The year 2006 marks the centennial of the 1906 Pure Food and Drug Act. While frequently considered the first major piece of federal legislation concerned with the purity and safety of medicines, it actually was the third, having been preceded by the Drug Importation Act of 1848 and the Biologics Control Act of 1902. The 1906 legislation captured the attention of the American citizenry, however, in part because of the attention brought to the issue of food safety by Upton Sinclair in his muckraking novel, *The Jungle*, and by the public media.

Five major national legislative initiatives had a direct impact on pharmacy in the 90-year span beginning with the Drug Importation Act of 1848. The other four were (1) the Biologics Control Act of 1902, (2) the Pure Food and Drug Act of 1906, (3) the Harrison Narcotic Act of 1914, and (4) the Food, Drug, and Cosmetic Act of 1938. Moreover, there were a number of amendments to the various laws, such as the Sherley Amendment of 1912 and the Durham-Humphrey Amendment of 1952. This essay reviews the major federal legislation through focusing on the Drug Importation Act; the Pure Food and Drug Act; and the Food, Drug, and Cosmetic Act; and places the legislation within the context of pharmacy practice of the period. This approach is of particular interest in light of the continuing debate concerning pharmacists’ compounding.

Legislation and Regulation

Legislation and regulation are not the same thing, and the differences are important when considering the impact on pharmacy. “Legislation” refers specifically to the creation of new laws. These laws may be passed by the appropriate process at any level of government: federal, state, or local. In the case of federal law, the process consists of a bill’s passage by both the Senate and the House of Representatives and the concurring signature of the president.

There are a number of steps wherein a bill can be effectively stopped, including the inability to get both legislative bodies to
agree to wording, or presidential veto, although the latter can be overridden by a large majority of the members of the legislature. A similar process is followed in the passage of state laws. A passed law typically enables another body to establish the rules about how the law will be administered, and if appropriate, how penalties will be assessed. Laws change when they are amended or voided by the originating legislative body. Some, however, simply outlive their relevance but remain on the books, although not enforced or enforceable.

Regulations, on the other hand, are the rules established by an agency which interprets the law. For example, the US Food and Drug Administration (FDA) has the rule-making responsibility for the Food, Drug, and Cosmetic Act. Other laws dealing with drugs of abuse and the promotion and distribution of medicines are under the purview of the Drug Enforcement Agency and the Federal Trade Commission. In the case of regulation, the agency responsible can modify, delete, and expand the rules, within specific processes, as it sees the need to implement the laws it is responsible for managing. In fact, regulations have a way of expanding far beyond the size of the enabling law. Consider as an example the Food, Drug, and Cosmetic Act of 1938, which covers a mere 19 pages. The Code of Federal Regulations Title 21, to enforce the law in force on June 1, 1938, and published in 1939, was printed in one volume of 109 pages. As of April 2005, the Code of Federal Regulations Title 21 requires nine volumes containing over 4,000 pages.

The Drug Importation Act of 1848

The importation of spurious and adulterated drugs was a major problem in the mid 1800s. From 1846 to 1848, the US was at war with Mexico, although the active fighting was essentially over with the capture of Mexico City in September 1847. The total number of deaths in the conflict was almost 13,000, most of which (11,000) were termed “ordinary deaths” but were due predominantly to disease. The death rate was largely attributed to the poor quality of food and medicines in the Army.

In 1848, the situation was little better in the civilian environment than it was in the military. New York was the port of entry for at least three quarters of all medicines imported into the US. Complaints about the quality of medicines imported from Europe were increasing. Many of the products were already banned in European countries, leaving the US as the sole remaining market. Dr. M. J. Bailey, the examiner of the New York port, provided an overview of the problem, noting that Peruvian bark was so adulterated that the dosage had to be increased to a teaspoon instead of the normal few grains. Opium was received that had only one third the standard morphine level, and blue mass was so adulterated that it contained only 7% mercury, instead of the normal 33.3%. Ohio representative and physician Thomas O. Edwards, describing the situation, claimed that the “United States has become the grand mart and receptacle of all the refuse merchandise of that description, not only from the European warehouses, but from the whole Eastern world.”

The New York College of Pharmacy and the New York Academy of Medicine were leaders in the fight for legislation to stem the flood of adulterated products. In 1848, President James K. Polk signed the Drug Importation Act of 1848. The law addressed only those medicines that were imported; there was no provision for substandard domestic products. It mandated inspection prior to admission to the country, and the standards to be applied were the pharmacopoeias and dispensaries of the US, London, Edinburgh, France, and Germany. If the product failed to meet the requisite standards, the owner could request a re-examination by a “competent analytical chemist possessing the confidence of the medical profession, as well as the colleges of medicine and pharmacy.” If the product failed the inspection, the substandard item was to be destroyed or deported at the expense of the owner. There also were requirements that any imported materials be clearly labeled with the location and true name of the manufacturer, and that any mislabeled items be forfeited. The responsibility for administration was given to the customs service, then part of the Department of Treasury.
The inclusion of the *United States Pharmacopoeia* (USP) as one of the official compendia was a significant first official governmental recognition. The importance of the 1840 USP to pharmacy was momentous, since for the first time pharmacists were involved in the revision process. They recommended a number of significant changes, including additions and revisions to existing monographs, and on the basis of these suggestions a new section was incorporated to provide assay and identification tests for chemical drugs. William Procter, Jr., subsequently identified as the Father of American Pharmacy, was the pharmacist most actively involved in the revision.

In a follow-up report in 1849, Edwards reported the results of examinations at the port of New York in a 6-month period, noting the names and weights of products stopped and their port of origin. Over 30,000 pounds of spurious yellow bark from a cinchona variety with no quinine from Bordeaux, Marseilles, and Cartagena was turned back, as were rhubarb root and opium from London.

By 1851, the situation had improved but not significantly. While the importation act was well meaning, the failure was in its application. With the exception of Bailey, many of the inspectors were appointed for their political connections rather than for their knowledge and analytical ability. One report noted that a shipment refused entry into New York was reshipped to Boston, where it was admitted and subsequently resold in New York. The College of Pharmacy of the City of New York invited the other colleges of the period (Philadelphia, Boston, and Cincinnati) to meet in October 1851 to develop steps to address the problem. One outcome of that conference was the agreement to meet in Philadelphia the following year to form a national association, the American Pharmaceutical Association.

Pharmacy of the period was synonymous with compounding; even manufacturing was a cottage industry that the pharmacist did in his own shop and for his own customers. The activities of grinding, macerating, comminution, sublimation, distillation, and desiccation preceded the preparation of suppositories, powders, elixirs, plasters, and other dose forms. Examples of William Procter’s compounding in 1847 included a tonic consisting of ammonium hydrochloride, syrups of ipecac, wild cherry, and balsam of Tolu flavored with orange flower water. The same day he prepared a mixture of Dover’s Powder (containing opium, ipecac, and potassium sulfate) divided into six powder papers.

Writing in 1869, Procter addressed the pharmacist’s role in the compounding of his own medicines: "When a pharmacist makes his own preparations he knows what they are, and is responsible for their quality; he graduates the supply to the demand, and thus renews his stock as often as it is needed. But when once he leaves this true standpoint and abandons his proper business as a preparer as well as dispenser of medicines, he is at the mercy of circumstances over which his control is very limited. The pharmacist who is daily engaged in preparing the medicines he vends, becomes so intimately acquainted with their properties that he can form a fair judgment of their quality when made."

**Pure Food and Drug Act of 1906**

The passage of the Pure Food and Drug Act of 1906 was a culmination of efforts that began in 1879 when Representative H. W. Wright of Pennsylvania introduced the first pure food bill, "for preventing the adulteration of articles, of food and drink." Harvey W. Wiley became the champion of the movement for food regulation after 1883, at least partly as a consequence of his experience with the German Imperial Board of Health. In spite of legislative deadlock over the passage of a new law, public opinion crystallized as a consequence of muckraking articles about adulterated food and patent medicines in popular magazines such as Collier’s and McClure’s, and the 1906 exposé of the Chicago meat-packing industry by Upton Sinclair in *The Jungle*. On December 6, 1905, after several previous unsuccessful attempts, Senator Weldon Heyburn of Idaho reintroduced his bill to prevent "the manufacture, sale or transportation of adulterated or misbranded or poisonous or deleterious foods, drugs, medicines, and liquors." The primary force behind the bill was the need to address the safety of foods; the issue of medicines was largely a consequence of the unlabelled alcohol and narcotic content in patent medicines. After what appeared to be yet another legislative deadlock, President Theodore Roosevelt demanded that the senate leadership bring the bill up for a vote.

On June 30, 1906, the last day of the Congress, the bill was signed into law.

The Pure Food and Drug Act of 1906 established a number of important points in the regulation of medicines, including the definitions of drugs and misbranding and the establishment of standards. In addition, the Act stated that the rules for domestic
products offered in interstate commerce that were adulterated or misbranded applied equally to imported drugs. Administration of the law was assigned to the Bureau of Chemistry in the Department of Agriculture.

The definition of the term "drug" in Section 6 included “all medicines and preparations recognized in the United States Pharmacopeia or National Formulary for internal or external use, and any substance or mixture of substances intended to be used for the cure, mitigation, or prevention of disease of either man or other animals.” Within the definition was the establishment of the standard by which medicines were to be judged for both purity and accuracy of labeling.

James Hartley Beal, Dean of Scio College of Pharmacy from 1887 to 1902, President of the American Pharmaceutical Association from 1904 to 1905, and Chairman of the United States Pharmacopeia (USP) Board of Trustees, had been active in the movement to support pure food and drug legislation for a number of years. It was Beal who was personally responsible for the inclusion of the USP and National Formulary (NF) as the official standards for the definition of adulteration under the new law.13

Section 7 defined adulteration as when an article, sold by a name recognized in the USP or NF, “differs from the standard of strength, quality, or purity, as determined by the test laid down in the United States Pharmacopeia or National Formulary official at the time of investigation.” It was also Beal who suggested what would become known as the “variation clause,” which allowed manufacturers to depart from the official standards as long as such deviations were clearly labeled. This clause removed much of the resistance of manufacturers to the inclusion of the USP and NF as the official standards.

Section 8 defined the types of misbranding that applied to drugs. The first was when an imitation was offered for sale under another name. The second was when an article was put in a container of another product or if the package was not clearly labeled with the quantity of alcohol or any one of a number of narcotics.

The eighth revision of the USP, dated 1900, was not printed and released until 1905. The first decade of the 20th century saw significant changes in the United States Pharmacopeial Convention as well as in the new revision. Owing in large part to a growing chemical industry and a corresponding decline in medicinals derived from natural products, the Committee on Revision faced issues of nomenclature and the increased involvement of manufacturers. To make the USP more relevant to physicians, average dose levels were added to the product monographs. The percentage of allowable...
imperfections, the “purity rubric,” was also included in the monographs. Products still under patent or with secret modes of manufacture were excluded from listing. Finally, specific bioassays were added for some products with the intention of adding more in following revisions.

The passage of the Pure Food and Drug Act of 1906 had an immediate impact on the USP. Joseph Remington, Chair of the Committee on Revision, wrote of the attention that was being paid to the role of the USP standards, especially by those who had earlier given them perfunctory notice. A number of corrections and additions were made, and a revised edition, USP VIII, was issued in 1908.

The second compendium included in the law was the NF, then in its third revision. Originally developed as a collection of formulas for the use of physicians to encourage them to prescribe pharmacists’ compounded products, the NF included standardized formulas that listed the ingredients quantitatively and qualitatively and provided the necessary processes for compounding. The third edition was released by the American Pharmaceutical Association in January 1906, with several major changes from the previous revision. The first change was the inclusion of an average dose for each formula; the second was the provision of quantities given in both metric and apothecaries’ measures. By the end of the year, NF III had been established under law as one of the official standards for American medicines.

Pharmacy as practiced in 1906 was still largely oriented toward compounding. In most states, aspirants could take the state board examination for licensure regardless of whether they had attended pharmacy school. The first state to mandate graduation from a college or school before taking the state board examination was New York in 1905. The normal degree for those attending the 2-year college course was a Graduate in Pharmacy (PhG). In 1910, the boards of pharmacy and colleges formed a national committee to develop a national pharmaceutical syllabus to provide guidance for the curricula necessary to take the board examinations. This minimum course was also the basis for established reciprocity standards between the states. A total of 130 hours in the 2-year college curriculum was required for the study of pharmacy, which included the “science and art of preparing, preserving, compounding and dispensing medicine.” The other general curricular areas were materia medica and chemistry.

In 1908 and 1909, C. S. N. Hallberg and Clyde M. Snow conducted a prescription ingredient survey under the direction of the USP Board of Trustees to aid in the revision by collecting statistics on what items were used. The survey was sent to members of the American Pharmaceutical Association; 117,000 prescriptions from 28 states representing all sections of the country were analyzed. The analysis looked at both the number of ingredients and the number of occurrences of the ingredients. The prescriptions averaged 1.84 ingredients. Of all the ingredients used, 1,242 (53.63%) were official in either the USP VIII or NF III; 624 ingredients (26.94%) were proprietary items. When occurrences of use were considered, over 91% were official in either the USP or NF and slightly more than 7% were proprietary. Over 93% of the items in the USP were used in the prescriptions, while 70% of the items in the NF were incorporated in the prescriptions.

Data clearly suggested that pharmacists were compounding by using official monographs. Peter Temin described the effect of the legislation, noting the immediate transformation of the USP and NF from private publications to official standards.

Food, Drug, and Cosmetic Act of 1938

The first test of the 1906 Pure Food and Drug Act occurred in court in 1908 when the labeling of a patent medicine, Cuforhedake Brane-Fude, was deemed to be false and misleading. The 1906 law did not address false or misleading therapeutic claims. In 1912, the Sherley Amendment was passed, adding to the definition of misbranding: “any statement, design, or device regarding the curative or therapeutic effect of such article or any of the ingredients or substances contained therein, which is false or fraudulent.”

Shortcomings of the legislation continued to be exposed, however, and by the early 1930s there was agreement that something should be done, but no consensus on what it should be. In 1931, the Bureau of Chemistry became the Food, Drug, and Insecticide
Administration (later the FDA) and was transferred from the Department of Agriculture to the Federal Security Agency. Walter Campbell, chief of the FDA, took his complaints about the deficiencies of the 1906 legislation to Rexford Tugwell in 1933. Tugwell, a member of Franklin D. Roosevelt’s “brain trust,” was an assistant Secretary of Agriculture. He, in turn, shared the issue with the president and gained his agreement to seek revision of the Pure Food and Drug Act. The Tugwell Bill was introduced to the Senate by Royal Copeland of New York in June 1933. Copeland, a homeopathic physician from New York, had been the Commissioner of Health for New York City. In spite of the failure to gain passage in 1933, Copeland continued to introduce new legislation at each session of Congress.

On September 7, 1937, the S.E. Massengill Company introduced a new product, Elixir of Sulfanilamide. Sulfanilamide had been available in tablet and powder forms but Massengill was the first to develop and market a sweet-tasting liquid for pediatric use. Diethylene glycol was selected for its taste and ability to dissolve the sulfadiazine; no safety tests were required or performed. Over 100 people, mostly children, died from ingesting the Elixir of Sulfanilamide. Under the 1906 Pure Food and Drug Act, the only infraction committed by Massengill was mislabeling the product as an elixir instead of a solution. If the product had been correctly labeled, there would have been no legal recourse—a fact that led to a high level of frustration and demand for the passage of new drug legislation. The deaths provided an impetus to the Copeland Bill, and the resulting Food, Drug, and Cosmetic Act was passed and signed into law by President Roosevelt on June 27, 1938.

Like the 1906 Pure Food and Drug Act, the Food, Drug, and Cosmetic Act of 1938 included a section on the importation of drugs. Also like its predecessor legislation, the 1938 Act focused on the manufacturer of products for interstate trade and only as an exemption addressed “the practice of the trade” and the labeling of prescriptions in the pharmacy.

Two sections of the new law referring to medicines (as opposed to food and cosmetics) are best known. The first is the definition of a new drug, and the second is Section 505, which established the requirement for manufacturers to apply for FDA authorization to market new drugs. The definition, in part, was “any drug the composition of which is such that such drug is not generally recognized, among experts qualified by scientific training and experience to evaluate the safety of drugs, as safe for use under the conditions prescribed, recommended, or suggested in the labeling.” The definition of “new drugs” also included products that had been...
determined to be safe but not used long enough to prove safety. The definition specifically exempted drugs marketed under the 1906 regulations if the labeling was the same. Proof of safety was the condition for marketing, and the FDA had authority to remove a drug from the market if subsequent tests showed that the product was unsafe for its intended use.

Other sections of the new law were equally important. The term "official compendia" was broadened through the addition of the third and newest compendium recognized by the 1938 legislation, the Homeopathic Pharmacopeia of the United States, to the previously identified USP and NF and their supplements. This addition also broadened the definition of "drug" as "any article recognized in any of the compendia and intended for use in the diagnosis, cure, mitigation, treatment, or prevention of disease in man or other animals and intended to affect the structure or any function of the body."

Chapter V of the Act specifically addresses issues of adulteration and misbranding, mostly relating to the manufacturer of covered items. Products that meet the standards of the compendia for strength and purity were not adulterated. In addition, products listed in the compendia but differing in strength or purity were not adulterated if the difference was clearly labeled. When two or more active ingredients are fabricated, the quality and kind of each must be identified. Labels must include identification of the manufacturer and an accurate statement of quantity.

Section 503 provides exemption to the labeling and packaging of products that are "processed, labeled, or repacked" at a site other than the original manufacturer. For the first time there is a specific provision for items dispensed under the legitimate order of a physician, dentist, or veterinarian. The label on prescriptions must include the name and place of the business of the dispenser (the word pharmacy is not used), the serial number of the prescription, the date of dispensing, and the name of the prescriber.

The USP XI became official in June 1936. The years leading up to the publication were marked by discussions between regulators and representatives of pharmacy, medicine, and manufacturing about the status of USP as an official compendium. For the first time, storage requirements appeared, albeit only for a limited number of monographs. Most monographs now contained a description along with physical properties, tests for identity, tests for purity, average dose in both metric and apothecaries’ systems, and storage requirements. Still included in most monographs were directions for manufacture. NF VI also became effective in June 1936. Like the USP, the revised NF included descriptions, tests for identity and purity, average dose in both measurement systems for many formulas, and directions for compounding. The NF also described the Prescription Ingredient Survey that was used to help determine which formulas should be included and which excluded. The tentative rule adopted was that items must be used in at least 20% of the drug stores in the US, or be an ingredient in at least one of every 10,000 prescriptions compounded.21

The fourth revised edition of the Homeopathic Pharmacopeia of the United States was published in 1936 under the authority of the American Institute of Homeopathy. Homeopathic practice was dominated by natural products, and this was clearly documented by the revision. Each botanical monograph included the order, family, and, usually the habitat and part of the plant used. All of the monographs included a description and preparations. The Homeopathic Pharmacopeia of the United States relied on the USP for tests of purity. Interestingly, the Homeopathic Pharmacopeia of the United States was seen as more important to the physician than the pharmacist since “only a portion of the former are within easy reach of the professional pharmacist who understands the preparation for homeopathic use.”22

Pharmacy was in a period of change. The requirement for the 4-year Bachelor’s Degree had been implemented in 1932, replacing the 3-year Pharmaceutical Chemist (PhC) degree that had become mandatory in 1925. The fourth edition of the Pharmaceutical Syllabus reported that successful completion of the degree required a minimum of 3,000 hours; over 2,300 were in required classes and over
a quarter of these in pharmacy subjects such as dispensing pharmacy, operative pharmacy, and pharmaceutical technique. For the most part, education seemed to reflect practice with a continued emphasis on compounding.

As anticipated, the FDA immediately developed regulations to implement the new legislation. Rules for labeling products were among the first to be established. Incidentally, this began the regulatory division between prescription and nonprescription products, which was largely based on labeling and the consumer’s ability to understand printed directions.

After 1938

In the years since the 1938 passage of the Food, Drug, and Cosmetic Act, there have been a number of amendments that affect pharmacy either directly or indirectly. Pharmacy was directly affected by the 1951 Durham-Humphrey Amendment, which took effect in 1952. The amendment codified the two classes of medicines: prescription and nonprescription. In addition, the confusion over the legality of telephone prescriptions and refills was addressed. Pharmacy was more indirectly affected by the 1962 Kefauver-Harris Amendment, which was passed in the wake of the thalidomide tragedy. The amendment imposed a requirement of efficacy as a premarketing condition, established good manufacturing practices, and addressed nomenclature. As Temin points out, none of these issues were directly related to the problems of thalidomide, but they did give the FDA a much more direct role in the approval process of new medicines. Neither of these amendments, nor any subsequent legislation, changed the recognition of the USP and other compendia as the standards for purity and composition of medicinal products. In 1975, the USP acquired the NF, and the two are now published as a single text. The eighth, and so far last, edition of the Homeopathic Pharmacopeia of the United States was published in 1979.

Observations

The perspective that emerges from these three landmark pieces of legislation is both consistent and clear. The underlying theme that runs throughout is the concern with spurious, adulterated, and mislabeled medicines. In that respect, the focus and force of the law was on manufacturers who willingly compromised the integrity of the product through changing it, or mislabeling it, or claiming it could do something it could not. The legislation in each case is silent about pharmacists and what they can or cannot do in their day-to-day practice of pharmacy.

The practice of compounding individual prescriptions, which had waned with the increase in large-scale manufacturing, has enjoyed resurgence. Owing in part to manufacturers’ discontinuation of products and formulations with limited use, shortages of some products, and increased need for individualized medications, many pharmacists have increased their compounding practices. In spite of the fact that the USP/NF no longer has the same relevance to pharmacy practice that it had in earlier times, largely because of the absence of compounding recipes and directions, the compendia have remained an important source for standards.

In 2005, the USP issued the long-awaited USP Pharmacists’ Pharmacopeia. This new edition of the USP provides monographs, including ingredients and directions, for approximately 110 of the most commonly compounded prescriptions. Moreover, there is a detailed section on compounding a number of dose forms, standards for microbial test limits and particulate contaminants, and a section on laws and legal requirements affecting compounding. It is clear that the historical theme of guaranteeing product safety from spurious and adulterated medicines, as typified in the Drug Importation Act of 1848, the Pure Food and Drug Act of 1906, and the Food, Drug, and Cosmetic Act of 1938, continues to be an important part of the USP, the compendium identified as the official standard in each Act.

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