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WHO Expert Committee on Specifications for Pharmaceutical Preparations

Twenty-eighth Report

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CONTENTS

WHO EXPERT COMMITTEE ON SPECIFICATIONS FOR PHARMACEUTICAL PREPARATIONS

Geneva, 14–19 December 1981

Members

Professor E. A. Babayan, Head of the Department of New Drug Evaluation, Ministry of Health, Moscow, USSR

Dr D. Cook, Acting Director-General, Drugs Directorate, Health Protection Branch, Department of National Health and Welfare, Ottawa, Canada

Dr P. O. Emafo, Director (Pharmaceutical Services), Federal Ministry of Health, Lagos, Nigeria

Dr S. S. Gothoskar, Drugs Controller (India), Directorate General of Health Services, New Delhi, India

Dr L. T. Grady, Director, Drugs Standards Division, The United States Pharmacopeia, Rockville, MD, USA

Mr C. A. Johnson, Secretary and Scientific Director, British Pharmacopoeia Commission, London, England

Professor J. Laszlovszky, Scientific Adviser, National Institute of Pharmacy, Budapest, Hungary

Dr M. Pesez, Scientific Adviser, Roussel-Uclaf SA, Romainville, France (*Chairman*)

Dr N. Rofael, Director, Pharmaceutical Control and Research Laboratories, National Organization for Drug Control and Research, Cairo, Egypt (*Rapporteur*)

Mr Tu Guoshi, Chief, Division of Pharmaceutical Chemistry, National Institution for the Control of Pharmaceutical and Biological Products, Ministry of Health, Beijing, China (*Vice-Chairman*)

Secretariat

Dr J. F. Dunne, Acting Chief Pharmaceutical Officer, Pharmaceuticals, WHO, Geneva, Switzerland

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Dr S. Kliouev, Senior Pharmaceutical Officer, Pharmaceuticals, WHO, Geneva, Switzerland

Mr B. Öhrner, Deputy Director, WHO Collaborating Centre for Chemical Reference Substances, Solna, Sweden (*Temporary Adviser*)

Dr P. R. Pabrai, Director, Central Indian Pharmacopoeia Laboratory, Ghaziabad, India (*Temporary Adviser*)

Miss M. Schmid, Technical Assistant, Pharmaceuticals, WHO, Geneva, Switzerland

Professor O. Sylla, Technical Adviser to the Ministry of Health, Faculty of Medicine and Pharmacy, Dakar, Senegal (*Temporary Adviser*)

Miss A. Wehrli, Pharmaceutical Officer, Pharmaceuticals, WHO, Geneva, Switzerland (*Secretary*)

WHO EXPERT COMMITTEE ON SPECIFICATIONS FOR PHARMACEUTICAL PREPARATIONS

Twenty-eighth Report

The WHO Expert Committee on Specifications for Pharmaceutical Preparations met in Geneva from 14 to 19 December 1981. The meeting was opened on behalf of the Director-General by Dr Ch'en Wen-chieh, Assistant Director-General, who stressed that a considerable increase in the provision of essential drugs was crucial to the effective application and extension of primary health care. Essential drugs have not only to be available, but should also be safe and effective. To this end their quality must be assured. Indeed, the provision of adequate quality control must be regarded as a critical element in the broader objective of providing effective health care delivery by the year 2000. While the "Certification scheme on the quality of pharmaceutical products moving in international commerce", adopted by the Twenty-eighth World Health Assembly in resolution WHA28.65 (*1*), provides valuable safeguards in relation to imported products, it is also important to offer countries some guidelines on how to develop their own quality control facilities as effectively as possible, having regard both to the resources available to them and to their specific needs.

1. THE FUTURE OF THE *INTERNATIONAL PHARMACOPOEIA*

1.1 National and regional pharmacopoeias

Most national and regional pharmacopoeias provide specifications on purity and potency which form the legal basis for the control of pharmaceutical products. With the introduction of new therapeutic substances and the growth of national registration and inspection systems, the role of pharmacopoeias has evolved so that they are now of greater importance than formerly. They provide standards that are publicly available and that allow independent evaluations of drug quality to be made at any stage after the drugs have left the manufacturer's care and prior to their utilization.

1.2 The *International Pharmacopoeia*

The *International Pharmacopoeia* provides internationally acceptable standards for the purity and potency of pharmaceutical products moving in international commerce that are available for adoption by Member States in accordance with Articles 21 (*d*) and 23 of the Constitution of the World Health Organization (*2*) and resolution WHA3.10 of the Third World Health Assembly (*3*).

Many national or regional pharmacopoeias rely increasingly on complex techniques of analysis that require expensive equipment and highly specialized personnel, but these methods are inapplicable in countries lacking these resources; and for the most part, they merely permit analyses to be carried out more rapidly than by the classical chemical methods.

Whereas earlier editions of the *International Pharmacopoeia* had relied heavily on material taken from certain national pharmacopoeias, the third edition (*4*), now in the course of publication in several volumes, aims to accommodate the needs of developing countries by offering sound standards for the essential drugs (*5*), which rely (wherever possible) on classical procedures. Volume 1, which became available in 1979, describes the general methods of analysis, while volume 2, published in 1981, contains quality specifications for 126 essential drug substances. Monographs on the remaining substances in the WHO model list of essential drugs (*5*) will be included in volume 3; several of these have not, as yet, been published in a national pharmacopoeia.

It is envisaged that volume 4 will include monographs on widely used excipients and dosage forms for essential drugs. The latter is a demanding objective. The use of a wide range of interchangeable excipients in finished products, and particularly in solid unit-dosage forms, creates difficulties because some of these substances are liable to interfere with the results of established and published pharmacopoeial methods. These difficulties are evident at national level; on a worldwide basis, they are compounded because of the greater number of excipients to be accommodated. None the less, the need to provide quality control laboratories in developing countries with guidance on the testing of final dosage forms is evident.

Accordingly, methods and proposed standards for identity, assay and impurity patterns of individual dosage forms of essential drugs will be developed wherever feasible. The proposed standards will first be tested on finished products of local manufacture in collabora-

ting laboratories in various parts of the world. On the basis of a survey of the results obtained, necessary adjustments will then be made to the original proposals to broaden their applicability.

To the same end, additional general advice on extraction and separation procedures will be included in the existing general monograph on solid oral dosage forms (*6*). This will permit a greater variety of dosage forms to be tested than is currently possible by application of national pharmacopoeial monographs.

1.2.1 *Summary*

Believing that the role and objectives of the *International Pharmacopoeia* are still not widely appreciated, the Committee urged that all possible means should be adopted to correct the position.

In summary, the functions and characteristics of the *International Pharmacopoeia* are:

(*a*) to provide specifications on the purity and potency of essential drug substances, widely-used excipient materials, and related dosage forms (*5*). These specifications should be adequate to assure the safety and efficacy of these products, as well as adequate reproducibility of their effects in clinical use, but they should not be unnecessarily stringent since this would increase the cost of the products. In the case of recently introduced products, specifications should be developed to ensure compatibility with the samples on which the toxicological properties and clinical efficacy and safety were initially established;

(*b*) to support such specifications with readily applicable methods of testing and analysis, with attention to the facilities available within control laboratories in developing countries;

(*c*) to provide general methods of analysis that would be applicable not only to materials included in the pharmacopoeia, but also to new products submitted for registration;

(*d*) to accommodate, where appropriate, a measure of flexibility into methods and requirements that will facilitate the use of the *International Pharmacopoeia* on a global basis, particularly in connexion with dosage forms; and

(*e*) to present all these elements in such a manner that the *International Pharmacopoeia,* or selected parts of it, can be officially adopted by any Member State.

Inter alia, the production of the *International Pharmacopoeia* helps to advance the setting of pharmacopoeial standards at national level,

in that it fosters a valuable exchange of experiences gained in a wide variety of countries.

2. INTERNATIONAL CHEMICAL REFERENCE SUBSTANCES

2.1 Reports from the WHO Collaborating Centre

Reports from the WHO Collaborating Centre for Chemical Reference Substances were reviewed by the Committee.[1]

2.1.1 *Establishment of new reference substances*

The following new International Chemical Reference Substances have been established:

anhydrotetracycline hydrochloride
benzylpenicillin potassium
4-epianhydrotetracycline hydrochloride
4-epitetracycline ammonium salt
ethosuximide
(–)-3-(4-hydroxy-3-methoxyphenyl)-2-methylalanine
methyldopa
nicotinamide
nicotinic acid
sulfamethoxazole
sulfanilamide
tetracycline hydrochloride
trimethoprim

2.1.2 *Replacement of current reference substances*

Replacement batches of the following International Chemical Reference Substances have been introduced:

benzylpenicillin sodium
dexamethasone
griseofulvin
hydrocortisone acetate
vitamin A acetate

The Committee noted with satisfaction that the analytical reports of the Centre had now been expanded to include more of the results obtained in the course of examination of the substances, as well as data submitted by the manufacturers. Information provided in confidence to the Centre by manufacturers cannot be revealed but all available information is taken into account in the assessment of the suitability of the proposed International Chemical Reference Substances.

[1] WHO Collaborating Centre for Chemical Reference Substances. *Report on the work in 1979* (unpublished document WHO/PHARM/80.504); *Report on the work in 1980* (unpublished document WHO/PHARM/81.508).

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