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Revision

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(For U. S. P. XVIII)

(The name of the member of the Subcommittee who served as Chairman is listed first.)

Panel on Allergy—Leslie N. Gay; Cyrus L. Blanchard, Baltimore, Md.; Alan R. Feinberg, Evanston, Ill.; Frank F. Furstenberg, Baltimore, Md.; Francis C. Lowell, Boston, Mass.; James A. McLean, Ann Arbor, Mich.; *John M. Sheldon, Ann Arbor, Mich.; Thomas E. Van Metre, Jr., Baltimore, Md.

Panel on Anesthesiology—John Adriani; Francis F. Foldes, Bronx, N. Y.; Arthur S. Keats, Houston, Texas; Charles B. Pittinger, Nashville, Tenn.; John E. Steinhaus, Atlanta, Ga.; Leroy D. Vandam, Boston, Mass.

Panel on Arthritic Disease Therapy—L. Maxwell Lockie; Theodore B. Bayles, Boston, Mass.; Richard H. Freyberg, New York, N. Y.; Joseph Lee Hollander, Philadelphia, Pa.; Charles A. Ragan, Jr., New York, N. Y.; John W. Sigler, Detroit, Mich.; Charles H. Slocumb, Rochester, Minn.; Harry E. Thompson, Tucson, Ariz.

Panel on Biologic Products—Keith B. McCall, *Chairman*, Lansing, Mich.; C. D. Barrett, Jr., Detroit, Mich.; Henry G. Cramblett, Columbus, Ohio; Paul F. Wehrle, Los Angeles, Calif.

Panel on Cardiovascular Therapy—Walter Modell; G. E. Burch, New Orleans, La. (1966); Leon I. Goldberg, Atlanta, Ga.; Bernard Lown, Boston, Mass.; Herbert Mark, Bronx, N. Y.; Joseph E. F. Riseman, Brookline, Mass.

Panel on Dermatology—Robert G. Carney; Rudolf L. Baer, New York, N. Y.; Richard E. Harrell, Ann Arbor, Mich.; Clinton W. Lane, St. Louis, Mo.; Adolph Rostenberg, Jr., Chicago, Ill.

Panel on Endocrinology—Arthur Grollman; Joseph W. Goldzieher, San Antonio, Texas; Robert B. Greenblatt, Augusta, Ga.; Roy Hertz, Washington, D. C. (1966–1967); Herbert S. Kupperman, New York, N. Y.; Albert Segaloff, New Orleans, La.

Panel on Gastroenterology—Dale G. Friend; H. Marvin Pollard, Bethesda, Md.; Marvin H. Sleisenger, New York, N. Y.; Frederick Steigmann, Chicago, Ill.; Dwight Wilbur, San Francisco, Calif.; Stewart Wolf, Oklahoma City, Okla.

* Deceased.

Panel on Hematology—William B. Castle; C. Lockard Conley, Baltimore, Md.; Robert W. Heinle, Kalamazoo, Mich.; Carl V. Moore, St. Louis, Mo.; Maxwell M. Wintrobe, Salt Lake City, Utah; Lawrence E. Young, Rochester, N. Y.

Panel on Infectious Disease Therapy—Harry F. Dowling; Maxwell Finland, Boston, Mass.; Wallace E. Herrell, Lexington, Ky.; William M. M. Kirby, Seattle, Wash.; John M. Leedom, Los Angeles, Calif.; J. P. Sanford, Dallas, Texas.

Panel on Neoplastic Disease Therapy—*David A. Karnofsky; Rose Ruth Ellison, Buffalo, N. Y.; Emil Frei, Houston, Texas; Thomas C. Hall, Walpole, Mass.; R. Wayne Rundles, Durham, N. C.; C. Gordon Zubrod, Bethesda, Md.

Panel on Neuropsychiatry—Melvin D. Yahr; Charles D. Aring, Cincinnati, Ohio; Russell N. DeJong, Ann Arbor, Mich.; Francis M. Forster, Madison, Wis.; Arnold P. Friedman, Bronx, N. Y.; Edward Charles Kunkle, Portland, Maine; Sidney Malitz, New York, N. Y.

Panel on Nutrition and Metabolism—Theodore B. Van Itallie; Grace A. Goldsmith, New Orleans, La.; Irving Graef, New York, N. Y.; Robert E. Hodges, Iowa City, Iowa; Jean Mayer, Boston, Mass.; Richard W. Vilter, Cincinnati, Ohio.

Panel on Ophthalmology—Irving H. Leopold; Bernard Becker, St. Louis, Mo.; W. Morton Grant, Boston, Mass.; John E. Harris, Minneapolis, Minn.; Herbert E. Kaufman, Gainesville, Fla.; Frank W. Newell, Chicago, Ill.; Marvin L. Sears, New Haven, Conn.

Panel on Parasitic Disease Therapy—Harold W. Brown; Hamilton H. Anderson, Maui, Hawaii; G. Robert Coatney, New Orleans, La.; Rodney C. Jung, New Orleans, La.; Harry Most, New York, N. Y.; Howard B. Shookhoff, Bronx, N. Y.

Panel on Pediatrics—Harry C. Shirkey; Henry L. Barnett, Bronx, N. Y.; Alfred M. Bongiovanni, Philadelphia, Pa.; James W. Etteldorf, Memphis, Tenn.; Robert J. Haggerty, Rochester, N. Y.; Marion E. Lahey, Salt Lake City, Utah; Paul A. Palmisano, Birmingham, Ala.; Edwin P. Stabins, Charleston, W. Va.

Panel on Radiology—Edward A. Carr, Jr.; Melvin M. Figley, Seattle, Wash.; Thomas P. Haynie, Houston, Texas; Philip J. Hodes, Philadelphia, Pa.; Walter M. Whitehouse, Ann Arbor, Mich.

* Deceased.

PREFACE

INTEREST has increased steadily in the quality of drug products, the standards that determine quality, and compliance with the standards, during the five-year period of preparation of this Pharmacopeia. This has resulted in greater emphasis on what is termed "good manufacturing practice," a concept that so defies definition that any rules that may be laid down are generally too vague for inclusion in a compendium of drug standards. However, procedures by which good manufacturing practice is implemented are decidedly related to drug standards, and consequently much of the revision embodied herein serves to necessitate and/or demonstrate compliance with what are regarded as the best practices. There was debate on whether such standards properly belong in the Pharmacopeia. The view prevailed, however, that the consequences of inadequacies in drug standards are so serious that any reasonable effort to extend the standards to make them more explicit is in the public interest. There is no disagreement with the fact that safety and efficacy, 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 U. S. P. occur in several federal statutes, the most significant being the recognition of the U. S. P. definitions and standards in the Food, Drug, and Cosmetic Act. This use of the U. S. P. standards as the basic measures of strength, quality, purity, packaging, and labeling imposes upon the Committee of Revision explicit strictures in respect to the need for clarity of presentation and for reliability and applicability of the U. S. P. standards. It is important to stress that these standards apply to the U. S. P. 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 is placed upon the Pharmacopeia.

The U. S. P. Organization—Revision of the Pharmacopeia is made possible by an independent, non-profit organization that derives financial support wholly and almost equally from sales of the published

volume and from fees for the U. S. P. 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 U. S. P. tests and standards.

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

The Revision Program—This is the second revision of the Pharmacopeia produced by the 1960–1970 General Committee of Revision. Just as for the revisions in the recent past, the work on this revision was organized by the assignment of the nine Subcommittees to the major areas of the program as indicated on page ix. Thus, the Subcommittee on Scope was responsible for the selection of the articles to be recognized. During the selection process, the five 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 x, several panels were appointed to assist the Revision Committee; and particular mention should be made of the U. S. P.–N. F. Joint Panel on Physiological Availability and the U. S. P. Panel on Sterilization Procedures. The work of the Joint Panel was confined to the need for standards on what has since become known as bioavailability and for methods to measure this attribute of a pharmaceutical product. The Panel met several times under the active leadership of Dr. Rudolph H. Blythe to evaluate the evidence of the interrelationship of formulation of the solid dosage forms and the availability for absorption of the contents thereof. The choice of methods proved very difficult. Since many of the data had been obtained by a simple modification of the apparatus described for the *Disintegration* test (see page 932), it had strong advocates; on the other hand, the limitations of the apparatus were such as to recommend another type of device by means of which gentler and better controlled treatment, i.e., stirring, was possible. For a description of the apparatus selected for U. S. P. purposes, see page 934. The Panel had access to data obtained on experimental animals, but the correlations between these and the *in vitro* data lacked persuasiveness in respect to making the choice of apparatus as well as of test conditions.

The U. S. P. Panel on Sterilization Procedures was appointed, with Dr. Henry D. Piersma as chairman, for the purpose of determining changes possibly needed in the U. S. P. standards as a consequence of the use of newer sterilization methods. The task proved to be much broader in scope than had been anticipated, and finally included an extensive review of the *Sterility Tests* chapter and the preparation of standards for an acceptable microbial profile of articles not intended to be sterile. The

implementation of these standards required a new and complex chapter entitled, "Microbial Limit Tests." Finally, this Panel was called upon to evaluate a procedure having a long history of study that is presented in another new U. S. P. general chapter entitled, "Antimicrobial Agents—Effectiveness."

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. As the program was carried out for this Pharmacopeia, most of the medical specialists making up the U. S. P. Subcommittee on Scope headed panels of fellow specialists 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 four pharmacists on the Subcommittee.

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.

The selection process for the articles recognized in this Pharmacopeia was subjected to influences of two sorts. First, the pressures that led to the lack of recognition of meritorious drugs in each of the three preceding revisions were still present and served to work against the admission of drug articles that had many valuable attributes. These pressures were countered, however, by a desire to recognize all articles of "equal therapeutic merit." The resultant of these two forces was to retain a much larger proportion of the U. S. P. XVII articles and to admit about the same number of new articles (about 256) as had been admitted for each of the recent revisions. In consequence, the total number of articles is 1103. This is the greatest number of titles that has appeared in any U. S. P. for 70 years. This increase is reflected both in a greater number of basic drug substances and in the number of dosage forms in which the basic substances are presented.

The Revision Committee maintained its conservatism in respect to the recognition of fixed combinations of drugs, restricting it to the vitamins, electrolyte solutions, a triple sulfonamide mixture, and the com-

binations of a local anesthetic with epinephrine. The combinations that constitute the oral contraceptives were not recognized as a group, although nearly all of the individual estrogens and progestins that make up these combinations are included.

The General Notices—The General Notices have been revised considerably, particularly in respect to containers, storage, and labeling. One of the important new provisions revises the definition of a single-dose container to require that the closure be such that any entry through it leaves evidence of its having been opened. The label of a single-dose container is required to state that the contents are intended for use at a single administration or promptly after opening. Another significant change is in defining "a cool place," a term long used on product labels and in advice to pharmacists without ever having been defined specifically. 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, preferably without enlarging the trim size of the finished volume. The problems raised by going to a two-column format in the monographs section led to the early rejection of that alternative. This left only the possibility of reducing the margins and condensing the headings by compressing the graphic and empirical formulas and the molecular weights. The adoption of these measures has made it possible to increase the information content per page by about 15 percent and thereby to accommodate more than 1100 monographs in 788 pages, in contrast to the 766 pages required for 905 monographs in U. S. P. XVII. These steps left little doubt that only by a distinct departure in format and style will it be possible to increase the information content per page in the future.

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. This is particularly noteworthy, inasmuch as no monograph is provided for crystalline zinc insulin, the basic substance from which all of the insulin dosage forms are derived,

The practice adopted for U. S. P. XVII for the word order of the components of the names of the salts of organic acids is continued herein, although the decision already has been taken for the future, as a part of cooperation with the U. S. Adopted Names program, that the name of the cation will be subordinated. Hence, the placement of the monograph for Sodium Amobarbital is determined now by the initial letter of Sodium, with the result that it is widely separated from the monograph

on Amobarbital itself; in the future, the word order will be reversed so that the title will be Amobarbital Sodium.

The increase in the references to products dried from the frozen state created the need for a term free from trademark restrictions (e.g., a term other than "lyophilized") and more suitable than "freeze-dried." Through exercise of the privilege of coining a new term where a real need exists, the word *cryodesiccation* has been introduced generally, at the suggestion of Dr. Alexander Gode.

The chemical subtitles used in the monographs are, in general, those currently preferred as the Index names by the Chemical Abstracts Service of the American Chemical Society. While these are not always the names most familiar to pharmaceutical chemists and they frequently fail to disclose common name interrelationships, they are advantageous in that they provide direct access to the world's chemical literature as this literature is indexed in *Chemical Abstracts.* Subsidiary names also chosen by the Chemical Abstracts Service are used in some instances where the preferred systematic chemical names are unduly cumbersome, but these names also provide ready access to the indexed literature. Consonant with the employment of Chemical Abstracts nomenclature, and also in the interest of uniformity of style, the ring systems in the graphic formulas of cyclic compounds are generally portrayed in the orientation preferred by the Chemical Abstracts Service.

Metric Terms and Their Abbreviations—While this revision was in preparation, an important change was adopted internationally in respect to the terms used for some of the smaller metric units of measure; thus, the term, nanometer, for which the symbol nm. is used, was adopted to replace the term, millimicron. However, the decision came too late for consideration for the text of this Pharmacopeia, and the symbol, mμ, has been continued.

The elimination of the English system of weights and measures has been entirely completed in presenting the doses of the Pharmacopeial products. In view of this, it seemed no longer necessary to use the unconventional abbreviation, Gm., for gram for the purpose of avoiding confusion with the abbreviation, gr., for grain. Thus, the internationally accepted abbreviation, g., is used throughout the body of the monographs, although, where needed, the word, gram(s), is used in the Dose statements.

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); short names (which too often conflict with existing trademarks); or "nonsense" names (which lack recognition value).

The USAN Program—A cooperative effort inaugurated in 1961 be-

tween 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 thus 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 published in an annual booklet, "United States Adopted Names," by the U. S. Pharmacopeial Convention.

Physiological 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 physiological availability. To provide suitable standards for the latter in respect to certain U. S. P. articles has been a goal of the Revision Committee during this revision period, through the work of the U. S. P.–N. F. Joint Panel on Physiological Availability, mentioned on page x. Full realization of this goal may be long in coming, but with the introduction of the *Dissolution* test and time limits for six kinds of tablets, definite progress has been made in this Pharmacopeia.

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 U. S. P. 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 5, under *Procedures*). The fact that U. S. P. Reference Standards are needed for most tests of content uniformity poses a special problem for the products that are subject to strict control as addicting drugs; for these (e.g., Meperidine Hydrochloride Tablets and Methadone Tablets) no U. S. P. Reference Standards are available and hence no content uniformity test is specified in the respective monographs.

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, particularly in the past two years, in dealing with special problems on tests and standards of individual products, and with validation of both the U. S. P. and the National Formulary Reference Standards. The Laboratory contributed especially in developing the *Dissolution* test and in working out the special test conditions for the several monographs in which the test is specified.

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. However, it was necessary to proceed to press with such standards as were available, leaving others to be provided later in some form, perhaps in a U. S. P. XVIII Supplement. 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.

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 U. S. P. Convention in producing this, the second Pharmacopeia to appear during this decade, 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 nine chairmen of the U. S. P. Subcommittees. High praise is due Dr. Butler for his conscientious and consistent attention to detail in fulfilling the assignments to his Subcommittee. He was assisted ably by his associate Chester L. French throughout the entire revision period. Mention needs to be made also of Drs. DeGraff and Osol, whose long experience on the Revision Committee was reflected in their outstanding contributions. As is mentioned earlier, Drs. Blythe and Piersma applied their talents unstintingly to the work of the Panels they headed in addition to carrying out the programs of their respective Subcommittees.

Individual Committee members to whom much is owed include Morris E. Auerbach, Lester Chafetz, C. Leroy Graham, David E. Guttman, and Joseph A. Zapotocky, all of whom not only completed their assignments creditably but showed commendable initiative in pursuing problems that arose in the course of doing so. On short notice, Murray M. Tuckerman undertook the review of the standards for reagents that was both taxing and tedious. To all others, upon whom lesser demands were made, genuine thanks are recorded.

A close working relationship has been maintained on many matters of common interest with the National Formulary Board of the A.Ph.A. through the N. F. Director of Revision, Edward G. Feldmann, and his helpful associates, particularly Durward F. Dodgen.

It has been a source of great strength to have the support of the Drug Standards Laboratory and, particularly since 1967, the counsel of the Laboratory Director, William J. Mader, in respect to critical evaluations of many U. S. P. tests and assays and in connection with providing more workable alternatives where special problems were encountered.

As with each revision of the Pharmacopeia that has appeared since 1947, 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 Kurt L. Loening, through whom there has been access to the vast facilities of the Chemical Abstracts Service. The index was prepared by Evelyn M. Tarsi of Easton, Pennsylvania.

The fact that this is the eighth 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, E. W. Roberson, and Mary Lou Dailey contributed significantly and earned this special citation.

Between 1966 and 1969, four persons served as advisors while attached temporarily to the U. S. P. headquarters staff for periods ranging from