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Twenty-First Report

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WHO EXPERT COMMITTEE ON SPECIFICATIONS FOR PHARMACEUTICAL PREPARATIONS

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CONTENTS

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WHO EXPERT COMMITTEE ON SPECIFICATIONS FOR PHARMACEUTICAL PREPARATIONS

Twenty-First Report *

1. INTRODUCTION

The WHO Expert Committee on Specifications for Pharmaceutical Preparations met in Geneva from 3 to 9 November 1964. Dr P. Dorolle, Deputy Director-General, opened the meeting on behalf of the Director-General and welcomed the participants. He expressed the thanks of the Organization for the assistance given by a number of the participants and other specialists who were collaborating in the difficult task of preparing and proposing at the international level specifications for the quality control of pharmaceutical substances. This work had, in the last few years, included revision of the specifications of the monographs and appendices of the three volumes of the first edition of the International Pharmacopoeia, and the preparation of specifications for new pharmaceutical substances introduced on the market in different countries. This co-operation made it possible for the WHO Secretariat to prepare the specifications that are now being proposed for the second edition of the International Pharmacopoeia. Meetings of consultants had been convened to discuss a number of problems concerning some of the specifications.

A provisional text of the second edition of the International Pharmacopoeia was sent on 9 March 1964 to members of the WHO Expert Advisory Panel on the International Pharmacopoeia and Pharmaceutical Preparations and a number of other specialists interested in this work with a covering letter asking for comments, which were examined for possible integration in the provisional text. It was thus possible to prepare the revised and completed provisional text, which was recently forwarded, in English and French, to the 118 Member States and 6 Associate Members of the World Health Organization. A letter from the Director-General,

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* Reports Nos. 1-7 were published under the name *Expert Committee on the Unification of Pharmacopoeias* and reports Nos. 8 and 9 under the name *Expert Committee on the International Pharmacopoeia ;* reports Nos. 10-20 were issued in mimeographed form only.

dated 28 October 1964, informed Member States of the despatch—by air mail—and asked Governments to submit comments within three months of the date of mailing. In the 526 monographs and 72 appendices of this provisional text, specifications are proposed for the quality control of the more important part of all pharmaceutical substances used in the different countries in various pharmaceutical forms and mixtures. It should prove of considerable help to countries in the difficult task of checking the quality both of the pharmaceutical preparations that they manufacture locally and of those that they import.

The control of the quality of pharmaceutical preparations presents difficulties in many countries, especially with the increasing number of pharmaceutical substances and pharmaceutical specialities now in international commerce and of pharmaceutical products made locally in the different countries for the internal market. A resolution of the World Health Assembly, WHA17.41,[1] called attention to the need to subject all pharmaceutical preparations, whether produced within a country for home consumption or for export or whether imported, to an adequate control, and to ensure that pharmaceutical preparations that are exported from a country will "comply with the same drug control requirements as apply to drugs for its domestic use". The Committee had before it a report expressing the general aspects of the problem, prepared by the WHO Secretariat, as well as the report of the WHO International Reference Centre for Chemical Reference Substances.

A volume containing proposed specifications for reagents mentioned in the International Pharmacopoeia had been published in 1963.[2] Specifications for other reagents used in connexion with tests and assay described in the second edition of the International Pharmacopoeia would be included in that publication.

It was hoped that, with the continued assistance of members of the WHO Expert Advisory Panel on the International Pharmacopoeia and Pharmaceutical Preparations and of other specialists, national laboratories for quality control, manufacturing firms, etc., it would be possible for the Secretariat to integrate comments received from Member States and other sources into the proposed text of the second edition of the International Pharmacopoeia and have the text ready for printing within the next few months. The publication will help all Member States and be in the interests of public health and international commerce.

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[1] *Off. Rec. Wld Hlth Org.*, 1964, **135**, 18.

[2] World Health Organization (1963) *Specifications for reagents mentioned in the International Pharmacopoeia*, Geneva.

2. REVISION OF DRAFT MONOGRAPHS AND APPENDICES FOR THE SECOND EDITION OF THE INTERNATIONAL PHARMACOPOEIA

A large part of the Committee's deliberations was devoted to a number of studies and comments obtained from working groups, specialists, manufacturing firms, etc., in different countries on the provisional text for the second edition of the International Pharmacopoeia.

The convening of the meetings of consultants had also made it possible to prepare some of the material for discussion by the Committee. The Committee noted with satisfaction that a meeting of consultants earlier in the year had examined many of the comments received and had proposed specifications that have been incorporated in the specifications in the provisional text sent to Member States on 28 October 1964, complementing the provisional text sent to members of the WHO Expert Advisory Panel on the International Pharmacopoeia and Pharmaceutical Preparations and other specialists, with the circular letter of 9 March 1964.

Another meeting of consultants on the specifications for the important new group of the semi-synthetic penicillins had made it possible to present the members of the Committee with a complete set of up-to-date specifications that would considerably help the setting-up of an official quality control of the preparations and their pharmaceutical forms in national laboratories for pharmaceutical quality control.

The principal subjects discussed in connexion with these specifications are given in the following paragraphs :

2.1 Order of the monographs; titles; chemical names; formulas

The Committee noted that there were practical advantages in arranging the monographs in the Pharmacopoeia in such a way that the monograph on the basic drug is followed immediately by the monograph or monographs on preparations of the drug, such as injections and tablets. This arrangement has already been adopted in some national pharmacopoeias. It was agreed that in the second edition of the International Pharmacopoeia the strictly alphabetical arrangement of the monographs used in the first edition should be abandoned, and that the monographs on preparations should follow immediately after the monograph on the basic drug.

The Committee examined a document setting out the titles, chemical names, formulas, molecular weights and equivalents recommended for adoption in the monographs. It was agreed to express molecular weights to five significant figures with, in most instances, two figures after the decimal point. It was also agreed to apply rounding-off rules for the last figure, in accordance with the recommendation of ISO, if these are available.

It was noted that the title "digitoxoside" had a generic implication, and it was agreed to replace it by the title " digitoxin ", which already has wide usage. The title " digitoxoside " would appear in the monograph as a synonym.

Proposals for the style and system to be followed for graphic formulas were received and approved.

2.2 General methods

2.2.1 *Determination of melting-range, melting-temperature and congealing-temperature*

The Committee considered a revised text of Appendix 6, entitled " Determination of melting-range, melting-temperature and congealing-temperature ", intended for the second edition of the International Pharmacopoeia.

As most commercially available apparatus for the determination of melting-points uses thermometers calibrated for partial immersion, both partial and total immersion types of thermometer were recommended for mention in the second edition of the International Pharmacopoeia. The emergent-stem correction should be also applied to the thermometers calibrated for partial immersion.

The revised text includes a definition of the term "melting-temperature about...", which means that the melting-temperature obtained by the method described should not differ by more than ± 2°C from the stated temperature. This term will be used in the identification tests of the International Pharmacopoeia when the melting-temperature is to some extent affected by the state of purity of the derivative obtained in the test.

2.2.2 *Radioactive pharmaceuticals*

The text of a general chapter on radioactivity based upon the relevant chapter in the seventeenth edition of the US Pharmacopoeia was agreed upon for use as an appendix to the second edition of the International Pharmacopoeia.

The necessity for applying tests for sterility and freedom from pyrogens was examined, and the Committee agreed that, where indicated, these requirements should be added to the individual monographs for products intended for injection. With respect to the pyrogen test, the Committee noted that test animals are to be used only once for tests on radioactive substances.

2.2.3 *Determination of calcium*

The Committee agreed that hydroxynaphthol blue and calconcarbonic acid should be used instead of calcein-thymolphthalein and methylthymol blue