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*WORLD HEALTH ORGANIZATION*

*TECHNICAL REPORT SERIES*

No. 487

# WHO EXPERT COMMITTEE ON SPECIFICATIONS FOR PHARMACEUTICAL PREPARATIONS

## Twenty-fourth Report

WORLD HEALTH ORGANIZATION

GENEVA

1972

PRINTED IN SWITZERLAND

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## WHO EXPERT COMMITTEE ON SPECIFICATIONS FOR PHARMACEUTICAL PREPARATIONS

*Geneva, 26 April – 1 May 1971*

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Dr E. Lang, CIBA-GEIGY Limited, Basle, Switzerland

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Mr B. Öhrner, WHO Centre for Chemical Reference Substances, Solna, Sweden (*Consultant*)

Dr J. Vacek, Pharmaceutical Officer, Pharmaceuticals, WHO, Geneva, Switzerland (*Secretary*)

Mr O. Wallén, Chief Pharmaceutical Officer, Pharmaceuticals, WHO, Geneva, Switzerland.

# WHO EXPERT COMMITTEE ON SPECIFICATIONS FOR PHARMACEUTICAL PREPARATIONS

## Twenty-fourth Report

The WHO Expert Committee on Specifications for Pharmaceutical Preparations met in Geneva from 26 April to 1 May 1971. Dr L. Bernard, Assistant Director-General, opened the meeting on behalf of the Director-General.

### 1. REVISION OF THE SECOND EDITION OF THE *INTERNATIONAL PHARMACOPOEIA*

In accordance with the recommendation made by the WHO Expert Committee on Specifications for Pharmaceutical Preparations in its twenty-third report,[1] consideration was given to the work necessary to initiate a general revision of the *International Pharmacopoeia*. It was decided that first consideration should be given to general monographs and general methods of analysis, since changes in these would have an impact on many of the individual monographs.

#### 1.1 Revision of general monographs for injections, tablets and other pharmaceutical forms

The Committee reviewed these subjects and recommended the following general guidelines for future work.

1.1.1 *General monograph on injections*

The Committee recommended that in revising this monograph injections should be considered in three classes, namely :

Small-volume injections — nominal volume of 20 ml or less and usually administered by syringe ;

Large-volume injections — nominal volume in excess of 20 ml and usually administered by infusion or slow drip ;

Solids for injections — substances converted into injections by the addition of a suitable solvent when required for use.

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[1] Unpublished document WHO/PHARM/70.456.

It was proposed that specifications of two kinds should be prepared — those applicable to all three classes of injections and those applicable only to a particular class.

The Committee drew up the following tentative list of special requirements for injections:

(1) *Applicable to all injections*

- (*a*) Methods of sterilization
- (*b*) Tests for sterility
- (*c*) Specifications for containers
  - (*i*) glass
  - (*ii*) plastic

(2) *Applicable to small-volume injections*

- (*a*) Tests for particulate matter
- (*b*) Added antimicrobial substances
- (*c*) Non-aqueous vehicles
- (*d*) Tests for nominal volume and prescribed excess volume
- (*e*) Use of multidose containers

(3) *Applicable to large-volume injections*

- (*a*) Test for pyrogens
- (*b*) Tests for particulate matter

(4) *Solids for injections*

- (*a*) Uniformity of weight
- (*b*) Additional labelling requirements

These requirements are commented on individually below.

(1) *Requirements applicable to all injections*

(*a*) *Methods of sterilization*

The Committee considered that the existing section on "Sterilization" in the monograph "Injections" does not adequately describe this important and technically complex subject. Moreover, neither sterilization by penetrating radiation (either gamma radiation or electron beam) nor gaseous sterilization is included and these are now widely accepted methods for certain preparations of drugs and medical devices.

An adequate discussion of sterilization would increase the monograph on injections to an undesirable length. It was recommended that the section on sterilization in the general monograph "Injections" should be confined to

a list of recognized methods of sterilization. It was further recommended that a new section on methods of sterilization should be prepared as an appendix in which a fuller description can be provided.

(*b*) *Tests for sterility*

The Committee recommended that the tests for sterility should be revised. It was proposed that the following points especially should receive attention: more comprehensive specifications for media, pretesting of media, a more sensitive test for fungi, an extension of the incubation period, an examination of sample size dependent upon the method of sterilization, and a statement of the problems of interpretation and the significance of test results.

It was noted that the revised Appendix 13, " Radioactivity ", included in the *Supplement 1971* to the second edition of the *International Pharmacopoeia* provided recommendations for sterility tests on radioactive pharmaceuticals.

(*c*) *Plastic containers*

The Committee noted that there was a need for specifications for the composition and properties of plastics in relation to their suitability as materials for containers for drugs. Such specifications should determine their compatibility, appropriate physical attributes, and transparency. Plastics are now used to manufacture containers for blood and injections generally, as well as for liquids that are not administered parenterally, and are also used to manufacture syringes and other injection devices.

Chemical and physical tests alone do not provide adequate specifications. Certain biological tests described in the eighteenth revision of the *United States Pharmacopeia*, which are carried out upon aqueous extracts, are not sufficiently sensitive to discriminate reliably between suitable and unsuitable plastics.

It was agreed that a study should be made of the information and data that are available from several groups in various countries with a view to developing appropriate recommendations for the assessment of the suitability of plastics.

(2) *Requirements applicable to small-volume injections*

(*a*) *Tests for particulate matter*

The Committee noted that, although quantitative limits for particulate matter in small-volume injections would be desirable, no suitable quantitative methods are at present available. It was recommended, however, that a requirement be added to the monograph " Injections " to the effect that solutions to be injected should not contain particles of foreign matter that can readily be observed on visual inspection.

(*b*) *Added antimicrobial substances*

The Committee recognized that the addition of antimicrobial substances to single-dose injections sterilized in their final containers should not be allowed.

Injections for intrathecal, intracisternal, and peridural injection must not contain added antimicrobial substances and should be presented in single-dose glass ampoules. The Committee considered that further specifications, such as close control of pH, may be needed for injections of this kind.

(*c*) *Non-aqueous vehicles*

The Committee considered that the present specifications for non-aqueous vehicles in the monograph "Injections" should be removed. It was recommended that when an injection contained a non-aqueous vehicle, the vehicle should be stated and specifications for it should be provided.

(*d*) *Tests for nominal volume and prescribed excess volume*

The Committee noted that limits are provided for "Volume of injection in a single-dose container". It was recommended that a method for determining volume should be added.

(*e*) *Multidose containers*

The Committee recommended that the use of multidose containers should be discouraged. Such containers should be used for injections only in exceptional circumstances and with caution.

(3) *Requirements applicable to large-volume injections*

(*a*) *Test for pyrogens*

The Comittee noted that all sterile injections should be free from pyrogens and that the pyrogen testing of some drugs presents special problems that could be taken into account in individual monographs. It was considered advisable to revise the present test, which does not require the use of a pyrogen reference preparation. It was recognized that the problem is complex, that an International Reference Preparation of Pyrogen prepared from *Shigella dysenteriae* exists, and that the solution of this problem requires the collaborative advice of the WHO Expert Committee on Biological Standardization.

From the standpoint of the *International Pharmacopoeia* it was necessary to determine first whether a pyrogen standard need be incorporated in the test to determine the sensitivity of different groups or strains of rabbits and, if so, what pyrogen standard should be used; and second whether the use of a standard would sensitize rabbits to the effects of pyrogens.