ensuring the excellence of our drug supply.

The second portion of the symposium consists of a presentation by Dr. William Horwitz, Deputy Associate Director for Science in the Bureau of Foods. Dr. Horwitz is also the Executive Director of the Association of Official Analytical Chemists and is on the Editorial Committee, along with Dr. Banes, for the *Journal of the Association of Official Analytical Chemists*. This association is one of the prime sources of standardized analytical methodology used in the enforcement of standards and tolerances in the FDA.

The final portion is covered by Mr. Hyman P. Eiduson, of the office of FDAs Executive Director of Regional Operations. Mr. Eiduson is responsible for the coordination and overall management of the activities of FDAs 20 field analytical laboratories. These laboratories are the "Front-Lines" in defending the consumer against adulterated and misbranded foods, drugs, and cosmetics. The final paper by Dr. Thomas Cairns and Mr. Robert Jacobson of the FDA Los Angeles District Laboratory is concerned with new approaches to FDAs analytical problems.

USP and the Development of Drug Standards†

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The history of the *United States Pharmacopeia* (USP), its role in maintaining the integrity of drugs, its relationship with the Food and Drug Administration, and the effect of advances in analytical methods on its standards are reviewed.

The *United States Pharmacopeia* (USP) enjoys a unique distinction among the world's official drug compendia. USP standards for the strength, purity, and quality of drugs are recognized by law as mandatory requirements enforceable by regulatory agencies of the United States and of the 50 states. If a product defined in a USP monograph fails to comply with any of the applicable pharmacopeial requirements, it is violative and subject to legal penalties. Yet the United States Pharmacopeial Convention is not an agency of the Government; it is a self-supporting, nonprofit, quasi-public institution. No other independent pharmacopeia exerts such a crucial influence on drug regulation. The flourishing condition of USP and its continuing leadership among pharmacopeial enterprises attest to its usefulness and effectiveness as an open forum where scientists from the academic, industrial, and governmental sectors can cooperate freely in evolving standards and methods of analysis for characterizing important drugs.

USP has played a major role in maintaining the integrity of drugs in the United States ever since the inception of the compendium more than one and a half centuries ago. The first national Pharmacopeia of the United States was conceived and brought forth by a convention of eminent physicians in 1820. They resolved to standardize those drugs "the utility of which is most fully established and best understood". Standards in the monographs assembled for the first American national compendium were intended to define articles of the highest quality and purity attainable through processes that assured the widespread availability of the drugs as medicinal agents. Thus, the standards reflected the composition of the better specimens of the products then distributed in the channels of commerce. Because scientific and technologic advances continually develop novel entities and improve the quality of drug articles already on the market, new monographs and more exacting standards are continually generated. Consequently, the first Pharmacopeial Convention foresightedly provided a mechanism for the periodic updating of the pharmacopeia through the ministrations of a scientific Committee of Revision. USP has lived in accordance with these precepts of the founding fathers ever since.

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USP standards were widely accepted as authoritative criteria for the quality of drugs throughout the 19th century. In 1906, when Congress passed the Pure Food and Drug Act, it formally accorded legal recognition to the monographs in the then current revision of USP, and most of the 50 states have since done likewise. The Federal Food, Drug, and Cosmetic Act of 1938 superseded the Pure Food and Drug Act, and Congress reconfirmed the precedent recognition of USP standards, tests, and methods as official requirements. However, the federal law now reserves a definitive veto power to the regulatory agency. The law states that if FDA finds a USP test or method inadequate for drug regulation, the Secretary of Health, Education and Welfare, "shall bring such fact to the attention of the appropriate body charged with the revision of such compendium, and if such body fails within a reasonable time to prescribe tests or methods of assay which, in the judgment of the Secretary, are sufficient for purposes of this paragraph, then the Secretary shall promulgate regulations prescribing appropriate tests or methods of assay in accordance with which such determination as to strength, quality, or purity shall be made". It is noteworthy that the Government has never found it necessary to exercise this veto or to set aside methods of analysis adopted by USP.

The actual process of evolving USP standards and test methods is a joint responsibility of a small headquarters staff and the pharmaceutical scientists in the USP Committee of Revision. The latter comprises a group of 50 volunteer scientists—biochemists, pharmacologists, microbiologists, pharmacists, chemists—elected by the United States Pharmacopeial Convention for a 5-year term. The drugs requiring monographs in the forthcoming revision of USP are designated by an expert group of volunteer physicians, constituted as a Committee on Scope, who select the most essential therapeutic agents currently in use and the best dosage forms for administering them. As a point of departure, tests and specifications are first solicited from the manufacturers of these products, and searches of the scientific literature are instituted. Tentative standards are suggested for assurance of excellence, and the originally proposed analytical methods are empirically tested for reliability and adequacy, or are supplemented or supplanted by methods deemed superior on the basis of findings in more recent investigations. In many instances, the

Committee arranges a collaborative study to test the suitability of a proposed analytical method. Success in a collaborative study is the best warranty that a method will prove reliable in all capable laboratories and not only on the home grounds of its progenitor.

Withholding of significant new data by manufacturers would inevitably result in the persistence of mediocre standards and archaic analytical tests, unless the missing information can be developed by more cooperative scientists elsewhere in industry, or by research laboratories in the academic or governmental sectors. Fortunately, USP has been able to enlist the aid of many interested research laboratories in its enterprises, particularly those of the Food and Drug Administration and of the Schools of Pharmacy.

Other avenues for eliciting data that lead to the revision of tests and standards are the USP publications entitled "Comment Proof" and "Pharmacopeial Forum". These periodicals, circulated on subscription, show the tentative monographs for drug articles and the chapters on general tests proposed for adoption in forthcoming USP issuances, after deliberations by panels of USP advisors. The Committee of Revision receives comments and recommendations for changes in these proposals from representatives of trade associations and of individual manufacturers; from government officials, including those from the Defense Personnel Support Center, the National Institutes of Health, the Veterans Administration, and the Food and Drug Administration; from scientists in schools of pharmacy and medicine; from scientists associated with foreign pharmacopeias, foreign companies, and foreign governments; and from unaffiliated scientists writing as private individuals.

These criticisms are reviewed by the headquarters staff in concert with the responsible subcommittees of the USP Committee of Revision. Changes that are deemed scientifically valid are then adopted, and the completed monographs are ready for promulgation. In this manner, USP evolves publicly scrutinized, objective, scientifically verified standards, as well as practicable tests and assays, through the collaborative efforts of highly qualified disinterested scientists. Except for voluntary contributions of time and resources expended by these scientists, USP receives no financial support from government, from industry, or from any academic institution.

Modern technology has proved equal to the task of providing analytical tests and assays possessing the requisite reliability, sensitivity, and speed. Once they are validated, USP is eager to adopt them. Among the analytical approaches recognized in the currently official drug compendia are: nuclear magnetic resonance spectrometry, high-performance liquid chromatography, x-ray diffraction spectrometry, thermal gravimetric analysis, and automated assays. In fact, USP sometimes suffers from an embarrassment of riches. It is often necessary to remind enthusiastic innovators that the primary purpose of USP revision is to improve standards and tests and drug quality, not to flaunt the capabilities of novel analytical techniques.

In general, advances in technology leads to stricter standards over the course of the years. A retrospective survey of USP revisions would disclose many examples of such progressive changes. But even this generalization does not hold universally. Some standards may appear to have become more permissive rather than more stringent as our store of new information is augmented. This seeming paradox is readily explained. In the absence of discriminating analytical methods, it is comforting to proclaim that the purity of a drug product should be very close to 100%, especially if there is a dearth of information about the occurrence of contaminants. Such has been the case with many drugs derived from natural sources including quinine and quinidine, folic acid and tocopherol, amphotericin and insulin. Unfortunately, the older analytical methods were not sufficiently discriminating to differentiate between the pure drug substance itself and closely related compounds. The introduction of more discerning chromatographic methods has disclosed, for example, that most specimens of quinidine salts now purveyed (including even "highly purified" reference standard substances) are contaminated with the corresponding dihydroquinidine salts and other cinchona alkaloids in amounts ranging from 2 to 17% of the total. Under these circumstances, it has been necessary for USP to adopt a realistic standard frankly recognizing that current specimens of quinidine salts are not even close to 100% pure, but that related cinchona alkaloids commonly occur as contaminants. The concentration of these impurities has been limited to the lowest practicable level consistent with the continued availability of the substance for drug use. Of course, much stricter limits necessarily would be imposed if any of the contaminating alkaloids were shown to be toxic and potentially hazardous to the patient. The precautionary tolerance for a possibly deleterious contaminant must be set well below the highest no-effect level observed when the drug is administered to test animals in a mode corresponding to the intended therapeutic usage. In general, USP rarely accords recognition to a drug substance whose purity is less than 95%. In fact, the lower limit for the vast majority of drug substances is 98%. For dosage forms, the permitted range of the active ingredient is the most restrictive that is consistent with the reliability of the assay and the capabilities of manufacturing practice. For example, the important cardioactive drugs Digoxin tablets and Digitoxin tablets are difficult to assay, and may contain as little as 50 μg of the steroid per tablet. Nevertheless, the monographs for these drugs require that they contain not less than 90% and not more than 110% of the declared quantity of the active ingredient.

These examples illustrate the principles guiding the construction of USP monographs. The drugs whose attributes they define and standardize are considered the most important medicinal agents currently in use. Although these articles comprise only a fraction of the products in commerce, USP has influenced the quality control of consumer goods far beyond its immediate scope. Historically, the monographs of the USP have been the model for the specifications in most of the published drug monographs for pharmaceuticals, and even for food substances, pesticides, and household products. Furthermore, USP requirements have been recognized as official in countries outside the United States, and its monographs have been borrowed by foreign pharmacopeias or have been worked out in concert with them. Thus, USP has been a powerful agent in enhancing both the quality control of drugs and the quality of consumer commodities throughout the world.