WHO Expert Committee on Biological Standardization

Twenty-eighth Report

nical Report Series

World Health Organization, Geneva 1977

This report contains the collective views of an international group of experts and does not necessarily represent the decisions or the stated policy of the World Health Organization

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WHO EXPERT COMMITTEE ON BIOLOGICAL STANDARDIZATION

Geneva, 16–22 November 1976

Members *

Dr Chou Hai-chun, Deputy Director of the Revolutionary Committee of the Peking Institute for the Control of Pharmaceutical and Biological Products, Peking, China

Professor S. G. Dzagurov, Director, Tarasevič State Institute for the Standardization and Control of Medical Biological Preparations, Moscow, USSR

Dr Sutas Guptarak, Deputy Director-General, Department of Medical Sciences, Bangkok, Thailand

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Dr J. Spaun, Director, Department of Biological Standardization, State Serum Institute, Copenhagen, Denmark

Mr J. R. Thayer, Chief Inspector, National Biological Standards Laboratory, Canberra, A.C.T., Australia (*Chairman*)

Dr D. P. Thomas, Head, Division of Blood Products, National Institute for Biological Standards and Control, London, England (*Rapporteur*)

Dr W. W. Wright, Deputy Associate Director, Pharmaceutical Research and Testing, Bureau of Drugs, Food and Drug Administration, Washington, DC, USA

Representative of the Food and Agriculture Organization

Dr Y. Ozawa, Animal Health Officer (Infectious Diseases), Animal Production and Health Division, Food and Agriculture Organization, Rome, Italy

Secretariat

Dr D. R. Bangham, Head, Division of Hormones, National Institute for Biological Standards and Control, London, England (*Consultant*)

Professor A. Eyquem, Chief, Immunohaematology and Immunopathology Service, Director of the Blood Transfusion Centre, Pasteur Institute, Paris, France (*Consultant*)

Dr F. T. Perkins, Chief, Biologicals, WHO, Geneva, Switzerland (*Secretary*)

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* Unable to attend : Professor Y. Chabbert, Chief, Unit for Studies on Sensitivity to Antibiotics, Assistant Director, Pasteur Institute, Paris, France ; Dr P. Tuchinda, Under-Secretary of State for Public Health, Ministry of Public Health, Bangkok, Thailand.

WHO EXPERT COMMITTEE ON BIOLOGICAL STANDARDIZATION

Twenty-eighth Report

The WHO Expert Committee on Biological Standardization met in Geneva from 16 to 22 November 1976. The meeting was opened on behalf of the Director-General by Dr Ch'en Wen-chieh, Assistant Director-General, who observed that much of the agenda of the meeting would be concerned with human blood components and derivatives. A WHO Working Group on the Standardization of Human Blood Products and Related Substances had met in Geneva from 5 to 10 July 1976, and the report of the Group was to be considered in detail as it contained a number of important recommendations. In addition to the establishment of a number of standards and reference preparations, a particular recommendation was the need for the formulation of requirements for the manufacture and control of blood products.

Antibiotics, said Dr Ch'en, were also to be considered and the requirements for antibiotic susceptibility discs would fulfil an urgent need. The increase in antibiotic resistance of organisms was causing concern in many countries and it was essential to be able to compare these findings between countries. The List of Biological Substances had been brought up to date and the substances listed alphabetically within each category in order to facilitate reference. Reference reagents had been reintroduced into the list because of many inquiries concerning the availability of those preparations.

GENERAL

The Committee noted the report of the WHO Working Group on the Standardization of Human Blood Products and Related Substances and considered that the treatment of one particular field in depth by a group of specialists in this manner had been most productive. When necessary, problems in other fields could with advantage be approached in a similar way. The Committee agreed that the report of the Working Group should be annexed to this report (Annex 1).

The use of international units to specify the potency of blood typing sera should be strongly encouraged since international standards have now been established for the four blood typing sera of the greatest practical importance—namely, those for A, B, D and c antigens. The use of the international units will lead to more accurate quantification in the control of potency of blood typing sera, and the use of titres—the traditional way of describing the strength of these sera—should be discouraged. The prophylaxis, monitoring, and treatment of haemolytic disease of the newborn has concentrated particular effort on the quantification of anti-D antibodies. The use of automated instruments for measuring the potency of sera has extended the working dilution range several hundredfold and, as a result, numerical values of endpoint " titres " are cumbersome. The production of sera is now more extensive than ever before, and standardization for their control (for potency, specificity, and stability) is necessary.

The Committee recalled the resolutions of the World Health Assembly that countries should adopt international units to express the potency of biological materials.[1] It is important that this be done widely and rapidly following the establishment of international standards. In those instances where national units differ from the international units the repercussions could be hazardous in clinical practice and cause difficulties in the international exchange of materials and information. It is important, therefore, that national authorities inform WHO of any decision not to use established international units and report the reasons for the decision.

The Fisher-Race nomenclature for Rh blood typing is becoming more widely accepted, and the Committee agreed that it should be universally adopted in the interests of simplicity and uniformity (Annex 1, Part B, section 1). The Committee was informed that studies were in progress to determine whether this system could conveniently be used with computers.

With regard to the collaboration of international scientific organizations with the Expert Committee on Biological Standardization (Annex 1, Part C), the Committee agreed that contact with such specialist organizations could facilitate the rapid dissemination and implementation of WHO recommendations on biological standardization. It could also ensure the availability of specialized help with particular problems and with the establishment of international reference materials. To avoid

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[1] See, for example, WHO Handbook of Resolutions and Decisions, Volume II, first edition, 1975, p. 16 (Resolution WHA26.32).

unnecessary duplication of effort it is desirable that scientific organizations planning to undertake work on setting up a proposed international biological standard should keep WHO informed. There has been a steady increase in the number and diversity of substances for which international reference materials are needed, and many of them are being promoted by international societies. To assist such work it had been proposed (Annex 1, Part C) that guidelines be formulated on the methods of setting up international biological standards (including advice on the selection of candidate materials and their processing under suitable conditions), the planning of collaborative studies, tests for long term stability, and the analysis, reporting, and interpretation of results. Such a document could also include guidance on the setting up of national and laboratory standards. The Committee agreed with this proposal and asked WHO to arrange for the formulation of such guidelines.

Standardization for prothrombin time estimations used in the control of anticoagulant treatment with coumarin drugs presents particularly complex problems (Annex 1, Part A, section 6). Standardization became possible only when a way was devised of relating the activity of one preparation of thromboplastin to another using the prothrombin time ratio method. Although this method is based on a procedure that does not conform to the theory of conventional comparative parallel line assays, it has been shown in several studies and in a number of laboratories to give reliable and reproducible results. It is also used extensively for the standardization of thromboplastin preparations. The scheme proposed for international standardization (Annex 1, Appendix 2) depends on the establishment of international reference preparations of certain currently used thromboplastins. Each preparation will have a number assigned to it—called the international calibration constant—to describe its thromboplastin activity relative to a single original reference material for which the value 1.0 has been defined.

These proposals for standardization are based also on the results of extensive studies conducted under the aegis of a joint panel of the International Committee of the International Society of Hematology and the International Committee of the Society of Thrombosis and Haemastasis, modified in the light of comments at a meeting convened by the two bodies in Kyoto, Japan, in September 1976. The proposals allow a choice of schemes for national control of prothrombin time tests and involve the use of an international calibrated scale for expressing the results of prothrombin time estimations. This scheme will have to be explained widely if its introduction into clinical practice is to be successful.

The procedures for calibration of thromboplastins require the use of plasma from patients on long-term coumarin treatment. National authorities should ensure that such plasma is obtained only under controlled conditions and with the knowledge and consent of the patient and his physician.

In view of the current extensive preparation and use of blood products and derivatives both for clinical use and as laboratory reagents, the Committee regarded the recommendation for the formulation of requirements for blood and blood products as particularly urgent.

SUBSTANCES

BLOOD PRODUCTS AND RELATED SUBSTANCES

1. Blood Typing Sera [1]

The Committee noted that the WHO Working Group on the Standardization of Human Blood Products and Related Substances had made a recommendation that national authorities should express potencies of blood typing sera in international units where these are available instead of using titres (Annex 1, Part A, sections 1.1 and 2). The Committee agreed that this was in accordance with resolutions of the World Health Assembly.[2]

The Committee noted also the recommendation of the WHO Working Group that general requirements for the production and testing of blood typing sera and ancillary reagents should be formulated. These requirements would include specifications for avidity and specificity, as well as potency, as these are critical characteristics of blood typing sera. The Committee requested WHO to arrange for the formulation of such requirements.

2. Anti-(A+B), Anti-C and Anti-E Blood Typing Sera

The Committee noted that the WHO Working Group on the Standardization of Human Blood Products and Related Substances had expressed the need for reference materials for anti-(A+B), anti-C and

[1] The Expert Committee on Biological Standardization preferred this term to " blood grouping antisera ", which was used by the WHO Working Group on the Standardization of Human Blood Products and Related Substances (Annex 1, page 25).

[2] WHO Official Records, No. 143, 1965 (Resolution WHA 18.1) ; No. 209, 1973 (Resolution WHA 26.32).

anti-E blood typing sera (Annex 1, Part A, section 1.3). The Committee agreed that such sera were needed and requested the Central Laboratory of the Netherlands Red Cross Blood Transfusion Service, Amsterdam, to obtain materials suitable for this purpose and to arrange collaborative studies.

The Committee noted also the recommendation that the suitability of the International Standards for Anti-A and Anti-B Blood Typing Sera be reassessed in the light of new knowledge of the ABO system. At the same time, however, it was informed that stocks of the International Standards for Anti-A and Anti-B Blood Typing Sera were depleted. The Committee therefore recommended that the stocks be replaced as soon as possible and requested the Central Laboratory of the Netherlands Red Cross Blood Transfusion Service to obtain materials suitable as replacements and to arrange for collaborative assays.

3. Anti-c Incomplete Blood Typing Serum

The Committee noted the results of the collaborative study of a proposed international standard for anti-c incomplete blood typing serum 76/160, which was coordinated by the Medical Research Council's Blood Group Reference Laboratory, London, England, and which showed that the preparation was stable. The participating laboratories agreed that the material was suitable for use as an international standard and the WHO Working Group on the Standardization of Human Blood Products and Related Substances endorsed this view (Annex 1, Part A, section 1.2).

The Committee established the preparation as the International Standard for Anti-c Incomplete Blood Typing Serum, Human, and, in agreement with the participants in the study, defined the International Unit for Anti-c Incomplete Blood Typing Serum, Human, as the activity contained in 0.61 mg of the International Standard for Anti-c Incomplete Blood Typing Serum, Human.

4. Anti-D Immunoglobulin

The Committee noted the advice of the WHO Working Group on the Standardization of Human Blood Products and Related Substances concerning the suitability of a freeze-dried preparation 68/419 to serve as an international reference preparation of anti-D immunoglobulin (Annex 1, Part A, section 2). An international study involving 17 laboratories in 11 countries had shown that the isotopic method of determining anti-D immunoglobulin gave results similar to those produced by the

manual and automated haemagglutination techniques. The material had been calibrated in international units by 11 laboratories, its activity having been compared with that of the International Standard for Anti-Rh_0 (anti-D) Incomplete Blood Typing Serum. This study showed that the immunoglobulin preparation had an activity of 150 IU per ampoule. The Committee established the preparation as the International Reference Preparation of Anti-D Immunoglobulin and noted that each ampoule contained 14.76 mg of the preparation (150 IU per ampoule).

The Committee agreed that any future replacement of the International Reference Preparation of Anti-D Immunoglobulin should also be assigned a unitage by comparison with the International Standard for Anti-Rh_0 (anti-D) Incomplete Blood Typing Serum.

5. Anti-Hepatitis B Immunoglobulin

The Committee noted that the WHO Working Group on the Standardization of Human Blood Products and Related Substances had reported that an international reference preparation was needed for the estimation of hepatitis B antibody (Annex 1, Part A, section 8.1). A batch of human anti-hepatitis B immunoglobulin that might be suitable for this purpose would be examined in a collaborative study organized by WHO. The Committee was informed that immunoglobulin from subjects immunized with an inactivated hepatitis B vaccine could also be made available and agreed that such a preparation should be included in the study. The Committee observed that there was an urgent need for such an international reference preparation.

6. Anti-Varicella Zoster Immunoglobulin

The Committee noted that the WHO Working Group on the Standardization of Human Blood Products and Related Substances had recommended the setting up of an international reference material for anti-varicella zoster immunoglobulin (Annex 1, Part A, section 8.2).

The Committee supported this recommendation and asked the Central Laboratory of the Netherlands Red Cross Blood Transfusion Service, Amsterdam, to obtain a suitable preparation.

7. Blood Coagulation Factor VIII

The Committee noted (Annex 1, Part A, section 3.1) that the first International Standard for Blood Coagulation Factor VIII had been established before sensitive tests for hepatitis B surface antigen (HBsAg)