Pharmacopoeias and Formularies

THE PHARMACOPEIA OF THE UNITED STATES OF AMERICA. SEVENTEENTH REVISION. Pp. lxvi + 1156. Distributed by Mack Publishing Company, Easton, Pa, U.S.A. $12.50, U.S.A.; $13.00 elsewhere.

The Seventeenth Revision of the Pharmacopeia of the United States of America, official from September 1, 1965, reflects in many respects the concern that has arisen during the past five years about the efficacy of drugs and the unavoidable risks of side-effects. This concern has influenced the selection of drugs to be included and the determination of what constitutes an adequate standard for the purposes of a pharmacopoeial monograph. The new revision contains 898 monographs and 85 chapters of general tests. Of the 156 new monographs, 76 are for basic drugs. Monographs omitted total 201.

The selection of drugs and preparations for inclusion and the deciding of acceptable standards for them raises the question—what is the purpose of a modern pharmacopoeia? The objects of the United States Pharmacopeia as determined by the Convention of March, 1960, are stated as "to provide authoritative standards for substances and their preparations that are used in the practice of the healing arts; the establishment of titles, definitions, descriptions, and standards for identity, quality, strength and purity, and also, where practical, methods for their examination and formulas for manufacturing".

Perusal of this revision clearly reveals that these declared objects have been only partially fulfilled. This sad fact inevitably leads one to ask whether such worthy objects can now be fulfilled in a book revised at five yearly intervals, even when supplements are issued between revisions.

The difficulty does not arise merely from the introduction of new drugs and preparations, from the development of new knowledge and new analytical techniques, or from the problems of selection and of drafting standards for many preparations. It arises from the need to provide meaningful standards desirably to be met by manufacturers issuing a particular drug or preparation and standards to which the drug or preparation must conform in order to protect the consumer against its deterioration, or the presence of harmful or potentially harmful impurities in pharmacologically significant amounts. These standards can rarely be precisely the same and it is the purpose of a pharmacopoeia to define the minimum standard that can be allowed for protection of the consumer both as regards potency and freedom from harmful impurities. But the setting of such minimum acceptable standards leaves undefined the standards to which manufacturers must work to afford that protection. There is a "twilight zone" with which a pharmacopoeia cannot cope in its traditional form. This is not of therapeutic significance for most drugs and preparations but it is so for many potent drugs. Among these are the antibiotics, quality control of which can only partially be effected by a written specification. In the United Kingdom this difficulty is overcome, so far as materials for parenteral injection are concerned, by the licensing procedure and regulations made under the Therapeutic Substances Act. But the Act does not overcome the problem of quality control for antibiotics destined for use by any other route. The dilemma has been met in the U.S.A. by the operation of amendments to the Food, Drug and Cosmetic Acts. Under them, all antibiotics intended for use in man are subject to production and testing controls under federal regulation, including batch certification before distribution. The U.S.P. monographs for antibiotics therefore merely refer to this fact and include only those aspects of identity, purity, potency and

packaging and storage that are of special interest to the physician and pharmacist. References to identity, purity and potency of antibiotics have in consequence become simplified and are no longer definitive as standards.

Will the procedure adopted for antibiotics be adopted in future for steroids, for psychotropic drugs, and for other potentially dangerous substances? If so, what remains the purpose of a pharmacopoeia? Surely not merely to provide information on available dosage forms, on 'categories of action' or on general methods of testing? Clearly a pharmacopoeia is still needed to ensure uniformity of content of active ingredient in preparations and to recognise and limit potentially harmful impurities whether these arise from manufacturing procedures or from changes subsequent to release.

An important new inclusion in the U.S.P. is a requirement for the uniformity of content of medicament in each tablet of a representative sample. This requirement is introduced for tablets containing a small amount of medicament, as, for example, digoxin or prednisolone. Each of 10 tablets from a sample of 30 is required to be assayed and the requirement for content uniformity is met if the results for each fall within 85 to 115% of the average of the tolerances specified in the monograph. If one of the 10, but not more than one, falls outside those limits, the remaining 20 tablets must be assayed individually and the requirements are met if not more than one of all the 30 tablets lies outside the limits of 85 to 115% of the declared content.

This edition of the U.S.P., like that of any modern pharmacopoeia, reveals the lack of molecularly specific methods for determining many active ingredients and a limited knowledge of the impurities that arise in the manufacture and storage of many drugs. It reflects the extent to which every modern pharmacopoeia is dependant upon knowledge possessed by the manufacturer of a particular drug for the compilation of specifications that will satisfactorily protect the consumer from the hazards of lack of uniformity and harmful impurities. Thus it is the case for monographs such as that on prednisone, in which the content of required steroid is assessed by comparing the amount of material with a reducing functional group with that of a standard preparation, and the drug's content of related foreign steroids is compared with that of a reference preparation (itself not wholly pure material) on a chromatogram simultaneously with cortisone and hydrocortisone. Infrared and ultraviolet spectra as well as optical rotation are used to confirm the identity of the material but much additional data is required to limit the content of the many other related steroids resulting from the preparation of such drugs. All too little is known of the specific toxic effects that arise clinically from such undetected mpurities. But a pharmacopoeia cannot set standards beyond those based on the information made available to it.

It is interesting to note that the steroids selected for inclusion in the U.S.P. XVII do not include dexamethasone, betamethasone or fludrocortisone and that estradiol benzoate, ethisterone, methyltestosterone, progesterone, among other included in the U.S.P. XVI, have now been omitted. The omission of ferrous gluconate, globin zinc insulin injection, nicotinic acid, novobiocin and chlorothiazide may come as a surprise for British readers, but such is the changing choice of medicaments by physicians in different countries.

The task of revision of the U.S.P. as of any pharmacopoeia becomes ever more formidable. It is the dedicated efforts of a vast team of workers and collaborators that have alone made possible even the partial fulfillment of their objectives. There is much to admire and to learn from the outcome.

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