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WORLD HEALTH ORGANIZATION
TECHNICAL REPORT SERIES
No. 567

WHO EXPERT COMMITTEE ON SPECIFICATIONS FOR PHARMACEUTICAL PREPARATIONS

Twenty-fifth Report

WORLD HEALTH ORGANIZATION
GENEVA
1975

ISBN 92 4 120567 9

PRINTED IN SWITZERLAND

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WHO EXPERT COMMITTEE ON SPECIFICATIONS FOR PHARMACEUTICAL PREPARATIONS

Geneva, 4–9 November 1974

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WHO EXPERT COMMITTEE ON SPECIFICATIONS FOR PHARMACEUTICAL PREPARATIONS

Twenty-fifth Report

The WHO Expert Committee on Specifications for Pharmaceutical Preparations met in Geneva from 4 to 9 November 1974. Dr A. S. Pavlov, Assistant Director-General, opened the meeting on behalf of the Director-General.

1. REVISED TEXTS OF DOCUMENTS RELATING TO QUALITY CONTROL AND CERTIFICATION OF PHARMACEUTICAL PRODUCTS

The Twenty-second World Health Assembly recommended that Member States adopt and apply the requirements entitled *Good Practices in the Manufacture and Quality Control of Drugs*, as formulated in the report of the Director-General,[a] and the *Certification Scheme on the Quality of Pharmaceutical Products moving in International Commerce*, as formulated in the report of the Director-General.[b]

The Twenty-third World Health Assembly requested the Director-General to continue to review, in the light of information obtained, the requirements embodied in *Good Practices in the Manufacture and Quality Control of Drugs* and the Certification Scheme and to report to the Twenty-fourth World Health Assembly.

The Expert Committee on Specifications for Pharmaceutical Preparations, in its twenty-fourth report,[c] undertook a review of comments received in respect of both documents from a number of Member States, and on the basis of these comments, proposed revised texts, which were, in turn, sent to all Member States for further comments in January 1974. At this stage comments were received from some 40 Member States, including the majority of countries that manufacture drugs for export.

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[a] WHO Official Records, No. 176, 1969, Annex 12, part 1, pp. 99–104.

[b] WHO Official Records, No. 176, 1969, Annex 12, part 2, pp. 104–105.

[c] WHO Technical Report Series, No. 487, 1972.

The Committee noted that although the comments raised no new points of principle, there were several recommendations for changes in the texts. In some cases, the comments were aimed at bringing the text more closely into line with a particular national practice or legislation ; however, because this could well conflict with other national practices, it was not always possible to adopt the recommendations made. In other cases, proposals were made for elaborating in more detail on some of the requirements, but it was thought that, unless the whole text were similarly amended, this might lead to an unbalanced document.

Several comments concerned the terms listed under " Definitions " and, although it was agreed that some of the suggested alternatives were in keeping with current practice, it was thought that any advantages gained by adopting them would be more than outweighed by the numerous problems created elsewhere by the introduction of new terms at this stage. This related particularly to the term " drug ". It was considered that a definition of " purity " was unnecessary because this term has no significant use in the text.

Due note was taken of comments that revealed ambiguities or vagueness in the text and might lead to misunderstandings. Suitable corrections were made. Several changes were made in the order of paragraphs within sections, so as to present the requirements in a more logical sequence.

The role of the quality control laboratory has been more clearly defined. The release of batches, which was previously linked solely to the analytical report, has now been changed to require a formal act of release by the quality control department.

In the Certification Scheme, substantial changes have been made in order to distinguish more clearly between the general Certification of Pharmaceutical Products and the issue of batch certificates.

Legislation in effect in some Member States might lead them to have reservations regarding their participation in the scheme. This fact has now been recognized by suitable additions to " Part III — Participation of Member States ". The responsibilities of exporting Member States have been extended by the introduction of a reference to the provision of authority to enforce standards.

The specimen certificate has been revised to recognize that " authorization " is not necessarily accompanied by the issue of permits. It now also provides for the situation in which the person responsible for placing the product on the market is not the manufacturer.

The Twenty-fifth World Health Assembly adopted a resolution requesting the Director-General " to undertake a study of the most feasible means of indicating by a uniform system of marking the limits of shelf life of pharmaceutical products under the conditions of their storage, as well as the date

of manufacture and batch number, and the maintenance of records which facilitate tracing of distribution, and to report thereon to a future World Health Assembly ".[a]

Accordingly means were sought to incorporate the elements set out in the above resolution both in the *Certification Scheme on the Quality of Pharmaceutical Products moving in International Commerce* and in the revised text of *Good Practices in the Manufacture and Quality Control of Drugs*, in such a way that the implementation of the Certification Scheme would constitute an important step to achieving the objectives of the resolution.

As part of the revision of *Good Practices in the Manufacture and Quality Control of Drugs*, it was agreed that the establishment of expiry dates and shelf life specifications, on the basis of stability tests performed by the quality control department of the manufacturer, be no longer optional. In the revised Certification Scheme expiry dates are required on the batch certificates. The inclusion of expiry dates on the labelling of finished products would provide a uniform system of indicating the shelf life under specified conditions of storage, if appropriate legislation existed in the importing countries.

The resolution also refers to information that could be used in tracing distribution when it is necessary to recall batches of finished products. In cases where the protection of public health is at stake, the prompt and complete recall of specific batches of finished drugs would be facilitated if appropriate legislation existed in the importing countries relating to the maintenance of records by importers and wholesalers.

Revised texts of *Good Practices in the Manufacture and Quality Control of Drugs* and *Certification Scheme on the Quality of Pharmaceutical Products moving in International Commerce*, incorporating the recommendations of the Committee, are included as Annex 1 to this report.

2. SPECIFICATIONS FOR RADIOPHARMACEUTICALS

The Committee undertook the revision of Appendix 13, " Radioactivity ", and Appendix 13a, " Table of physical characteristics of radionuclides " of the International Pharmacopoeia, and the revision of existing monographs on radiopharmaceuticals. It also considered a number of new draft monographs for radiopharmaceuticals.

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[a] World Health Organization, *Handbook of resolutions and decisions of the World Health Assembly and the Executive Board, vol. I, 1948-1972*, Geneva, 1973, p. 143 *(Resolution WHA25.61)*.

2.1 Revision of appendices

The Committee undertook the revision of the texts, based on drafts prepared by consultants, which had taken into account developments in the field. The revision concerned especially the procedures used in the detection and measurement of radiation, including the newer techniques of radiation spectrometry employing semiconductor devices, and difficulties arising in the determination of radionuclidic and radiochemical purities. The " Table of physical characteristics of radionuclides " was expanded to include all radionuclides mentioned in the monographs, including radionuclidic impurities.

The revised texts of Appendices 13 and 13a are contained in Annex 2.

2.2 Revision of existing specifications

The Committee considered a number of proposals by consultants for revision of the existing monographs, together with certain amendments made necessary by changes in Appendix 13, " Radioactivity ". The amendments accepted included requirements for the radiochemical purity of Cyanocobalamin (^{57}Co) and of Cyanocobalamin (^{58}Co) at expiry, more explicit instructions for the assay of iodine-125 and mercury-197, and more appropriate directives for pyrogen testing of Iodinated (^{125}I) Human Serum Albumin Injection and Iodinated (^{131}I) Human Serum Albumin Injection. Of special note was the distinction made in the monograph on Sodium Pertechnetate (^{99m}Tc) Injection between molybdenum-99 prepared by neutron irradiation of molybdenum and molybdenum-99 derived from uranium fission.

The texts of the revised monographs on radiopharmaceuticals are reproduced in full in Annex 2, so that the proposed international requirements are readily available in a single document.

2.3 Proposed specifications for new radiopharmaceuticals

The Committee considered several new draft monographs that had been developed as a result of collaboration between a number of institutions engaged in studies on radiopharmaceuticals and of consultations with the appropriate experts and with the International Atomic Energy Agency.

Provisional specifications were adopted for the following radiopharmaceuticals :

Indium (^{113m}In) Chloride Injection
Indium (^{113m}In) Pentetate Complex Injection