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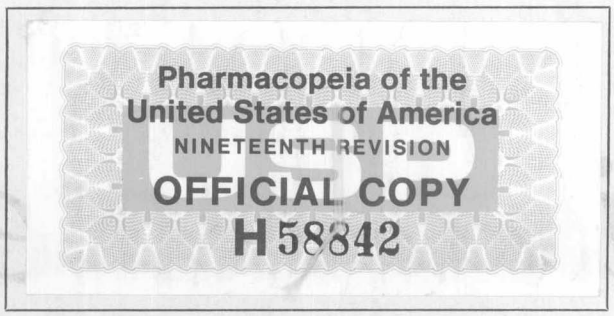

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Panel on Gastroenterology—J. Edward Berk, M.D.; G. Gordon McHardy, M.D.; New Orleans, La.; James L. A. Roth, M.D., Ph.D., Philadelphia, Pa.; Fenton Schaffner, M.D., New York, N. Y.; Howard M. Spiro, M.D., New Haven, Conn.; David C. H. Sun, M.D., Phoenix, Ariz.; Louis Zetzel, M.D., Boston, Mass.

Panel on Gynecology, Obstetrics, and Urology—Daniel L. Azarnoff, M.D.; Theodore M. King, M.D., Ph.D., Baltimore, Md.; Winston K. Mebust, M.D., Kansas City, Kans.; Robert A. Munsick, M.D., Ph.D., Albuquerque, N. M.; James Warren, M.D., Ph.D., St. Louis, Mo.

Panel on Hematologic and Neoplastic Diseases Therapy—Isadore Brodsky, M.D.; Ernest Beutler, M.D., Duarte, Calif.; Michael C. Brain, D.M., F.R.C.P., Hamilton, Ontario, Canada; Marcel E. Conrad, Jr., M.D., Washington, D. C.; Frank H. Gardner, M.D., Philadelphia, Pa.; Thomas C. Hall, M.D., Los Angeles, Calif.; Edward S. Henderson, M.D., Buffalo, N. Y.; S. Benham Kahn, M.D., Philadelphia, Pa.; Frank A. Oski, M.D., Syracuse, N. Y.; Oscar D. Ratnoff, M.D., Cleveland, Ohio; William Regelson, M.D., Richmond, Va.; R. Wayne Rundles, M.D., Ph.D., Durham, N. C.; Frederick Stohlman, Jr., M.D., Boston, Mass.

Panel on Infectious Disease Therapy—Ernest Jawetz, M.D., Ph.D., and Calvin M. Kunin, M.D.; Sydney M. Finegold, M.D., Los Angeles, Calif.; Jack M. Gwaltney, Jr., M.D., Charlottesville, Va.; William L. Hewitt, M.D., Los Angeles, Calif.; H. Corwin Hinshaw, M.D., San Francisco, Calif.; Gladys L. Hobby, Ph.D., East Orange, N. J.; Richard B. Hornick, M.D., Baltimore, Md.; William M. M. Kirby, M.D., Seattle, Wash.; Jay P. Sanford, M.D., Dallas, Texas; Marvin Turck, M.D., Seattle, Wash.; Arthur C. White, M.D., Indianapolis, Ind.

Panel on Neurological Disease Therapy—Melvin D. Yahr, M.D.; Robert C. Duvoisin, M.D., New York, N. Y.; Arnold P. Friedman, M.D., Tucson, Ariz.; Lewis P. Rowland, M.D., New York, N. Y.; Peritz Scheinberg, M.D., Miami, Fla.; Richard P. Schmidt, M.D., Syracuse, N. Y.; William A. Sibley, M.D., Tucson, Ariz.

Panel on Ophthalmology—Irving H. Leopold, M.D.; Leonard Apt, M.D., Los Angeles, Calif.; Bernard Becker, M.D., St. Louis, Mo.; Philip P. Ellis, M.D., Denver, Colo.; W. Morton Grant, M.D., Boston, Mass.; John E. Harris, M.D., Minneapolis, Minn.; Herbert E. Kaufman, M.D., Gainesville, Fla.; Frank W. Newell, M.D., Chicago, Ill.

Panel on Parasitic Disease Therapy—Harry Most, M.D.; Ernest Bueding, M.D., Baltimore, Md.; Rodney Jung, M.D., New Orleans, La.; Robin D. Powell, M.D., Iowa City, Iowa; Myron G. Schultz, M.D., Atlanta, Ga.; Howard B. Shookhoff, M.D., Bronx, N. Y.; Paul Thompson, M.D.,* Athens, Ga.; Jerome P. Vanderberg, M.D., New York, N. Y.

Panel on Pediatrics—Harry C. Shirkey, M.D.; Cheston M. Berlin, Jr., M.D., Hershey, Pa.; Jack W. Bills, M.D., Van Nuys, Calif.; Thomas M. Cashman, M.D., Honolulu, Hawaii; Sanford N. Cohen, M.D., New York, N. Y.; Alan K. Done, M.D., Rockville, Md.; Virgil M. Howie, M.D., Huntsville, Ala.; Benjamin M. Kagan, M.D., Los Angeles, Calif.; Bernard L. Mirkin, M.D., Ph.D., Minneapolis, Minn.; Paul A. Palmisano, M.D., Birmingham, Ala.; Harris D. Riley, Jr., M.D., Oklahoma City, Okla.; Charles F. Weiss, M.D., Jacksonville, Fla.; Sumner J. Yaffe, M.D., Buffalo, N. Y.

Panel on Psychiatric Disease Therapy—Melvin D. Yahr, M.D.; Ronald R. Fieve, M.D., New York, N. Y.; Daniel X. Freedman, M.D., Chicago, Ill.; Leo E. Hollister, M.D., Palo Alto, Calif.; Nathan S. Kline, M.D., Orangeburg, N. Y.

Panel on Radiologic Contrast Media—E. James Potchen, M.D.; M. Paul Capp, M.D., Tucson, Ariz.; Ronald G. Evens, M.D., St. Louis, Mo.; Harry Fischer, M.D., Rochester, N. Y.; Michael Holzer, M.D., Albuquerque, N. M.; Melvin P. Judkins, M.D., Loma Linda, Calif.; P. Ruben Koehler, M.D., Salt Lake City, Utah; Elliott Lasser, M.D., San Diego, Calif.; Mark M. Mishkin, M.D., Philadelphia, Pa.; Nikolaus Schad, M.D., Giessen, West Germany.

Panel on Electrolytes and Parenteral Therapy—W. Gordon Walker, M.D.; Saul W. Brusilow, M.D., Baltimore, Md.; H. Earl Ginn, Jr., M.D., Nashville, Tenn.; Martin Goldberg, M.D., Philadelphia, Pa.; Robert D. Lindeman, M.D., Oklahoma City, Okla.; Raymond H. C. Meng, M.D., Ph.D., Nashville, Tenn.; Elbert P. Tuttle, Jr., M.D., Atlanta, Ga.; Stanley J. Dudrick, M.D., Houston, Texas.

Panel on Toxicology—Henry W. Elliott, M.D., Ph.D.; Eric Comstock, M.D., Houston, Texas; Charles H. Hine, M.D., Ph.D., San Francisco, Calif.; Harold C. Hodge, Ph.D., San Francisco, Calif.

Panel on Dosage Forms—William H. Barr, Pharm.D., Ph.D.; George D. Denmark, Pocasset, Mass.; Joseph F. Gallelli, Ph.D., Bethesda, Md.; Leon Lachman, Ph.D., Garden City, N. Y.; Tom S. Miya, Ph.D., West Lafayette, Ind.

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* Deceased.

Foreword

The axiom that *What is past is prologue* is perhaps never more poignant than when applied to a long-established institution such as The United States Pharmacopeia, now in its 154th year of service to the public through the selection, naming, and standardization of drugs. We are indebted to those past stewards of the USP legacy over the years who consistently have maintained and strengthened these endeavors to assure the highest possible quality of drugs. Most immediately of these, Dr. Lloyd C. Miller, who directed the USP revision program for two decades [1950–1970] with such distinction, is deserving of the utmost appreciation and esteem.

As this Pharmacopeia goes to press, negotiations are being completed for the acquisition by USPC of The National Formulary. This historic consolidation of USP and NF brings together two significant traditions, with all the strengths of both now united and at the ready to fulfill still larger purposes which demand our efforts and energies.

That continual striving for the achievement of good, to better, to best—depending upon the state of development of the particular revision or policy—that continual striving for excellence for the benefit of the public, was part of the heritage and responsibility handed on in 1970 to a largely new headquarters staff and a new Committee of Revision for 1970–1975, culminating in the publication of USP XIX.

Here is the new Pharmacopeia; here is a new, unified, biprofessional organization; here is the new beginning.

William M. Heller

Rockville, Maryland
August, 1974

Preface to USP XIX

Interest in the quality of drug products, the standards that determine quality, and compliance with the standards, has continued to increase during the five-year period of preparation of this Pharmacopeia. Renewed emphasis also is being given the related concepts of *good manufacturing practice* and *bioavailability* (see *Biological Availability*, page xv) as part of the attention currently being focused upon the health care of the nation. There is no disagreement with the fact that safety and efficacy, and bioavailability, as well as certain other attributes of drugs, are clearly dependent upon good manufacturing practice in production, so that new tests have been devised and more rigorous standards have been set up for existing procedures with the general objective of improving quality. To be mentioned particularly in this connection are the revisions in or the introduction of tests for content uniformity, microbial limits, and dissolution rate.

Legal Status of the Pharmacopeia—References to the USP occur in several federal statutes, the most significant being the recognition of the USP definitions and standards in the Food, Drug, and Cosmetic Act. This use of the USP standards as the basic measures of strength, quality, and purity, and the recognition of USP requirements for packaging and labeling, impose upon the Committee of Revision explicit strictures in respect to the need for clarity of presentation and for reliability and applicability of the USP standards. It is important to stress that these standards apply to the USP article while in the hands of the practitioner, just as fully as during the time it is under the control of the manufacturer.

The impact of the 1962 Amendments to the Food, Drug, and Cosmetic Act on the Pharmacopeia is evident in the absence of virtually all standards for the drug products classed as antibiotics, since the above-cited legislation placed all responsibility for this upon the Food and Drug Administration. The Amendments, however, did not change the provisions of the Act whereby prime responsibility for the standards for the insulin-containing products, which also must be batch-certified by the FDA, is placed upon the Pharmacopeia.

Those portions of the Food, Drug, and Cosmetic Act which specifically refer to the Pharmacopeia are presented in the chapter, *Legal Recognition of The United States Pharmacopeia*, page 693, as a matter of information.

The USP Organization—Revision of the Pharmacopeia is made possible by an independent nonprofit organization that derives financial support wholly from sales of the published volume and from fees for the USP Reference Standards. The revision and reference standards programs are closely interrelated, since the use of the Reference Standards is an important means of demonstrating compliance with the USP tests and standards.

Administration of the business aspects of the organization is the responsibility of the USPC Board of Trustees, the roster of which is listed on page vi, whereas the preparation of the Pharmacopeia and the establishment of the USP Reference Standards are the responsibility of the USP Committee of Revision (see page vi).

The Revision Program—This revision of the Pharmacopeia, produced by the 1970–1975 General Committee of Revision, marks the first such compendium to appear since the 1970 Convention delegates placed all Pharmacopeial activities on a five-year cycle rather than on a decennial basis as in the past. Although the USP has been completely revised on a quinquennial basis since 1940, the election of the Committee of Revision had continued as a decennial event until 1970. Other constitutional amendments (see *Abstract of the Proceedings of the United States Pharmacopeial Convention of 1970*, page xxxi) created the new post of Executive Director, provided for expanded informational services in connection with USP drugs, and generally paved the way for more continuous representation and communication between the Convention officials and the Convention membership.

Just as for the revisions in the recent past, the work on this revision was organized by the assignment of the twelve Subcommittees to the major areas of the program as indicated on page vii. Although the Subcommittee on Scope was responsible for the selection of the therapeutic articles to be recognized, a major departure from past procedures was made by assigning to the Subcommittee on Formulations the task of selecting the pharmaceutic ingredients to be recognized. During the selection process, the nine Subcommittees concerned with tests and standards concentrated on the general tests and on the specific problems carried over from the prior revision. As is indicated on page viii, several panels were appointed to assist the Revision Committee; and particular mention should be made of the USP Panel on Microbiological Attributes and Procedures and the USP–NF Joint Panel on Primary Requirements. The Panel on Microbiological Attributes and Procedures, under the chairmanship of Dr. Henry D. Piersma, continued an extensive review of

the chapters on *Sterility Tests* and *Sterilization* in particular, and also reviewed and made recommendations on the many helpful comments received from reviewers of *USP Comment Proof* (see on this page) on these and on the chapters on *Antimicrobial Preservatives—Effectiveness, Microbial Limit Tests,* and *Microbiological Attributes of Non-sterile Pharmaceutical Products.* The Joint Panel on Primary Requirements was appointed, with Dr. Joseph A. Zapotocky as chairman, to review the General Notices of both the USP and the National Formulary with the special aim of achieving identical text for both compendia in the interest of clarity and uniformity—a goal that has been accomplished with very few exceptions, none of which is of such nature as to cause difficulty—and to work similarly for greater uniformity between the general chapters common to both compendia. Noteworthy success in the latter endeavor may be recorded also, though the exigencies of the publication schedule imposed some limitations in this regard.

Continuing the trend in recent revisions of the Pharmacopeia, the tests and assays in the monographs rely ever more heavily upon the newer chromatographic and spectrometric techniques. High-pressure liquid chromatographic methods, perfected only within this revision period, have been employed in several monographs, particularly those for steroid drugs. Gas-liquid chromatography and thin-layer chromatography have been utilized far more frequently than in previous revisions, as have infrared spectrophotometry and spectrophotofluorometry. X-ray diffraction spectrometric methods and atomic absorption spectrophotometric methods have been introduced as Pharmacopeial tests for the first time. These discerning techniques, which have permitted the establishment of more reliable tests for identity, quality, purity, and strength, are described in the extensively revised chapters on *Chromatography* and *Spectrophotometry, Colorimetry, Turbidimetry, Nephelometry, and Fluorometry.*

The Scope Program—The value of the Pharmacopeia to the medical profession lies chiefly in its usefulness as a select list of therapeutic articles. This goes far in determining the prestige that a pharmacopeia enjoys generally, yet the basis for the selection is not easily stated. The general objective is that the Pharmacopeia shall include those articles that represent the best teaching and practice of medicine and pharmacy. However, difficulties arise in giving full effect to this principle in a program that is executed by a committee of experts, each of whom has considerable freedom of individual action. For this Pharmacopeia, most of the 20 medical specialists making up the USP Subcommittee on Scope headed panels of fellow specialists (as indicated on page ix) who were asked to evaluate the articles used within their specialties. These evaluations were reported to the Subcommittee as a whole, and the makeup of the list reflected the sum total of judgments based upon these reports. The pharmaceutical matters arising during the course of the selection process were the responsibility of the five pharmacists on the Subcommittee.

The selection process for the articles in this Pharmacopeia has seen considerable refinement. While maintaining the fundamental philosophy of selecting only the best, established drugs, the Subcommittee on Scope devoted much thought and attention to making the admission program as logical, systematic, comprehensive, and useful as possible. To this end, the drugs were reviewed by indications, and the reasons underlying both the recommendations of the advisory panels and the admission voting by the Subcommittee were ascertained. The resulting information documents the Subcommittee's drug selection decisions not only for drugs admitted to the Pharmacopeia, but also for drugs considered and not approved for admission.

Experience has shown that more inquiries arise in regard to the basis for the omission of an article from the Pharmacopeia than for any other aspect of the selection process. While such information clearly has no place in the Pharmacopeia, its dissemination otherwise is a proper concern of the Revision Committee, and particular attention must be paid to careful documentation.

More articles have been admitted to this revision than have appeared in any USP for 75 years. This is a reflection of the decision by the Subcommittee on Scope to bestow USP recognition on all drugs of equivalent medical merit. In consequence, the total number of articles is 1284.

The Subcommittee on Scope maintained its conservatism with respect to the recognition of fixed combinations of drugs, restricting it to those wherein each component contributes unequivocally to the intended effect.

Finally, the Subcommittee has adopted a policy of continuous admission. Henceforth, drug selection for the Pharmacopeia shall keep pace with new drug introductions, and it is planned that the Subcommittee's decisions on admission will be published periodically in a companion volume to the Pharmacopeia, *The USP Guide to Select Drugs.*

USP XVIII Interim Revisions—One USP XVIII Supplement was issued, and it became official November 1, 1971, except where otherwise noted. In addition to new text, it contained the texts of the First and Second USP XVIII Interim Revision Announcements, which had become official earlier. Subsequently the Third through the Sixth USP XVIII Interim Revision Announcements were issued, between June of 1972 and November of 1973. Thereafter, the subjects of USP revision were taken up with a view toward preparation of USP XIX, inasmuch as proposed revisions had begun to appear in *USP Comment Proof* early in 1973.

USP Comment Proof—Beginning in February, 1973, an innovation to replace the galley and page proof booklets distributed to selected persons in previous revisions was instituted, in the form of 48 weekly issues per year of offset-reproduced sheets

showing revised and new proposed USP text for monographs and general chapters. USP Comment Proof is unique in that it shows the reviewer at a glance which monographs and chapters have been —and which have not been—revised by the USP Committee of Revision. The new monographs and chapters appear in Comment Proof as typescript copy. USP Comment Proof is offered on subscription at a nominal fee to all interested parties who would not ordinarily see proposed copy during the revision stage. Thus, those other than the appointed voluntary experts involved in USP revision have access to the latest proposed revisions in the official standards and tests and can readily transmit their comments and suggestions to USP headquarters for consideration by the Revision Committee.

The General Notices—The General Notices and Requirements (hereinafter referred to as the "General Notices") have been revised considerably, particularly in respect to containers, labeling, and abbreviations for metric units. Definitions are introduced for single-unit, multiple-unit, and unit-dose containers. Another significant change is the provision that in the absence of a specific requirement in the individual monograph for a dosage form, the label of such article shall bear an expiration date assigned for the particular formulation and package of the article. Newer abbreviations that are currently in use for metric units have been adopted, as shown on page 9. One of these, "μg" to replace "mcg" throughout the book to denote microgram(s), is adopted with the acknowledgment that the abbreviation "mcg" is still commonly employed to denote microgram(s) in labeling and in prescription writing, so that for purposes of labeling, "mcg" may be used instead of "μg." Other, less prominent revisions have been made in the General Notices, in keeping with current needs, a fact which speaks for urging users of the Pharmacopeia to give careful study to the entire section.

Format and Style—The substantial increase in the number of the articles admitted forced consideration of every suitable means to expand to a maximum the amount of text that comprised a page. By means of the larger page size and two-column format, it has been possible to increase the textual content per page by about 15% and thereby to accommodate 1284 monographs in 570 pages, in contrast to the 788 pages required for 1103 monographs in USP XVIII.

Responding to an often-expressed preference by users of the Pharmacopeia, a division of the monographs section is made whereby monographs on drug substances and dosage forms are given first, followed by the group of monographs on articles known as pharmaceutic ingredients. Alphabetic cross-references are made between the two sections of monographs for ease of reference. Furthermore, the format within a given monograph is modified so as to present the primarily informational portions of the text first, followed by the text comprising requirements, the latter section of the monograph being introduced by a boldface double-arrow symbol. Thus, the informational portions preceding the double-arrow symbol generally include those designated as category; usual dose; usual dose range; usual pediatric dose; sizes available; dispensing information; description; and solubility. This distinctive separation of the informational from the mandatory requirement text serves two purposes, namely the convenient classification of the types of information of most concern to the physician and the pharmacist into one location in the monograph, and the designation of all text following the double-arrow symbol as requirements that must be met by the article.

Decisions affecting the alphabetic order of the monographs must always be arbitrary and, to some extent, in conflict with the well-established rules of indexing. For example, the group of seven monographs for the products containing insulin are placed together, since they are all closely interrelated in respect to both content and use.

As a part of cooperation with the U. S. Adopted Names (USAN) program, the word order for the names of most organic compounds follows the USAN principle that the pharmacologically active portion is named first; e.g., Amobarbital Sodium rather than "Sodium Amobarbital" as used in USP XVIII.

The running heads at the top of the page denote, in italics, that section of the monographs or general chapters in which the page occurs, and also, by means of an alphabetic keyword in boldface type, the general alphabetic location of the title of the first monograph or chapter on the left-hand page or the last monograph or chapter on the right-hand page.

Just as the informational is separated from the requirements text among the monographs, so are the general chapters segregated. Thus, the general chapters pertaining to Pharmacopeial requirements are grouped under the main heading, General Tests and Assays, while the general chapters that "contain no standards, tests, or assays, nor other mandatory specifications, with respect to any Pharmacopeial article," are grouped under the main heading, General Information, Processes, Techniques, and Apparatus.

Categories, Doses, and Dispensing Information (see *General Notices*, page 6)—With the aim of increasing the usefulness of the Pharmacopeia to pharmacists and others, and also in accordance with the first resolution passed at the 1970 Convention, the USP category and dose information has been expanded to include more information about the *Usual pediatric dose*. Also, the *Sizes available* information has been correlated more closely with the dosage information. The *Dispensing information*, as is explained in the General Notices, serves as a basic reminder or general guide to the pharmacist, who may vary or omit it in accordance with the best interests of the patient or the particular circumstances involved.

Chemical Names, CAS Registry Numbers, and Graphic Formulas—The chemical subtitles given in

the monographs are Index names used by the Chemical Abstracts Service (CAS) of the American Chemical Society. They are provided only in monographs the titles of which specify substances that are distinctly definable chemical entities. In cases where the chemical substance per se is official, the subtitles are not repeated in monographs on dosage forms containing the substance. While these subtitles are not always the names most familiar to pharmaceutical chemists and sometimes fail to disclose definitive compositions and common name relationships, they are advantageous in that they provide direct access to the world's chemical literature as this literature is indexed in *Chemical Abstracts*. The first subtitle is the inverted name currently used in the Indexes. The second subtitle is the uninverted form of the name formerly used in the Indexes and generally is identical with, or closely resembles, the name used by the International Union of Pure and Applied Chemistry. The two subtitles are frequently identical, and a Chemical Abstracts synonym is occasionally supplied as a third subtitle.

Monographs carrying chemical subtitles generally carry also CAS Registry Numbers. These italicized, bracketed numbers function independently of nomenclature as invariant numerical designators of unique unambiguous chemical substances in the CAS registry and thus find wide, convenient use.

Consonant with the employment of Chemical Abstracts nomenclature, and also in the interest of uniformity of style, the orientation of ring systems and the depiction of stereoisomeric features in graphic formulas are generally consistent with CAS practices. A circle within a hexagon is used in graphic formulas to represent the bonding in benzene rings and all others that contain six atoms of any kind that are connected in conjugate (Kekulé) style in one or more of the individual resonant structures that contribute to the hybrid structure actually present in the molecule.

Automated Methods (see *General Notices*, page 4)—A new chapter on *Automated Methods of Analysis* is included in this Pharmacopeia, for purposes of information. As is stated in the General Notices, automated procedures employing the same basic chemistry as those procedures given in the monographs are recognized also as being suitable for determining compliance with the USP standards of identity, strength, quality, and purity. However, it is essential that the results obtained thereby are of equivalent accuracy; and where a difference appears, or in the event of dispute, only the result obtained by the procedure given in this Pharmacopeia is conclusive. The place of automated methods in modern analytical techniques is thus recognized, and it is logical to predict increasing applications of such methods for the future.

Description (see *General Notices*, page 6)—With this revision, the text that appears under the heading *Description* is designated as primarily informational, as is evident from its location in the individual monograph. Thus, it is not part of the mandatory requirements. This change in Pharmacopeial policy reflects the continuing trend away from reliance on subjective criteria, however useful they may be from the standpoint of information, and toward precision and specificity in standards.

Metric Terms and Their Abbreviations—The metric system of weights and measures is used throughout this Pharmacopeia, and the abbreviations employed are listed in the *General Notices*, on page 9.

Percentage and ppm—Simply as a matter of preference in style, statements of test limits in the monographs are in terms of percentage, for values exceeding 1 part per million.

Nomenclature—It has long been clear that the problems of finding and establishing simple names for drug substances cannot be solved to the satisfaction of all who use the names or substances. There is little general appreciation of the restrictions that bar the choice of numbers or alphanumeric combinations (which risk confusion); abbreviations (which lack explicitness); or "nonsense" names (which lack recognition value).

The USAN Program—A cooperative effort inaugurated in 1961 between the American Medical Association and the United States Pharmacopeial Convention flourished from the outset. The organizing agencies were joined, in January of 1964, by the American Pharmaceutical Association, as the publisher of the *National Formulary*, to form what has been known since as the United States Adopted Names ["USAN"] Council. During 1967, the participation of the U. S. Food and Drug Administration was invited in order to coordinate the work of the Council with that required of the federal government under the Food, Drug, and Cosmetic Act. The Council consists of five persons conversant with the needs and problems of naming drugs. The Council's output appears in a monthly column in the Journal of the American Medical Association, and is incorporated, along with other names for drugs (including public, proprietary, chemical, and code-designated names) in an annual book, *USAN and the USP Dictionary of Drug Names*, by the U. S. Pharmacopeial Convention.

Biological Availability—The attributes of a drug product that make possible full and consistent utilization of its active ingredient are dependent upon the product's formulation and an exercise of production control—and, in turn, such attributes determine what is now commonly termed bioavailability. To provide suitable standards for the latter in respect to certain USP articles continues to be a goal of the Revision Committee. Full realization of this goal may be long in coming, but with the introduction of the in-vitro *Dissolution* test into a larger number of monographs, definite progress has been made in this Pharmacopeia. The new dissolution test for Digoxin Tablets is particularly significant, because the rate of dissolution for this article has been shown to correlate closely with the bioavailability of the article.

The term *bioequivalence* has come to the fore quite

recently. Two or more different specimens of what purport to be the same strengths of the same type of dosage form of a given drug substance are said to be bioequivalent when their bioavailabilities are similar. It is the ultimate objective of the Pharmacopeia to provide standards ensuring that all specimens of a given dosage form are bioequivalent.

Content Uniformity—The principle of requiring a demonstration of uniformity in respect to the content of the active drug substance in solid dosage forms (e.g., tablets) in a given container was introduced in USP XVII, and it has been extended substantially in this Pharmacopeia.

For at least two reasons, the extension of this requirement to many more solid dosage forms is important; first, it serves to give assurance that successive units from a given container will provide substantially equal amounts of drug, and, second, it calls for a great increase in the analytical labor involved. Here, the Committee of Revision faced the need for an arbitrary decision. The desirability of minimizing the variation in content uniformity was beyond debate; however, on practical grounds there seemed to be little need to add the requirement to the testing of tablets that contain relatively little diluent or excipient and thus can be controlled satisfactorily through the *Weight Variation* test, as for example, in the case of tablets of the sulfonamides. As a result, the Revision Committee struck a compromise whereby the content uniformity test is required for all tablets offered in the 50-mg size or smaller, provided only that a method is available for determining the drug content in single tablets. Wherever possible, use is made of the assay provided in the monograph; but where this fails, a special method is provided. In this connection, especially, it was essential to take account of the many advantages of automated analytical equipment, not all of which can be adapted to the regular assay methods. In consequence, a special mention of automated procedures is included in the General Notices (see page 4, under *Procedures*). Previously, the fact that USP Reference Standards are needed for most tests of content uniformity posed a special problem for the products that are subject to strict control as addicting drugs; for these (e.g., Meperidine Hydrochloride Tablets and Methadone Hydrochloride Tablets) no USP Reference Standards were available and hence no content uniformity tests were specified in the respective monographs. However, in this Pharmacopeia, USP Reference Standards are provided for such addicting drugs and content uniformity tests are included in accordance with the principles enunciated above.

Container Standards—The new compendial definitions for single-unit, multiple-unit, and unit-dose containers, as part of the revision of the General Notices, are mentioned on page 8. Another new development in container standards is the introduction of a new general chapter entitled *Containers—Permeation*, which sets forth a moisture permeation test capable of indicating whether a multiple-unit container is tight enough to protect the contents from evaporation and from gain of moisture. This is based upon an analytical method developed by the Drug Standards Laboratory, working under the auspices of a joint USP–NF–FDA committee named to study the subject, and it was validated in an interlaboratory collaborative study. Thus, for the first time, official standards are set to demonstrate compliance with the existing definitions for *Well-closed container* and *Tight container* (see *General Notices*, pages 7 and 8). For the future, study will continue with a view to providing further standards for differentiating among categories of containers and for determining the suitability of a particular container for its intended use.

Stability of Drug Products—Aspects of drug product stability that are of primary concern to the pharmacist in the dispensing of medications are the subject of a new general chapter intended only for purposes of information, entitled, *Stability Considerations in Dispensing Practice*.

Sizes of Surgical Sutures—Significant revisions in the limits on diameter and on knot-pull tensile strength for various kinds of surgical sutures are reflected in the monographs on Absorbable Surgical Suture and Nonabsorbable Surgical Suture. In addition to the established USP size designations for sutures, the corresponding metric sizes that serve to achieve a close conformity with the system of sizes given in the current European Pharmacopoeia are introduced. The size correlations are intended to facilitate international uniformity with respect to standards for sutures.

Drug Standards Laboratory—Under the joint sponsorship of the American Medical Association, the American Pharmaceutical Association, and the United States Pharmacopeial Convention, the Drug Standards Laboratory came into being in 1961. The Laboratory has increased steadily in effectiveness and productivity in dealing with special problems on tests and standards of individual products, and with validation of both the USP and the NF Reference Standards. The Laboratory contributed especially in developing the test for moisture permeation of containers, as well as in participating in studies involving chromatographic methods, tests for heavy metals, and water determination.

Reagent Standards—It has long been axiomatic that success in conducting Pharmacopeial tests and assays is dependent upon the use of reagents of the highest quality; in many cases, exceptional purity requirements must be met. To that end, efforts have been made to ascertain where special precautions are essential and to provide suitable specifications. The USP–NF Joint Panel on Reagents, with Fred A. Morecombe and Dr. Samuel M. Tuthill as co-chairmen, has provided specifications for almost all of the reagents required in this Pharmacopeia; those that could not be completed in time for inclusion herein will be supplied through interim revision. In addition to serving as co-chairman of the Joint Panel, Mr. Morecombe coordinated the com-

pilation of the Reagents, Indicators, and Solutions for this Pharmacopeia in the capacity of special USP consultant.

Reference is made in the section on Reagents to the specifications prepared and published under the aegis of the American Chemical Society, for the reason that these specifications are being followed closely by reagent producers in the United States. To a still larger extent than in USP XVIII, reliance is placed upon the ACS specifications, in that generally for reagents covered in the current edition of ACS *Reagent Chemicals*, the corresponding USP entry specifies the use of the ACS reagent grade of the substance.

Credits—As with any group effort, the weight of responsibility for success in producing the Pharmacopeia falls more heavily on some than on others. Thus, while the Revision Committee as a whole served as the elected agent of the USP Convention in producing this compendium, great credit is due the host of those not on the Revision Committee who contributed helpfully out of a sense of public service and thereby greatly enhanced the Committee's effectiveness.

The individual contributions of some members of the Revision Committee were such as to merit special mention. This is true, particularly, of the 12 chairmen of the USP Subcommittees. High praise is due Dr. Elliott for having lent his superbly effective talents to the work of the Subcommittee on Scope with such conscientious and consistent attention that he seemed to serve as virtually a member of the USP staff. The latter reflection is equally true for Dr. Chafetz, on the side of the tests and assays revision; he carried an unparalleled share of the work with unusual thoroughness and skill. Mention needs to be made also of the special contributions of Drs. Owen (dose and dispensing information); Timm (biologics and microbiology); Shangraw (formulations and pharmaceutic ingredients); Azarnoff (bioavailability); and Miller (radiopharmaceuticals). Chairmen Graham and Woodside, who assumed their respective chairmanships in 1973 to fill vacancies, took up their added responsibilities with impressive zeal and completed their assignments expertly. Scarcely enough can be said in honor of the late Dr. Guttman, whose dedicated and excellent work on the Committee of Revision for more than 12 years [1962–1974] stands as a tribute to the man and to the USP.

Individual Committee members to whom much is owed include Dr. Martin I. Blake, Dr. Klaus G. Florey, Dr. Salvatore A. Fusari, Dr. Alfonso R. Gennaro, Dr. Bernard Z. Senkowski, Irwin S. Shupe, and Dr. Arthur J. Zimmer, all of whom not only completed their assignments creditably but showed commendable initiative in pursuing problems that arose in the course of doing so. To this group belong also Dr. Samuel M. Tuthill, who was assisted ably by his associate Dr. Chester L. French throughout the revision period, and Dr. Joseph A. Zapotocky, who has served creditably on the Committee continuously since 1960 and who in this revision period acted with utmost diligence and ability as chairman of the panels concerned with the General Notices and with compendial style. To all others, upon whom lesser demands were made, genuine thanks are recorded.

The Constitution and Bylaws of the USP Convention (see page xxiii) deliberately and carefully separate the management of the organization from the revision of the Pharmacopeia. Thus the Board of Trustees, under the wise and gifted leadership of Dr. Paul L. McLain, has not participated directly in the revision process. Nevertheless, the ability of the organization to pursue the revision program at a greatly increased tempo and with innovative ideas has been made possible only by the firm support of the Board. And certainly, no other Board in USP history has been as active in exploring and developing new areas of service for the compendium and the compendial organization. The rewards of its endeavors will be harvested many times over in future revision periods.

A close working relationship has been maintained on many matters of common interest with the National Formulary Board of the APhA through the Director of the NF, Dr. John V. Bergen, and his helpful associate Dr. Charles H. Barnstein.

It has been a source of great strength to have the support of the Drug Standards Laboratory and the counsel of the Laboratory Director, Dr. Lee T. Grady, with respect to critical evaluations of many USP tests and assays and in connection with providing more workable alternatives where special problems were encountered.

The continued cooperation and valued assistance of the FDA laboratory is acknowledged.

As with each revision of the Pharmacopeia that has appeared since 1947, Dr. Clarence T. Van Meter has contributed increasingly in respect to chemical nomenclature and the accurate portrayal of the graphic formulas, and the compilation of the table of Molecular Formulas and Weights. In this effort, invaluable help has come from Dr. Kurt L. Loening and his associate Joy E. Merritt, through whom there has been access to the vast facilities of the Chemical Abstracts Service. The index was prepared by Carol Miller of Easton, Pennsylvania.

The fact that this is the ninth consecutive revision of the Pharmacopeia handled by the firm is alone a reason for paying grateful tribute in generous measure to the staff of the Mack Printing Company for patient assistance and much valued advice during the time that this revision was in press. Despite unexpected interruptions and delays that affected the even flow of copy in both directions, the special efforts of H. Leslie Varley, Evelyn M. Sloyer, Evelyn M. Tarsi, and Mary Lou Dailey contributed significantly and earned this special citation.

Headquarters Staff

To the members of the headquarters staff, and most especially to those whose contribution in terms

of selfless dedication and superior achievement far exceeded what may reasonably be expected from any employee, the Executive Director records this expression of lasting gratitude.

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History of the Pharmacopeia of the United States

In January, 1817,[1] Dr. Lyman Spalding, of New York City, submitted to the Medical Society of the County of New York a plan to create a National Pharmacopœia.[2] He proposed dividing the United States as then known into four districts—Northern, Middle, Southern, and Western. The "Western" District embraced all states west of Pennsylvania and the Southern District all states south of the District of Columbia.

The plan provided for calling a Convention in each of these districts, to be composed of delegates from all medical societies and schools situated within them. Each District Convention was to draft a Pharmacopeia, and appoint delegates to a General Convention, to be held in Washington, D. C. At this General Convention the four District Pharmacopeias were to be compiled into a single National Pharmacopeia.

Doctor Spalding's plan was approved by the committee to which it was referred, and subsequently, through the agency of the Medical Society of the State of New York, it went into effect. This society issued circulars requesting the cooperation of the several incorporated State Medical Societies and such medical bodies as constituted a faculty in any incorporated university or college in the United States. Where there was as yet no incorporated medical society, college, or school, voluntary associations of physicians and surgeons were invited to assist in the undertaking.

The U. S. Pharmacopeial Convention—This general plan succeeded, and the first United States Pharmacopeial Convention assembled in Washington, D. C., on January 1, 1820. Samuel L. Mitchill, M.D., was elected President, and Thomas T. Hewson, M.D., Secretary.

Draft pharmacopeias were submitted to the Convention only by the Northern and Middle Districts. These were reviewed and consolidated, and after adoption were referred to a Publication Committee, of which Dr. Lyman Spalding was Chairman. The first U. S. Pharmacopeia was published December 15, 1820, in both Latin and English. Within its 272 pages were listed 217 drugs considered worthy of recognition.

Before adjourning, the first Convention adopted a Constitution and Bylaws, with provisions for subsequent meetings of the Convention and a revised Pharmacopeia every ten years. In 1900 the Pharmacopœial Convention was incorporated in the District of Columbia (see page xxii). Sixteen Convention meetings have been held in Washington, D. C., since 1820, the most recent having been a special meeting (as distinct from a regularly scheduled meeting) held on April 14, 1973 (see page xxxii).

At the 1940 meeting, the Convention directed that the Pharmacopeia be revised every five years. Authority for the issue of interim supplements whenever necessary to maintain satisfactory standards had been granted forty years earlier. The 1940 Convention also arranged for revising the Constitution and Bylaws, a step that required calling an interim session in 1942. Some of the revised Bylaws took effect at once, one important result of which was that the Board of Trustees became responsible for naming the Director of Pharmacopeial Revision. Also, under the new Bylaws, a Nominating Committee was to select nominees for the Committee of Revision prior to each decennial meeting.

The last decennial meeting was held in 1970, and at that meeting the Convention, by constitutional amendments, placed all Pharmacopeial activities—not just the revision of the Pharmacopeia itself—on a five-year cycle rather than on a decennial basis; created the new post of Executive Director; provided for expanded informational services in connection with USP drugs; and generally paved the way for more continuous representation and com-

[1] Much of the USP history appears in the prefaces of the individual editions. USP XIII, pages xvii to xli, gives a rather detailed résumé of the history up to the time of its publication.

[2] With the Fourteenth Revision, the spelling "Pharmacopœia" was changed to "Pharmacopeia," and although the corporate title has not been changed formally, the use of the diphthong is being discontinued generally.