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WHO EXPERT COMMITTEE ON SPECIFICATIONS FOR PHARMACEUTICAL PREPARATIONS

Twenty-second Report

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WHO EXPERT COMMITTEE ON SPECIFICATIONS FOR PHARMACEUTICAL PREPARATIONS

Geneva, 14–19 October 1968

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WHO EXPERT COMMITTEE ON SPECIFICATIONS FOR PHARMACEUTICAL PREPARATIONS *

Twenty-second Report

The WHO Expert Committee on Specifications for Pharmaceutical Preparations met in Geneva from 14 to 19 October 1968. Dr P. Dorolle, Deputy Director-General, opened the meeting on behalf of the Director-General. Dr T. Canbäck was elected Chairman and Professor M. A. Attisso Vice-Chairman. Mr C. A. Johnson and Mr R. J. Samson were appointed Rapporteurs.

1. QUALITY CONTROL OF DRUGS

In 1967,[1] the Twentieth World Health Assembly requested the Director-General to take a number of measures to assist Member States in their efforts to improve the quality control of drugs. In particular, it called for the formulation, as soon as possible, of principles for quality control procedures that should be applied to drug manufacturing practice. A draft document incorporating such principles, accompanied by a number of recommendations concerning factors to be considered in maintaining good manufacturing practices, was subsequently submitted to the Twenty-first World Health Assembly under the title " Draft Requirements for Good Manufacturing Practice in the Manufacture and Quality Control of Drugs and Pharmaceutical Specialities ", and was favourably received. The draft had also been sent to Member States with the purpose of obtaining comments. The response indicated that no substantial changes were necessary,

* Earlier WHO Expert Committees that produced reports on this subject were known as "WHO Expert Committee on the Unification of Pharmacopoeias" (1st to 7th reports) and subsequently as "WHO Expert Committee on the International Pharmacopoeia" (8th and 9th reports). The 10th to 20th reports, using the present title, were issued in mimeographed form only. The 21st report was published as *Wld Hlth Org. techn. Rep. Ser.*, 1965, No. 307.

[1] Resolution WHA 20.34, *Off. Rec. Wld Hlth Org.*, No. 160, p. 19.

although certain points of detail needed further clarification. The comments were reviewed and the revised draft was adopted, with minor amendments, by the Committee. The final text is reproduced in Annex 2 ; some principles on which quality control should be based are discussed in Annex 1.

2. DETERMINATION OF MORPHINE IN OPIUM

2.1 Present status

The Committee reviewed the progress of work to date on this project. Collaborative tests on the modified Mannich method of the Austrian Pharmacopoeia IX proved disappointing and further work, based on the recommendations of Schultz & Schneckenburger,[1] was undertaken. Much better results have been obtained by this modification of the method, although they are still too variable to permit unqualified recommendation of the technique. The Schultz & Schneckenburger method involves the use of an alumina column, and variation in the quality of alumina used is believed to contribute to the variability of the results. A source of supply of specially standardized alumina has been arranged and a third round of collaborative tests has been undertaken. An alternative method of extraction and purification prior to precipitation of the morphine, based on a partition chromatographic method described by Smith, Levine & Banes,[2] was also tested. Results obtained by the Schultz & Schneckenburger method were substantially higher than those given by the partition chromatographic method, and the coefficient of variation was lower. The morphine dinitrophenylether produced by the Schultz & Schneckenburger method was slightly more contaminated with small quantities of impurities than was that produced by the chromatographic method, but the extra contamination was by no means sufficient to account for the higher results obtained. It is felt that the results given by the Schultz & Schneckenburger method are not only more precise, but also more realistic, and the Committee agreed to continue work on the procedure.

2.2 Future work

The Schultz & Schneckenburger method will undergo detailed study in a single laboratory in order to discover factors that might contribute to the variability of results.

Confidence in the proposed Schultz & Schneckenburger assay method would be greatly increased if it were found to give, for a given sample of opium, results that showed satisfactory correlation with the actual factory

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[1] *Arch. Pharm. (Weinheim)*, 1965, **298**, 548.

[2] *J. Ass. off. agric. Chem.*, 1968, **51**, 180.

yields of morphine from the same sample. The necessary data might be obtained by direct inquiries addressed to leading processers. In addition, it would be extremely useful if the processers were willing to furnish similar figures correlating actual factory yields of morphine with those theoretically expected on the basis of results obtained by their routine assay method. However, this project may well be delayed until the new study of the variables involved in the Schultz & Schneckenburger method is completed. If modifications of the technique are found to be desirable, details could then be furnished to the opium processing factories.

The Committee decided to seek the co-operation of a few official opium test laboratories in assaying, by means of their normal routine methods, the five opium samples used in the collaborative study referred to above. The results could then be compared with those obtained in the collaborative study.

3. PROPOSED SPECIFICATIONS FOR ANTITUBERCULOSIS DRUGS

The Committee began work on certain specifications for antituberculosis drugs that are not included in the second edition of the *International Pharmacopoeia* [1] but that are widely used in UNICEF/WHO-assisted field projects.

Draft specifications prepared by the State Institute for the Control of Drugs, Prague, in the style of the *International Pharmacopoeia*, and on the basis of published data and information supplied by manufacturers, were examined by the Committee after they had been reviewed, verified, and commented on.

3.1 Calcium benzamidosalicylate, pyrazinamide, and ethionamide

The Committee accepted, subject to the making of minor changes in the text of the specifications, the proposed monographs on calcium benzamidosalicylate and pyrazinamide. The monograph submitted on ethionamide will be completed by including a description of a thin-layer chromatographic method for the detection of possible impurities.

3.2 Thioacetazone, thioacetazone tablets, and thioacetazone and isoniazid tablets

The Committee asked the Secretariat to ascertain the principal types of impurities that may be found in thioacetazone, thioacetazone tablets,

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[1] World Health Organization (1967) *Specifications for the quality control of pharmaceutical preparations*—second edition of the *International Pharmacopoeia*, Geneva.

and thioacetazone and isoniazid tablets. Depending on the information received, an appropriate method for the detection of impurities will be established.

3.3 Ion-exchange chromatography

Since assay of the substances noted above involves the use of ion-exchange chromatographic techniques, a description of such techniques was examined and accepted.

3.4 Further work

The Committee decided that priority should be given to the establishment of specifications for the following antituberculosis preparations: ethambutol, isoniazid and para-aminosalicylic acid tablets, and calcium benzamidosalicylate and isoniazid tablets.

4. INTERNATIONAL CHEMICAL REFERENCE SUBSTANCES

4.1 Evaluation and use

The Committee considered the general factors that should be taken into account in the evaluation and use of international chemical reference substances. One such factor is the complications arising from polymorphism; for example, the infrared spectrum of a given chemical reference substance may differ from that of the residue obtained by evaporating an extract of a dosage form of the drug. It may be possible to circumvent this problem by the use of solution spectra.

In order to assess the extent to which contaminants may interfere with an assay, the Committee considered that, whenever applicable, the technique used to assay a drug and its dosage forms should be used as an additional means for detecting contaminant spots on thin-layer chromatograms of international chemical reference substances. For example, it would be useful to employ blue tetrazolium to detect contaminants on corticosteroid chromatograms, and ultraviolet absorbance as a means for detecting contaminants on thin-layer chromatograms of the semisynthetic penicillins. When a reference substance is used for comparison in an ultraviolet absorption assay, a small amount of a contaminant that is highly absorbing at the wavelength concerned can significantly affect the accuracy of the determination.

Consideration should also be given to the possibility of assessing such interference (1) by comparing the absorptivity of the reference substance