. The qNMR and LC-MS methods also have the potential to enhance pharmacopeial efforts in sourcing suitable reference materials. *USP* also recognizes new trends in pharmaceutical manufacturing such as “continuous manufacturing technologies.” It remains to be seen as to how these new trends will be adopted for herbal medicine production and the impact of these approaches on future pharmacopeial standards.

Considering the constant challenge of economically motivated adulteration, there is an unmet need for non-targeted methods that can detect such adulteration (e.g., adulteration of dietary supplements with prescription drugs and their

Considering the constant challenge of economically motivated adulteration, there is an unmet need for non-targeted methods that can detect such adulteration.

unapproved drug analogs, as well as with other dietary supplements and natural product articles with unapproved drug admixtures). LC-MS procedures could serve as non-targeted approaches to detect adulteration with synthetic drugs or drug analogs.

Science of standards beyond monographs. *USP* ECs and staff engage in several activities to support the standard-setting work and move the science forward. EC members and *USP* staff have published several articles in peer-reviewed journals on the topics of quality, safety, and nomenclature.^{29,40-42} Besides the use of *Pharmacopeial Forum* as a primary

portal for seeking stakeholder input, new avenues such as Stimuli Articles and roundtable discussions are used for seeking public input on issues such as rational limits for pesticide residues, DNA methods for botanical identification, and standards for cannabis and cranberry (*Vaccinium macrocarpon*, Ericaceae) fruit. Focused Expert Panels have been formed on topics such as standards for cannabis, development of multi-criteria decision-based modeling approaches to assess safety of multi-ingredient dietary supplements, and evaluating the potential hepatotoxicity of green tea extract. *USP* Expert Panels are convened when additional specialized expertise beyond the EC is needed.

Novel ingredients. As the supply chain for botanicals becomes increasingly global — both in terms of adoption of traditional herbs from other cultures by American consumers and increased use of botanicals as a part of health systems around the world — *USP* prioritization and admission criteria are playing an important role in admitting botanicals into the compendia by focusing on the botanicals that provide maximum public health impacts of *USP*’s standard-setting work.

Conclusions

USP’s public health mission has remained steady and consistent from the organization’s inception in 1820 to the present, and it is reflected in the current mission statement: “to improve global health through public standards and related programs that help ensure the quality, safety, and benefit of medicines and foods.” To remain relevant as science advances, timely adoption of the innovative ways of manufacturing and quality assurance is essential. In tune with the fast-paced technological developments and novel challenges, and to maintain its relevance and usefulness as a pharmacopeia, *USP* is rapidly adapting, and in some cases leading, in modernizing public standards with the introduction of new, fit-for-purpose technologies and modalities. Trust in quality standards is more important now than ever before, given that standards drive quality across the global supply chain. Based on its 200-year legacy of making contributions to botanical standards, *USP* is poised to continue its public health mission for the future. HG

Author Declarations

Four of the seven authors are employees of USP, which is a nonprofit organization that sells documentary and physical reference standards to sustain its activities. The views presented in this article do not necessarily reflect those of the organizations for which the authors work. No official support or endorsement by these organizations is intended or should be inferred.

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References

1. Brown W. *Pharmacopoeia simpliciorum et efficaciorum, in usum nosocomii militaris, ad exercitum Federatum Americae Civitatum pertinentis; hodiernae nostrae inopiae rerumque angustiis, feroci hostium savitiae, belloque crudeli ex inopinato patriae nostrae illato debitis, maxime accommodata.* (Alternative title: *Lititz Pharmacopoeia*). Philadelphia, PA: Syner & Cist; 1778.
2. Brinckmann JA. Pharmacopoeial Wild Medicinal Plants of North America. In: Máthé Á, ed. *Medicinal and Aromatic Plants of North America*. Dordrecht, The Netherlands: Springer; 2020 [In press].
3. Tazewell W. *Vade-mecum medicum, in duas partes divisum, quarum prior, nosologiae Cullinaeae; posterior, compendium materiae medicae et pharmacopoeae, exhibet.* Philadelphia, PA: A.J. Dugour and Durand; 1798.
4. Jackson J, Warren JC. *The Pharmacopoeia of the Massachusetts Medical Society*. Boston, MA: E & J Larkin; 1808.
5. Mitchell SL, Seaman V. *Pharmacopoeia Nosocomii Neo-eboracensis (Pharmacopoeia of the New York Hospital)*. New York, NY: Collins & Co; 1816.
6. Sonnedeker G. The founding period of the US Pharmacopoeia: II. A national movement emerges. *Pharmacy in History*. 1994;36(1):3-25.
7. The Authority of the Medical Societies and Colleges. *The Pharmacopoeia of the United States of America*. 1820.
8. Vogel VJ. American Indian Influence on the American Pharmacopoeia. 1976; Paper presented at the American Association for the Advancement of Science, Boston, MA. Available at: <https://files.eric.ed.gov/fulltext/ED138390.pdf>. Accessed March 22, 2020.
9. Tirumalai G, Long A. United States Pharmacopoeial Convention: Respecting the past, moving confidently into the future. 2013. Available at: www.histpharm.org/ISHPWG%20USA.pdf. Accessed March 22, 2019.
10. General Convention for the Formation of the American Pharmacopoeia. *The Pharmacopoeia of the United States of America*. 2nd ed. New York, NY: S. Converse; 1830.
11. National Medical Convention. *The Pharmacopoeia of the United States of America*. Philadelphia, PA: John Grigg; 1831.
12. Powers J. History, Significance and Future of the National Formulary. *Food and Drug Cosmetic Law Quarterly*. 1946.
13. Committee on National Formulary. *The National Formulary of Unofficial Preparations, First Issue*. Washington, DC: American Pharmaceutical Association; 1888.
14. Higby G. *In Service to American Pharmacy. The Professional Life of William Procter, Jr.* Tuscaloosa, AL: The University of Alabama Press; 1992 (reprinted 2019).
15. Flannery MA. Government as apothecary: Civil war pharmacy and the common good. *Pharmacy in History*. 2019;61(1):3-14.
16. Schiff PL Jr., Srinivasan VS, Giancaspro GI, Roll DB, Salguero J, Sharaf MH. The development of USP botanical dietary supplement monographs, 1995-2005. *J Nat Prod*. 2006;69(3):464-472.
17. Lloyd JU. History of the vegetable drugs of the Pharmacopoeia of the United States. *Bulletin of the Lloyd Library*. Vol. 18, Pharmacy Series No. 4; 1911.
18. Smith T, Gillespie M, Eckl V, Knepper J, Reynolds CM. Herbal supplement sales in US increased by 9.4% in 2018. *HerbalGram*. 2019;123:62-73.
19. *New York and Brooklyn Formulary of Unofficial Preparations*. New York, NY: College of Pharmacy; 1884.
20. Higby GJ. *One Hundred Years of the National Formulary: A Symposium*. Madison, WI: The American Institute of the History of Pharmacy; 1989.
21. Worthen DB. Good Enough for America. *Int J Pharm Compounding*. 2014;18(1):20-29.
22. USP. Legal Recognition – Standards Categories. USP website. Available at: www.usp.org/about/legal-recognition/standard-categories#dietary-suppl. Accessed March 22, 2020.
23. Brinckmann JA, Huang L. American ginseng – A genuine traditional Chinese medicine. *Medicina nei Secoli-Arte e Scienza/Journal of History of Medicine*. 2018;30(3):907-928.
24. Squibb ER. Report of the Committee on the Pharmacopoeia. Philadelphia, PA; 1870.
25. Wahl T, Brinckmann JA. A modern state-federal framework for a regulated US cannabis industry. *HerbalGram*. 2019;122:60-69.
26. Giancaspro GI, Kim NC, Venema J, et al. The Advisability and Feasibility of Developing USP Standards for Medical Cannabis. *Pharmacopoeial Forum*. 2016;42(1).
27. Sarma ND, Wayne A, ElSohly MA, et al. Cannabis Inflorescence for Medical Purposes: USP Considerations for Quality Attributes. *J Nat Prod*. 2020;83(4):1334-1351. <http://dx.doi.org/10.1021/acs.jnatprod.9b01200>.
28. Anderson L, Higby GJ. *Spirit of Voluntarism: A Legacy of Commitment and Contribution - The United States Pharmacopoeia 1820 -1995*. Washington, DC: USP; 1995.
29. Ma C, Oketch-Rabah H, Kim NC, et al. Quality specifications for articles of botanical origin from the United States Pharmacopoeia. *Phytomedicine*. 2018;45:105-119.
30. USP. Guideline for Assigning Titles to USP Dietary Supplement Monographs. 2016. Available at: www.usp.org/sites/default/files/usp/document/get-involved/submission-guidelines/guideline-for-assigning-titles-to-usp-dietary-supplement-monograph.pdf. Accessed March 22, 2020.
31. USP. Products from Natural Origin for Health Purposes: Transitioning from Dietary Supplements to Dietary Supplements and Traditional Medicines – Stimuli to the Revision Process. *Pharmacopoeial Forum*. 2013;38(3). Accessed January 1, 2020.
32. USP. Herbal Medicines Compendium. Available at: <https://hmc.usp.org/>. Accessed March 22, 2020.
33. U.S. Food and Drug Administration. Inactive Ingredient Search for Approved Drug Products: Frequently Asked Questions. 2019. Available at: www.fda.gov/drugs/drug-approvals-and-databases/inactive-ingredient-search-approved-drug-products-frequently-asked-questions. Accessed March 22, 2020.
34. U.S. Food and Drug Administration. Inactive Ingredient Search for Approved Drug Products. 2020. Available at: www.accessdata.fda.gov/scripts/cder/iig/index.cfm. Accessed March 4, 2020.
35. USP. FAQs: Excipients. 2020. Available at: www.usp.org/frequently-asked-questions/excipients. Accessed March 22, 2020.
36. USP. USP Dietary Supplements Reference Standards Catalog. 2020. Available at: <https://static.usp.org/doc/referenceStandards/dailyds/catalog.pdf>. Accessed March 22, 2020.
37. USP. Guideline for the Admission of Dietary Supplement Ingredients to the USP–NF Monograph Development Process. 2017. Available at: www.usp.org/sites/default/files/usp/document/get-involved/submission-guidelines/guideline-for-the-admission-of-dietary-supplement-ingredients.pdf. Accessed March 22, 2020.
38. HMC. Guideline for Assigning Titles to USP Herbal Medicines Compendium Monographs. 2014. Available at: https://hmc.usp.org/sites/default/files/documents/Nomenclature_guideline/HMC%20Nomenclature%20Guidelines%20v.%201.0.pdf. Accessed March 22, 2020.
39. USP. Be part of the standards development process. 2020. Available at: www.usp.org/dietary-supplements-herbal-medicines/development-process. Accessed March 22, 2020.
40. Oketch-Rabah HA, Roe AL, Rider CV, et al. United States Pharmacopoeia (USP) comprehensive review of the hepatotoxicity of green tea extracts. *Toxicol. Rep*. 2020;7:386-402.
41. Patrick M, Kim HA, Oketch-Rabah H, Marles RJ, Roe AL, Calderón AI. Safety of guarana seed as a dietary ingredient: A review. *J Agric Food Chem*. 2019;67(41):11281-11287.
42. Oketch-Rabah HA, Marles RJ, Brinckmann JA. Cinnamon and cassia nomenclature confusion: A challenge to the applicability of clinical data. *Clin Pharmacol Ther*. 2018;104(3):435-445.