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WHO Expert Committee on Biological Standardization

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Geneva, 7–13 November 1978

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WHO EXPERT COMMITTEE ON BIOLOGICAL STANDARDIZATION

Thirtieth Report

GENERAL

The WHO Expert Committee on Biological Standardization met in Geneva from 7 to 13 November 1978. The meeting was opened on behalf of the Director-General by Dr V. Fattorusso, Director, Division of Prophylactic, Diagnostic, and Therapeutic Substances.

The Committee was informed that recent developments, at the National Institute for Biological Standards and Control, London, in the technique of weighing hygroscopic materials at very low controlled humidities, have revealed problems of unexpected magnitude in the weighing of samples of international standards.

It has been recognized for many years that the exhaustive drying applied to international standards in order to attain satisfactory stability has produced a product that may take up water rapidly from the atmosphere when the ampoule is opened, unless the material is carefully protected from ambient humidity. It has been the practice to provide, where possible, guidance on the rate of water uptake by certain international standards and reference preparations. Such guidance, however, has been based on experimental results obtained with slow weighing procedures, and new techniques have revealed that moisture uptake of 100 g/kg may occur at 50% relative humidity within two or three minutes of opening the ampoule. In the case of the proposed reference preparation of bleomycin, moisture is taken up at a rate equal to that shown by phosphorous pentoxide, at least to a content of 70 g/kg, in one minute, at 20% relative humidity. By using special equipment, which is complicated and expensive, weighings of the bleomycin preparation may be effected at relative humidities low enough to prevent undesirable errors, but such equipment is not generally available—even to many national control laboratories.

The problem may be largely avoided by distributing an international standard in freeze-dried form and assigning a defined number of international units per ampoule, thus making it unnecessary to weigh quantities of the standard preparation. The total contents of the ampoule are removed with an appropriate solvent and the final

volume is accurately adjusted. The Committee recommended that, whenever possible, future international standards and reference preparations should be prepared so as to allow the unit to be defined on the basis of the total contents of an ampoule. The Committee emphasized that, when such a procedure is used, satisfactory evidence is essential, in each case, to demonstrate that the amount of liquid filled into each ampoule does not vary by more than ±1.0% (*1*, page 111).

The Committee defined certain new international units on the basis of ampoule contents and recommended that the WHO International Laboratories for Biological Standards should be authorized to restate the existing definitions of international units currently expressed in weights and for which the content of international units in each ampoule is known with the necessary precision. This restatement was desirable because present weight designations may be misinterpreted to mean that a portion of material contained in the ampoule may be weighed out and represents a number of units calculable from the weight definition. This procedure is not valid and may cause large errors, since it is known that the contents of a single ampoule are not necessarily homogeneous and since the error that may occur in attempts to weigh the total contents of an ampoule by difference is likely to be significantly greater than the error (±1%) involved in distributing the liquid into the ampoules. A further advantage of the definition based only on the total contents is that particles of glass inadvertently introduced at the time of opening the ampoule will not lead to inaccuracies in use.

It is for these reasons that, for many years now, recipients of ampoules of standards that have been accurately filled have been instructed to use them on the basis of the total number of units stated to be in each ampoule. The proposed restatements of the definitions would avoid the dangers inherent in weighing, but would not alter the value of the International Unit.

In the case of a number of existing international standards and reference preparations, and future materials that cannot be freeze-dried from aqueous solution, the weight definition of the unit of activity will have to be retained. The weighing of such materials will need particular care, and the Committee recognized that the experience and equipment necessary for handling hygroscopic materials may not be available in many national control laboratories. Details of appropriate handling procedures should be made available to users.