

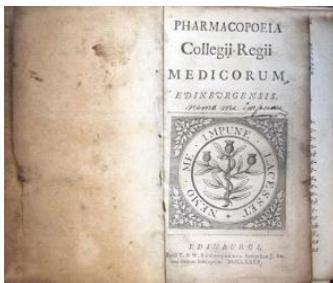
United States Pharmacopeial Convention: Respecting the past, moving confidently into the future

Geeta Tirumalai & Angela Long



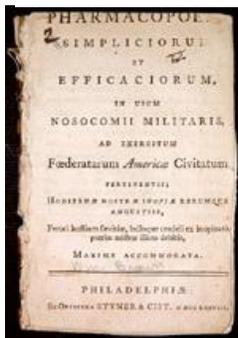
Colonial Medicine

For almost two hundred years after the Pilgrims landed in Massachusetts Bay in 1620, there was no authoritative resource to ensure the quality of medicines or a system for naming them in America. In the early years of colonial America and the young republic, there were a number of apothecaries, blacksmiths, midwives, and others who “practiced medicine” by providing their own preparations or popular English medicines to treat the ill. Educated physicians from England did not come to America, America only had a few homegrown ‘practitioners’ trained through apprenticeships. There were no



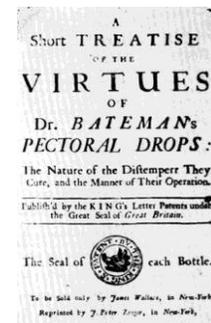
Edinburgh Pharmacopoeia 1735

medical societies, hospitals, or medical schools until after the mid 1700s. Clergymen and public officials also “treated” the population under their authority, and relied on imported books and dispensatories based on the Edinburgh and London Pharmacopoeias.



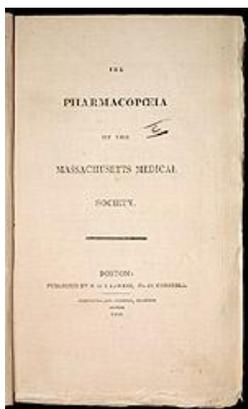
Lititz Pharmacopoeia (Lily Library)

During the Revolutionary War a few local pharmacopoeias were published. The *Lititz Pharmacopoeia* was the first in 1778, compiled by William Brown who was trained in Edinburgh. Another small pharmacopoeia was published for the French military hospitals in North America, the *Compendium Pharmaceuticum* by Jean Francois Costé. After the war ended the use of these works diminished and for the most part American physicians went back to using British pharmacopoeias and dispensatories. Physicians began to emerge during these early years of the republic, and they practiced both medicine and pharmacy by diagnosing diseases, and compounded and dispensed medicines. But still there was no assurance that these medicines were composed of quality materials and even if they were potent. John Morgan, who established the first medical school in America in Philadelphia in 1765, proposed the “composing a pharmacopoeia for use by Physicians and Practitioners of Pennsylvania” at a meeting and on June 3, 1788 passed a motion to appoint a committee to “form a Pharmacopoeia for use of the College.” But by 1789, the interest in a pharmacopoeia just for Pennsylvania had dwindled. Support grew, instead, for creating a national pharmacopoeia that would bring order to these preparations



Pamphlet Dated 1731. Original preserved in the New York Academy of Medicine Library. (Smithsonian photo 44286-D)

throughout the nation. Prominent national and medical figures such as Benjamin Franklin spoke not only about a formulary but of “some Standard amongst ourselves” for America. But this goal proved to be challenging in a country that was still undeveloped and sparsely populated, pharmacy could be practiced without a license, and the joint practice of medicine and pharmacy prevailed. This effort did not come to fruition and no pharmacopoeia was published at this time to support the nationalistic fervor of some of the leading physicians of the time who wanted the “full range of truly American medicinal plants” (Sonnedecker, *A National Movement Emerges* 1994) to be included.

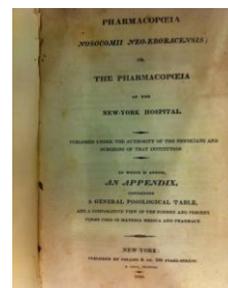


Pharmacopoeia of the Massachusetts Medical Society

The distinction of the first American Pharmacopoeia went to the *Massachusetts Pharmacopoeia*, published in 1808 by the Massachusetts Medical Society (Sonnedecker, *A National Movement Emerges* 1994). Two young physicians, James Jackson and John Collins Warren took on the responsibility to identify those articles that cured diseases and best methods of preparation, and named them using English versus Latin names. The *Massachusetts Pharmacopoeia* was intended to be a standard of uniformity for medicinal articles to be adopted by all “professional men” in the United

States, although compliance with it was not required. It relied on “self-government among independent and reliable practitioners, rather than government intervention” (Sonnedecker, *A National Movement Emerges* 1994). The New Hampshire Medical Society adopted it but South Carolina, although supportive of the idea of a national pharmacopoeia did not see it as a “national” effort representing the differences between diseases and their treatment in different parts of the country. Nonetheless, it was a significant achievement and proved to be a model for future efforts. An *American New Dispensatory* based on the *Massachusetts Pharmacopoeia* published by James Thacher, a Boston physician and Revolutionary veteran gave further credibility to the Massachusetts effort.

Ten years later, in 1816, Samuel Latham Mitchill, along with Valentine Seaman, published the *Pharmacopoeia of the New York Hospital*, again for the use of hospital interns. But Mitchill had greater ambitions of breaking free of the ‘colonial’ yolk of Britain. Mitchill along with Lyman Spalding and Jacob Bigelow, who later became the founders of the *USP*, had their own motivations to start a ‘national’ pharmacopoeia. Spalding espoused uniformity, Mitchill, nationalism, and Bigelow saw a pharmacopoeia as supporting the native materia medica.



Pharmacopoeia of the New York Hospital

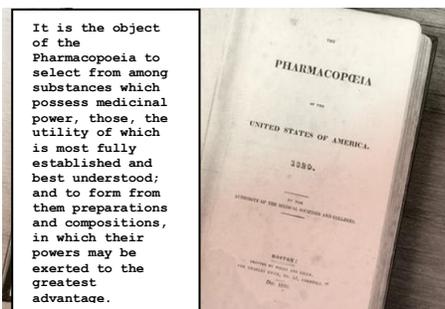
Spalding drew the initial plan and coordinated the group. His goal was to fulfill the urgent need for uniform standards for medicines that could be utilized across the country. Mitchill used his influence

in medical and political arena (he was also a United States senator) to promote the idea. Bigelow with his expertise in plant drugs and the publication process, served as editor of the *USP*. On January 6, 1817, during a meeting of the New York County Medical Society, Lyman Spalding formally proposed the framework for the establishment of an American pharmacopoeia in the United States of America. It was proposed that four pharmacopoeial conventions would be held in the four regional districts. Each would produce or select a pharmacopoeia, and would send delegates to the national convention in Washington, January 1, 1820. The pharmacopoeia would be revised every ten years. The state medical societies would adopt it thereby giving it authority. A committee of the State Medical Society of New York adopted the project of establishing a “uniform Pharmacopoeia throughout the United States” (Sonnedecker, *A National Movement Emerges* 1994) and named an influential implementation committee. The society sent a circular to other medical societies and schools around the nation marking the beginning of democratic participation in the revision of *USP*.



Founding of the US Pharmacopoeia

Less than three years later, on January 1, 1820, 11 of the 16 delegates - all physicians - gathered in Old Senate Chamber of the U.S. Capitol building to form the United States Pharmacopoeial Convention and create the first Pharmacopoeia of the United



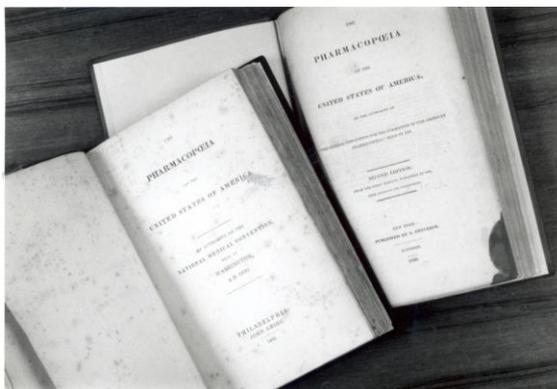
1820 USP

States. Holding the Convention at the U.S. Capitol underscored its national significance and democratic procedure although no government support or enforcement of the pharmacopoeia was expected (Sonnedecker, *A National Movement Emerges* 1994). The first *Pharmacopoeia of the United States of America* containing 221 monographs was

successfully published by the end of that year. It was made up of five sections, beginning with the front matter, the historical introduction and preface, followed by the materia medica, a list of 221 drugs; a secondary list of 71 drugs for substances of “doubtful efficacy”; a section on weights and measures; and an untitled section of 329 preparations and compositions (Anderson and Higby 1995). In terms of content, the pharmacopoeia reflected the therapeutics of the time including tonics, strong laxatives, diuretics, and flavoring herbs. The preparations included cerates, confections, decoctions, extracts, honeys, infusions, liniments, mixtures, ointments, pills, plasters, powders, spirits, syrups, tinctures, troches, vinegars, washes, waters, and wines. No techniques were included, just recipes. There was nothing to address the purity of chemicals - chemical formula, identifications or assays which are hallmarks of a modern

pharmacopeia. In 1828, a second printing of the pharmacopeia was released with corrigenda that corrected a number of errors in the first edition.

By the time the first decennial revision, a schism had developed between two of the most influential medical centers of the day, New York and Philadelphia. There were different interpretations of a section of the founding convention plans for future revisions, with Mitchill interpreting it as three delegates from each district, and the Philadelphia medical leaders thinking that the local medical societies were to send three delegates to the convention and were also late in submitting the names



to Mitchill. He used this fact to keep out the Philadelphians who had been very critical of the 1820 edition. Rival conventions were held in New York and Washington. Mitchill presided over the New York Convention and two sessions were held on January 1, 1830 and June 2, 1830 as there were not many delegates in the former session.

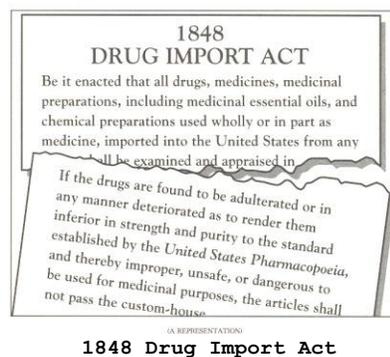
1830 revisions - NY & Washington

The Washington Convention was held on January 1, 1830, as had been stipulated in the founding documents. Two separate first revisions were issued, one in 1830, the New York edition as a result of the New York Convention and the other in 1831, the Philadelphia edition out of the Washington Convention. The New York edition was revised in a hurry on the premise that if it was published earlier it would give it primacy. But there were a number of errors. The Washington Convention was more deliberate in its process. It appointed a Committee of Revision with two members from different states and once the contents were drafted, they solicited feedback from the Philadelphia College of Pharmacy thus marking the entry of organized pharmacy into the pharmacopeial revision process. The New York edition also lacked a detailed preface, robbing it of any authority or credibility. The Philadelphia edition gave an informative preface about how choices were made with regard to nomenclature and admission of new drugs and preparation, and included “many practical suggestions” made by pharmacists. In the preface of the Philadelphia edition, George Wood stressed the need for uniformity and that it was the pharmacopeia’s most salient contribution to medical and pharmacy practice. The Philadelphia edition survived based on it being a more thoroughly revised pharmacopeia than the New York edition and the fact that Philadelphia College of Physicians supported and publicized it with pharmacists. Bigelow also threw his weight behind the 1830 Philadelphia edition. With the death of Mitchill in 1831, the New York medical establishment withdrew from pharmacopeial revision for the next 50 years.

Throughout the nineteenth-century, members of the Convention continued to follow the guidelines laid out in the preface of the first pharmacopoeia, meeting every ten years in Washington, DC. Under

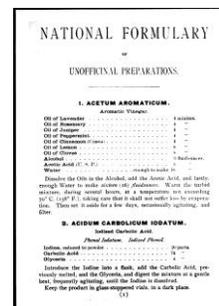
the stewardship of great leaders and physicians like George B. Wood and Franklin Bache for the next four decades, the United States Pharmacopoeia (*U.S.Ph*) achieved sustained prominence and gained further recognition as a national standard. Bache and Wood also authored the *United States Dispensatory (USD)* that provided fuller descriptions and explanations of preparations but deferred to the authority of the *U.S.Ph*. The 1840 *U.S.Ph* revision contained numerous changes and new features and was said to be a “completely revised pharmacopoeia” (Anderson and Higby 1995). In 1848, an important step toward solidifying *U.S.Ph*’s role as a recognized national standard came with the passage of the *Drug Import Act*, which mandated that drugs imported into the country must comply with *USP*’s quality standards for strength and purity.

Pharmacists became an integral part of pharmacopeial revision process during the 1850 revision that continues to this day along with physicians and other scientists in related disciplines. The 1860 (*USP IV*) and 1870 editions were not structurally any different from the earlier editions, but did include newer remedies and processes as well as technical methods. The Civil War distracted professionals responsible for its revision and did not alter the content much to meet the war time needs. *USP IV* for the first time included potency standards for cinchona, opium and scammony and the committee wrestled with problems in measurement science (metrology). It was the most popular edition up to that time. The 1870 edition included metric weights and measures tables, after the US Congress made the metric system legal in 1866.



At the close of the nineteenth-century, in 1880, pharmacist Charles Rice, the newly appointed Chair of the Committee of Revision, initiated a complete revision and modernization of the *USP* reflecting advances that had been made in pharmaceutical chemistry. Antiquated pharmaceutical recipes were replaced with specific chemical formulas and precise tests for purity. A single alphabetical listing replaced the separate lists; short descriptions of all crude drugs, common adulterants, as well as parts by weight were included in the monographs. This edition also broke free of the dominance of the nomenclature discussions in the preface and instead focused on pharmaceutical technology. There was a separate section of reagents and tables - various test solutions and volumetric solutions, specific gravity and solubility tables (Anderson and Higby 1995). In addition, Dr. Rice established the first subcommittees and pioneered the use of revision circulars to give each member of the 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.

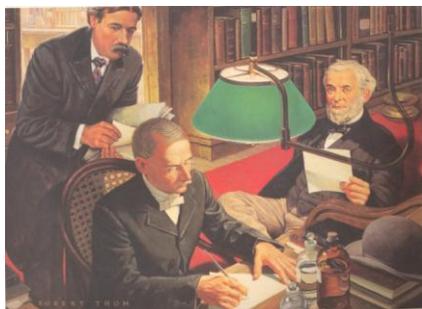
Dr. Rice had also served as head of the Pharmacopeia Committee at the American Pharmacists Association (APhA), that later published the *National Formulary (NF)* in 1888. As early as 1856, the APhA promoted the “standardization of names and formulas for dosage forms of drugs not described elsewhere” (Powers 1946) . The first edition was named *National Formulary of Unofficial Preparations*. It included primarily formulas that



First NF

pharmacist’s could compound including elixirs, emulsions, fluid extracts, tinctures, solutions, syrups, and dosage forms of the time. Over time with the emergence of pharmaceutical manufacturing in the late 1800s and the lessening of pharmacist-compounded medications, the *NF* began to focus on drugs that were not included in the *U.S.Ph*. Thus, the *U.S.Ph* was to include “drugs of first choice therapeutically” and *NF* “for other drugs whose extent of use justified development of a monograph” (Sonnedecker, Changing character of the National Formulary 1890-1970 1989). Although there was no legal recognition of the *NF* it was well established by the time the 1906 Federal Food and Drug Laws provided a role for both the *U.S.Ph* and *NF* in defining whether a drug should be deemed adulterated under federal law. The *NF* along with the *U.S.Ph* went a long way in establishing uniformity in drugs, nomenclature and preparations.

Once the work of *NF* was completed, Rice turned his attention to revising *U.S.Ph* for the next decennial revision in 1890. For this revision, Rice solicited the opinion of outside experts who were not members of the Committee of Revision. This has been the mainstay of USP’s revision process ever since. In 1892, the Revision Committee voted to change the abbreviation of the compendium



Rice, Remington & Squibb

from “U.S. Ph” to “USP.” *USP VII* completely switched from parts-by-weight to metric system. It also did not include patented and trademarked drugs. In Remington’s words “One of the principal objectives of a Pharmacopoeia is to establish standards, to prove the identity and purity of the substances admitted; in order to make such operative, it is necessary to

have more than one source of supply or manufacture”

(Anderson and Higby 1995).

This exclusion of patented drugs proved to be an ongoing matter of debate, as the changes in medicine, and pharmacy increasingly called for the scope of the pharmacopoeia also follow suit. But it wasn’t until the 1940s that they were cleared for consideration into the pharmacopoeia. Synthetic compounds began to replace “mineral and vegetable drugs.” Federal regulations started intervening in the manufacture and marketing of drugs. These developments demanded more from the USP in terms of time, expertise, and financial obligations that led to major procedural and organizational changes. The next major turning point in USP’s history was initiated during the Pharmacopoeial

Convention of 1900, when then Convention President, Horatio C Wood, urged the Convention to create a written Constitution and Bylaws. “The new Constitution and Bylaws defined for the first time the institutions entitled to have representation at the Convention”, (Anderson and Higby 1995) and called for the creation of USP’s first Board of Trustees.

Moreover, the members of the 1900 convention passed a resolution directing the Board of Trustees to officially incorporate the United States Pharmacopeia in the District of Columbia. The July 11, 1900 certificate of incorporation gave

USP’s newly created Board of Trustees power over the “management and control of the affairs, funds, and property” of the organization.” (Anderson and Higby 1995)



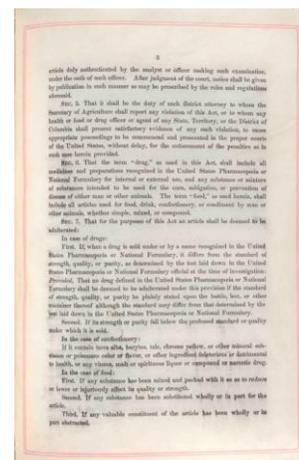
Horatio C Wood

USP VIII became official in 1905 with significant changes. Average doses, allowable percentages of impurities, specific assays for several drugs, and nomenclature of synthetic drugs and chemicals made their way into the pharmacopoeia. It included a disclaimer that the standards for purity and strength in the compendium are for substances used solely for medicinal purposes. It also included the first official biological product, diphtheria antitoxin. (Anderson and Higby 1995)

Another significant event for USP at the turn of the century was the passage of the 1906 Food, Drug, and Cosmetic Act by the federal government.

Although individual states had increasingly recognized *USP*, this legislation strengthened USP's role by mandating that drugs “sold under or by a name recognized in the *United States Pharmacopeia* or *National Formulary*,” must meet the standards of strength, quality, or purity stipulated in these compendia. The impact that this legislation had on the *USP* and *NF* was significant and it elevated the position of the compendia. The 4th ed. of the *NF*, the first after the Act was passed, was published in 1916. It introduced standards for identity, strength quality and purity as well as distinctive titles and formulas. Official formulas for parenteral solutions, “Ampuls,” were also

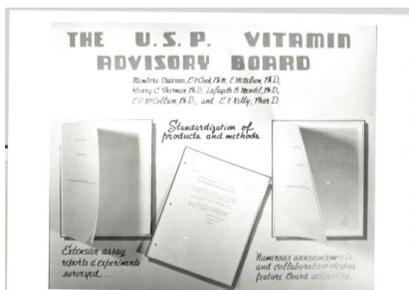
included for the first time. Due to the passage of the 1906 Act, there was more scrutiny of the *USP* and more discrepancies and errors were brought to the attention of the Committee. 243 monographs were deleted; notable amongst them were standards for whiskey and brandy. Small pox vaccine was added to *USP IX*. The 9th revision of the *USP* also addressed the issue of scope. Remington remained steadfast in his stand on excluding patented drugs from *USP IX*.



1906 FD&C Act

E. Fullerton Cook took over the reins of the Committee of Revision and *USP X* replaced Part 1 and II of *USP IX* with Monographs, and General Tests, Processes and Apparatus. Only preparations that had some claim to efficacy were included. As a result many common drugs used widely by

physicians and patients ended up with no public standards. It wasn't until the next revision that



USP Vitamin Advisory Board

more actively in the revision of the *USP*. Cook also reintroduced advisory panels so the best minds in science, pharmacy and medicine could participate in the revision of the pharmacopeia. The USP Vitamin Advisory Board included leading experts Lafayette Mendel and Elmer V. McCollum, and its work led to the first vitamin standard to be included in the *USP*. This period also saw closer cooperation between USP and government agencies with the importance of bioassay methods growing as also the developments in legislative (1902 Biologics Act) and scientific areas. The assays that determined the potency of digitalis led to the Bureau of Chemistry, the predecessor to the Food and Drug Administration (FDA) providing packaged, standardized product samples, or “reference standards”, for industry to comply with methods in



USP Chinese Translation

USP X. The 1920's marked the advent of the USP Reference Standards program with standards for Vitamin A and D content in cod liver oil. During the period 1900 and 1930, the *USP* was translated into Spanish and then Chinese, both being important contributions to international public health. There were other innovations in the publication of the *USP* such as the continuous revision in the 1930s to keep pace with rapid developments in medical and pharmaceutical science and industry. The *NF* also saw major revisions in the 1930s. The sixth edition of the *NF* included monographs on ampuls and tablets with standards for identity, strength, purity and quality and admissions into the *NF* were based on science. Obsolete drugs were discontinued and “additional chemical, biological and proximate assays were developed and introduced” (Powers 1946). The 11th revision of the *USP* in 1936 saw obsolete items such as fluidextracts and tinctures being removed. A number of biologicals were added such as the scarlet fever antitoxin, rabies and typhoid vaccines and ephedrine.



1938 FD&C Act

The 1938 Food, Drug & Cosmetic (FD&C Act) expanded the role of both the *USP* & *NF* in the adulteration and misbranding provisions of federal law, regarding naming, identity, and strength, quality and purity, and also provided a role for *USP*'s and *NF*'s packaging and

labeling requirements. The Act had far reaching effects on how the USP and NF worked. The *USP* evolved from 'continuous revision' to a five year publication cycle in the 1940s. The *NF* also included provisions to issue revision supplements and being published every five years instead of 10 years. The publication schedules were also synchronized and slowly the differences between *USP* and *NF* monographs became almost indistinguishable over the next few decades as the *NF* also started admitting drugs based on their therapeutic value as opposed to just extent of use. In contrast to the USP's reluctance to set up a laboratory in earlier revision cycles, the American Pharmaceutical Association, the publishers of *NF*, saw the need for a well equipped laboratory to research and test new methods and procedures. A laboratory was established in 1938 at the Association's headquarters. It also saw efforts to coordinate the scope of the two compendia. As a result of diagnostic agents being recognized as "drugs" in the 1938 Act, *NF VII* included a chapter on diagnostic substances.

USP XII in 1942 was the first revision published under the five year schedule and it included monographs for injections for the first time, and compressed tablets finally were included although they were in use since Charles Rice's time. There were also some firsts for the FDA. Insulin in 1941 and increased production of Penicillin in 1944 during World War II led to the Congress of the United States adding sections to the 1938 FD&C Act requiring FDA to certify insulin and penicillin products in response to appeals from USP and AMA. *USP XIII* was the first revision to have monographs under English titles following the *NF* decision to switch to English titles earlier. Five of the oils that were official since the 1820 USP, were dropped from *USP XIII* and the first adrenal hormones and seven penicillin preparations were introduced. For the first time, the "unqualified admission of proprietary products without regard to patent status" (Anderson and Penningroth, Good Work and True 2000) were included.

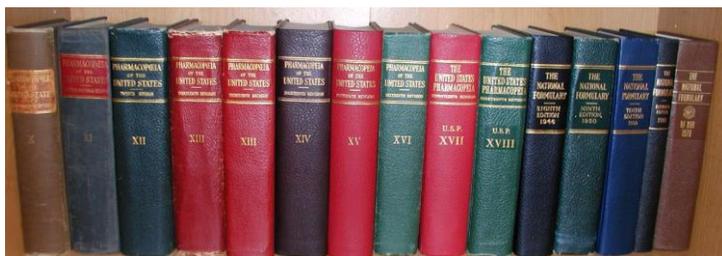


USP XIV

USP XIV saw the disappearance of the diphthong, the "œ" in the word Pharmacopeia on its title page. Patented drugs were indicated with an asterisk and there was also a warning against violating property rights of the patent and trademark holders. It included five antibiotics, and the first official monograph for antihistamine. Folic acid was first included in *USP XIV*, as also the first two official anticoagulants, heparin and bishydroxycoumarin, and amphetamine.

With continued official legal recognition, USP grew and expanded its efforts to promote public health during the mid twentieth-century. In 1950 after years of working out of the homes of its volunteers, USP purchased its first permanent headquarters on Park Avenue in New York City, which was urgently needed to support USP's rapid expansion. To cultivate this growth, the USP Board of Trustees appointed Lloyd Miller to serve as Director of Revision in 1949, making him USP's first

salaried employee. *USP XV* released in 1955, included new steroid products, combined diphtheria and tetanus toxoids and pertussis vaccine (DTP), and excluded several older remedies such as cascara sagrada extract and fluid extract, ephedrine, and estradiol. The General Tests section was extensively revised with modern tests and assays. The General Notices section was revised collaboratively with APhA's Revision Committee, so the two compendia were as close to conformance as possible. It also included detailed standards for official biologicals that previous revisions did not. Miller also insisted on clarity and consistency in style and a *USP Style Guide* provided guidelines for the publication. Dosage ranges and the classification of drugs according to pharmacological category was introduced in *USP XV* and *XVI*. Due to the rapid introduction of new drugs into the market, the *USP* was to a certain extent outdated when a new revision was published so the Committee of Revision decided to include a list of "provisional admissions" in the *XVI* revision that were worthy of admission but did not have monographs at the time of publication. These would then be elaborated through *Supplements*. The *XVI* revision most notably included the first chemical assay for vitamin D; diuretics, human blood cells, and influenza virus and poliomyelitis vaccine were some others. During Miller's tenure the *USP* would also grapple with nomenclature issues, specifically in selecting nonproprietary names in the *USP* and the need for a *USP* research laboratory. In response to these challenges, *USP* took on its first auxiliary publication, the United States Adopted Names or *USAN* that was a combined effort of the AMA, *USP* and APhA. It also established the Drug Standards Laboratory with funding provided by the AMA, APhA, and *USP* in the 1960s thus supporting the expansion of the Reference Standards program.



USP X-XVIII; NF 8-12

The 1962 Kefauver-Harris amendments to the FD&C Act introduced key changes affecting *USP*. FDA for the first time was given authority to require GMPs (current good manufacturing practices). Also for the first time drugs

were required to be cleared by FDA for both safety, and efficacy, before marketing; this obviated the need for a *USP* committee on scope, since all newly marketed drugs were required to be deemed both safe and effective. Beginning with the *XVII* revision official antibiotic monographs included "only those aspects of identity, purity, potency, and packaging and storage that are of special interest to the physician and pharmacist" (United States Pharmacopeial Convention 1965) reflecting the requirement that FDA certify all antibiotics. *USP XVII* and *XVII* included several technical innovations such as standards for plastic prescription containers, content uniformity standards for some tablets and capsules, and caution statements for few dangerous drugs such as digoxin and methotrexate. Reference Standards (there had been only 37 in 1950) grew considerably in *USP XVIII* but did not include narcotic agents and radioactive agents. The most challenging problem of

this time was the bioavailability of solid dosage forms and setting practical bioavailability standards proved to be elusive. As a start *USP XVIII* included dissolution tests for six monographs replacing the disintegration tests. Another technical advance that was anticipated, Good Manufacturing Practices (GMP), was “monitoring potentially harmful bacteria” in the production process and chose “four index organisms” to serve as a warning signal (Anderson and Higby 1995, 359). The General Tests, Processes and Apparatus section included three chapters on effectiveness of antimicrobial agents in parenterals and ophthalmic solutions. The 1960s also saw drugs in the currently official *USP* and *NF* being included in third-party health care plans and those of the federal government drug coverage (Anderson and Higby 1995, 374).

The USP maintained its headquarters in New York for nearly twenty years before relocating to Washington, DC area in 1969, a move that was prompted by the need for more space and a closer proximity to the FDA that had expanded its operations and authority as a result of the Kefauver-Harris Act. One of the major technical issues facing the Committee of



OTA Report

Revision during the 1970s was that of bioequivalence. The OTA Drug Bioequivalence Study in 1974 criticized “current standards and regulatory practices” in assuring bioequivalence for drug products and did not spare either the FDA’s Good Manufacturing Practices or compendial standards of *USP and NF*. It charged that the “physical tests and assay procedures of much greater sensitivity” (Anderson and Higby 1995, 465) than those specified by the compendia existed, objected to the initial dissolution test in *USP XVIII* among other issues. It also called for a single compendial organization to “revise drug and drug product standards continuously on the basis of the best available technology.” (Anderson and Higby 1995, 466). William Heller, the Executive Director, responded that organizational changes were already underway with the purchase of the *NF* and the drug standards laboratory. He also indicated that the panel failed to differentiate between manufacturing processes that were under FDA authority and “regulatory standards and tests for raw materials and finished drug products” (Anderson and Higby 1995, 466) that were in the compendia.

After long and protracted negotiations, USP successfully purchased the *NF*, along with the Drug Standards Laboratory in the 1975 from the APhA. The USP released the first combined edition of the *USP-NF* in 1980. It also began publishing the *Pharmacopeial Forum* in 1975 to publicize revision proposals and to solicit public comments. The 1970s and 1980s were



USP-NF Merger

dominated by organizational and business issues with major reorganization of staff as well as the Committee of Revision. A major focus of the revision activity in the early 1970s was focused on drug selection and this was formally separated from standard-

setting providing expanded opportunities for USP. In 1973, the first edition of the *USP Guide to Select Drugs* was published. It was a listing of drugs admitted into *USP XIX* and arranged according to pharmacological/therapeutic categories based on the *American Hospital Formulary Service* classification. This was all in the hopes that a federal formulary would be established aimed at Medicare and Medicaid programs. This did not come to fruition due to a number of reasons such as physician opposition, drug efficacy requirement of the 1962 Act, acquisition of the *NF* and difficulty in the drug selection program, and as a result USP withdrew altogether from drug selection, which had been a part of USP's mission since 1820.

The 1970 convention resolution had called for including therapeutic information in the *USP*. *USP XIX* included brief dispensing information and expanded the dosage section but these were “nonenforceable” information in the official monographs that concerned a number of stakeholders. Most supported a separate volume clearly identified as nonofficial and the FDA wanted no distinction between approved and nonapproved uses of drugs. USP Board endorsed the separate volume but wanted it to be an extension of *USP*. This led to the birth of the *USP Dispensing Information (USP DI)* in 1980. *USP XIX* in 1975 had 1284 monographs which was a substantial increase from *USP*



USP Reference Standards

XVIII. It also included complex tests and methods, partly in response to the OTA report. Liquid chromatography was introduced and was increasingly used in later revisions. The first excipient monograph also made its way into the pharmacopeia. System suitability tests were introduced in *USP XIX*. *USP XX-NF XV* was the first combined volume and it discontinued dispensing information that was published in a

separate publication *USP DI*. The Reference Standard program took over the distribution of reference substances of controlled drugs from NIMH in 1972 and the antibiotic reference standards from the FDA in 1975. The number of reference standards grew from about 250 in 1970 to 700 in 1975 (Anderson and Penningroth, Good Work and True 2000) and about 1200 Reference Standards were available in 1988. Most of the innovations between 1970 and 1990 were in the areas of dissolution tests, microbial limit tests, and standards for particulate matter in parenterals. Setting



USP-NF Electronic

excipient standards was challenging as traditional parameters of strength and purity were not as important as particle size or surface area. Another major technological advance was the public offering of the sixth supplement to the *USP XXII-NF XVII* in an electronic version in 1992. The growth in the number of monographs admitted into *USP-*

NF continued into the 1990s with *USP XXII-NF XVI* covering a majority of the top 2000 drug substances and products with over 3,200 monographs.

By the mid-eighties USP had once again outgrown its current space in Rockville, MD that it had purchased in 1970, and began construction on a new building for its headquarters, known today as Twinbrook II. At the time of this building's completion in 1989, USP was increasingly making efforts to improve its international activities, and promote public health around the world. In 1989, the USP along with representatives from the Japanese and European Pharmacopoeia formed the Pharmacopoeial Discussion Group to support the international harmonization of pharmaceutical monographs. Most notable of the harmonization efforts at this time was the *NF* monograph on 'Lactose Monohydrate' which was the first monograph to be harmonized.



USP, Rockville, 1989

USP 23-NF 18 published in 1995 included a new section on nutritional supplements that included four new general chapters, on disintegration-dissolution, manufacturing practices, microbial limits and weight variation. It also worked to replace, reduce and refine tests and assays that used live animals. 250 rabbit pyrogen tests were replaced by the Bacterial Endotoxin Test, an in vitro procedure. Mouse safety test was deleted from antibiotic monographs. Veterinary drugs also made their appearance in *USP 23*. Two new chapters dealing with bioavailability and bioequivalence were introduced. Apothecary units were deleted and metric units were used for prescription and dispensing. Computer generated graphic formulas was another first in this revision.



USP website announcement

In 1996, USP introduced its first web site. *USP 24-NF 19*, published in 2000, saw the deletion of federal and other texts that were based on federal regulations as now they were freely available from government websites. Along with a GMP general chapter, two other information chapters dealing with FD&C Act requirements and Controlled Substances

Act (CAS) were deleted. The 1997 FDA Modernization Act (FDAMA) provided a role for USP-NF monographs related to compounding, including the USP chapter on compounding, as part of a Congressional initiative to address pharmacy compounding. FDAMA also included a special role for USP standards related to determining when Positron Emission Tomography (PET) drugs might be deemed adulterated. PET tracers were addressed in 11 monographs and a general chapter on radiopharmaceutical in PET compounding was developed. Three radiolabeled monoclonal antibodies were introduced, the first antibodies to be included in the *USP*. Microbiology was another area where the standards were extensively revised. A general chapter on biocompatibility of materials, and cell permeability was introduced although standards for biomaterials themselves were deferred to later revisions. Chapters on quality of biotechnology drug products were also prepared.

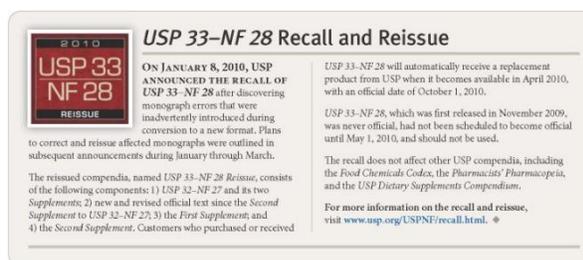
The Bacterial Endotoxin test chapter was entirely harmonized and a single reference standard was developed.



USP-NF Online

USP 25-NF 20 published in 2002 started the annual publication of the USP-NF and also as an online product. Two Supplements were published between annual editions. This revision created safety criteria for admission of dietary supplement monographs and classes for these monographs. In USP 28-NF 23 published in 2005, chromatographic assays were developed for a number

of drug substance monographs replacing titration assays as the FDA required stability-indicating assays for these articles. The process of continuous revision continued with standards for pharmaceutical waters, packaging and storage, labeling and of multidosage and single dose vials, cautionary statements on ferrule and cap overseals for neuromuscular agents, control of heavy metals, medical gases, heparin, glycerin, sterile compounding, elemental impurities being some of the significant revisions. A major initiative of redesigning monographs was initiated in 2009 with “~4,000 monographs in the USP 33–NF 28 were redesigned, encompassing more than 4,100 pages, over four million words, and many figures and tables” (United States Pharmacopeial Convention 2010), with the



USP-NF Recall Notice

intent of not changing any of the substantive monograph requirements. There were significant errors in this massive undertaking and for the first time in USP history, a revision was recalled and reissued in 2010.

USP's international expansion and interests continued to grow into the twenty-first century, leading in 2005 to the establishment of USP's first international office in Basel, Switzerland. This was followed by the opening of international laboratories in India in 2006 and China in 2007 and soon after in Brazil in 2008. USP has also engaged in a number of global health initiatives that help support the efforts of under-resourced countries to build capacity to combat substandard and counterfeit medicines.



FCC & USP DS

During the first two decades of this century USP has also successfully launched several new publications including the *Pharmacists Pharmacopeia*; the



MC & HMC Online

newly acquired *Food Chemical Codex (FCC)*; *Dietary Supplements Compendium (DSC)*; and two online only publications *Medicines Compendium (MC)* and *Herbal Medicines Compendium (HMC)*. USP has also translated the *USP-NF* into Spanish, Russian and Chinese.



USP Reference Standards

Currently, *USP-NF* remains the oldest continuously published pharmaceutical compendia, growing to include over 4000 monographs, and 3,000 reference standards which are recognized as the standard of quality in more than 140 countries around the globe.

Today, the USP continues to strive to fulfill its mission “to improve global health through public standards and related programs that help ensure the quality, safety, and benefit of medicines and foods” with the active participation of its volunteers and staff.



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