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WHO Expert Committee on Biological Standardization

Twenty-ninth Report

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CONTENTS

WHO EXPERT COMMITTEE ON BIOLOGICAL STANDARDIZATION

Geneva, 6–12 December 1977

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WHO EXPERT COMMITTEE ON BIOLOGICAL STANDARDIZATION

Twenty-ninth Report

GENERAL

The WHO Expert Committee on Biological Standardization met in Geneva from 6 to 12 December 1977. The meeting was opened on behalf of the Director-General by Dr Ch'en Wen-chieh, Assistant Director-General.

The Committee considered that one of the most useful documents made available at the meeting was Guidelines for the Preparation and Establishment of Reference Materials and Reference Reagents for Biological Substances. It was formulated for the guidance of international associations that were helping in setting up international standards as well as for the guidance of national authorities that were faced with the task of establishing national standards. The guidelines had been amended in the light of comments received from a number of scientists, and further amendments were made by the Expert Committee. The final version was annexed to the report (see Annex 4).

Another important matter was the Requirements for the Collection, Processing and Quality Control of Human Blood and Blood Products (see Annex 1). It was agreed that it would be most useful to have a single set of requirements applicable to all organizations and laboratories involved in the collection or fractionation of blood and blood products.

There is a need for better understanding of the distinction between estimates of hormone concentration using bioassays, which are based on the biological activity or function of a hormone, and estimates using binding assays (particularly radioimmunoassays), which are based on aspects of hormone structure that may not be related to biological activity or function. Failure to understand this distinction had led to considerable confusion in the literature and in clinical practice, and the confusion is even worse when the results of structure-based assays are misinterpreted as measures of biological activity. Measures recommended by the Expert Committee in its twentieth, twenty-first, and twenty-sixth reports had proved insufficient to maintain a clear distinction between the results of these two types of assay.

Experience gained in various assay performance studies, including the WHO human reproduction matched reagent programme, shows that the results of radioimmunoassay determinations cannot always be reproduced reliably with different sets of reagents. In addition, preparations containing heterogeneous forms of a hormone can yield markedly different potency ratios when tested in different *in vivo* and *in vitro* comparative bioassay systems.

It is recommended, therefore, that a report of an assay shall always be accompanied by a statement of the assay method employed, the standard used and its stated unitage, and the calibration method used (bioassay or binding assay). Unless this is done, confusing and possibly dangerous misinterpretations of potency estimates may be made. The Committee requested WHO to investigate this further in order to formulate guidance on the use of hormone preparations.

The Committee observed that until now the international unit of activity of all international reference materials has been expressed as that contained in a given weight or volume of the preparation contained in a sealed ampoule. The Committee has been aware for some time that the activity of some reference materials may not be distributed evenly throughout the freeze-dried preparation and that it may therefore be misleading to give the impression that the unit of activity is contained in a given weight of the preparation. In practice, irrespective of the definition of the unit by weight or by volume, for those preparations that have been filled as accurately reproduced volumes, instructions are given to the user to treat the contents of an ampoule as containing a defined number of units. The Committee was informed that there appears to be no legal objection to assigning a finite number of international units to the contents of an ampoule of material. Such a policy, however, calls for great accuracy in filling and care in freeze-drying in order to ensure that the variation of fill is not greater than 1%.

The Committee was informed of the increased use of certain antitumour antibiotics for the treatment of human tumours and leukaemias in a number of countries, some of which have national reference materials for control purposes. The measurement of activity, however, causes problems, and although an antitumour activity test in animals can be included in the original characterization of the preparation such tests cannot be used for the quantitative assessment of individual batches. For routine batch control, reliance must be placed partly on quantitative antimicrobial activity tests. The Committee noted that some of these antibiotics are pure crystalline materials, for which a chemical reference preparation would be suitable, while others consist of a mixture of several closely

related components requiring a biological test for the measurement of activity; for these products biological reference materials are needed.

The Committee agreed that guidelines on the quality control of antitumour antibiotics would be useful to many countries and requested WHO to formulate such guidelines.

The Committee was informed of new developments in the determination of the haemagglutinin content of influenza vaccines. Recent methods in which the quantitative measurement of haemagglutinin is determined by an antigen/antibody reaction have shown that haemagglutinin content correlates closely with the ability of the virus haemagglutinin to stimulate the production of antihaemagglutinin. It appears that the only effective means of controlling the potency of the vaccines is to provide each year a reference material in which the haemagglutinin content has been calibrated in micrograms of haemagglutinin per millilitre together with a specific antiserum. The Committee agreed to accept the generous offer of the National Institute for Biological Standards and Control, London, to provide haemagglutinin from current infectious strains annually, but it pointed out that such preparations should not be referred to as international reference materials but described as WHO Influenza Virus Reference Haemagglutinin, each preparation being identified by the year in which it was prepared.

The Committee was informed that there has been considerable progress in the standardization of allergens and that three international organizations [1] had formed an International Joint Steering Committee on Allergen Standardization. Several allergen extracts, with their matching antisera, had been prepared and a study on the standardization of an anti-IgE preparation was about to start. This progress had been made possible by the use of radioimmunoassay techniques and other *in vitro* methods. The Committee looked forward to seeing the reports on the preparations.

The Committee noted that many of the sets of requirements for biological substances were formulated more than 10 years ago and now need revision to take account of the developments that have since taken place in technology. Revision of the Requirements for Rabies Vaccine for Human Use is particularly needed, and the spread of rabies in many countries gives the matter greater urgency. The newer rabies vaccines are not only safe to be given prophylactically but are more potent, so that only 14–21 doses are needed after known exposure to street virus.

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[1] The International Association of Allergology, the International Association of Biological Standardization, and the International Union of Immunological Societies.

In discussions on the progress being made in the establishment of reference materials it became apparent that the analysis of the results, for which statistical services are required, is a lengthy process and frequently delays the completion of the study. In an attempt to resolve this problem the Committee asked WHO to explore the possibility of obtaining additional biometric services. It was suggested that institutes specializing in the analysis of the results of biological assays might be able to help.

SUBSTANCES

ANTIBIOTICS

1. Erythromycin

The Committee noted that supplies of the International Standard for Erythromycin were becoming depleted and that the National Institute for Biological Standards and Control, London, had taken steps to replace it.[1] A suitable preparation of erythromycin had been obtained and dispensed into ampoules so that each contained approximately 75 mg of the dried powder.

Samples of the first international standard and the proposed second international standard had been sent to seven laboratories in six countries for comparison in a collaborative assay. The results had been received from all laboratories and were being analysed.

The Committee authorized the National Institute for Biological Standards and Control to establish the preparation as the second international standard for erythromycin and on the basis of the results of the collaborative assay and with the agreement of the participants, to define the international unit.

2. Streptomycin

The Committee noted that supplies of the second International Standard for Streptomycin were becoming depleted and that the National Institute for Biological Standards and Control, London, had taken steps to replace it.[2] A suitable preparation of streptomycin sulfate had been obtained as a dry powder but because of its hygroscopic nature it had been dissolved, dispensed into ampoules as an aqueous solution, and

[1] Unpublished working document WHO/BS/77.1170.

[2] Unpublished working document WHO/BS/77.1168.

REFERENCE REAGENTS

37. Leptospira Reference Sera

The Committee noted that the importance of leptospirosis as a zoonosis is becoming more fully understood and that there is a need for reference sera against a greater number of leptospiral serotypes.[1] Only 58 of a possible 164 serotype antisera are available or in the course of preparation.

The Committee requested the Central Veterinary Laboratory, Weybridge, to find out whether additional sera exist in the reference centres and to determine whether additional materials could be prepared so that all such sera can be made available in view of their importance in human and veterinary medicine.

REQUIREMENTS FOR BIOLOGICAL SUBSTANCES

38. Requirements for the Collection, Processing and Quality Control of Human Blood and Blood Products

The Committee noted that in accordance with the request in its twenty-eighth report[2] proposed requirements for the collection, processing, and quality control of human blood and blood products had been prepared.[3] They contained five parts.

Part A. Requirements for the collection of source materials.
Part B. Requirements for single donor and small pool products.
Part C. Requirements for the manufacture of blood products and related substances.
Part D. Requirements for the control of plasma fractions.
Part E. National control requirements.

The Committee agreed that each part was important and must be considered in conjunction with the other parts of the document. In order to achieve common standards of good manufacturing practice the requirements applied to all establishments whether they were carrying out all or only part of the functions of collection and fractionation.

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[1] Unpublished working document WHO/BS/77.1177.
[2] WHO Technical Report Series, No. 610, 1977, p. 20.
[3] Unpublished working document WHO/BS/77/1144 Rev. 1.

After making a number of minor amendments to the document, the Committee adopted the Requirements for the Collection, Processing and Quality Control of Human Blood and Blood Products and agreed that they should be annexed to this report (Annex 1).

39. Requirements for Meningococcal Polysaccharide Vaccine

The Committee was informed that several technical developments had taken place in the production of meningococcal polysaccharides in the past year and that these had important implications for the Requirements for Meningococcal Polysaccharide Vaccine. The Committee noted that the main development was an improvement of the stability of the Group A polysaccharide brought about by the addition of lactose.[1] The Committee was informed that the Requirements, formulated in 1975 and revised in 1976, now required further revision. In order to avoid the need to refer to three documents the Committee agreed that the revisions included in the twenty-eighth report [2] should be included with the latest revisions to form a composite addendum. The Committee adopted the addendum and agreed that it should be annexed to this report (Annex 2).

40. Requirements for Inactivated Influenza Vaccine

The Committee noted that the International Reference Preparation of Influenza Virus Haemagglutinin (Type A) was not typical of the haemagglutinin in the current infectious strains of influenza virus.[3] The preparation was therefore inappropriate for use in the control of haemagglutinin content of inactivated influenza vaccines, and the Committee accordingly discontinued the International Reference Preparation of Influenza Virus Haemagglutinin (Type A).

The Committee agreed that the discontinuation of this reference preparation necessitated changes in the Requirements for Inactivated Influenza Vaccine.[4] The Committee considered the amendments to be made and agreed that they should be annexed to this report (Annex 3).

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[1] Unpublished working document WHO/BS/77.1166.

[2] WHO Technical Report Series, No. 610, 1977, p. 52.

[3] Unpublished working document WHO/BS/77.1147.

[4] WHO Technical Report Series, No. 384, 1968, p. 43.

41. Guidelines for the Preparation and Establishment of Reference Materials and Reference Reagents for Biological Substances

In accordance with a recommendation of a Working Group on the Standardization of Human Blood Products,[1] WHO had formulated Guidelines for the Preparation and Establishment of Reference Materials and Reference Reagents for Biological Substances, for distribution principally to scientific societies.

The Committee noted that the provision of WHO working standards based on the use of a master ampoule system had been suggested for some particular substances. The Committee accepted this proposal and agreed that it would bring well calibrated standards within the reach of many countries that might not otherwise be able to prepare them.

The Committee considered that the guidelines would be most useful to those intending to assist in the establishment of international and national reference materials. After making some minor amendments, it adopted the Guidelines for the Preparation and Establishment of Reference Materials and Reference Reagents for Biological Substances and agreed that they should be annexed to this report (Annex 4).

42. Requirements for Rabies Vaccine for Veterinary Use

The Committee noted that very few countries in the world were considered to be free of rabies.[2] The Committee was informed that vaccination of domestic animals in affected countries plays an essential part in the control of the disease in both animal and human populations.

Although Requirements for Rabies Vaccine for Human Use have been formulated [3] they are not entirely appropriate for vaccines used in animals. The Committee agreed that similar requirements for veterinary use were needed and asked WHO to take the necessary steps to draw them up.

43. The Need for Revision of Some Requirements for Biological Substances

The Committee noted that as a result of several advances in technology a number of tests in several requirements are no longer in current

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[1] WHO Technical Report Series, No. 610, 1977, Annex 1, pp. 40–41.

[2] Unpublished working document WHO/BS/77.1159.

[3] WHO Technical Report Series, No. 530, 1973, p. 22.

use.[1] Furthermore, some additional tests are now necessary, especially where new cell substrates are being used or where further potential contaminating organisms could now be detected. The Committee agreed that some of the requirements formulated more than 10 years ago should be revised and asked WHO to undertake this task. The requirements involved are :

Requirements for Diphtheria and Tetanus Toxoid
Requirements for Pertussis Vaccine
Requirements for Dried BCG Vaccine
Requirements for Rabies Vaccine for Human Use
Requirements for Poliomyelitis Vaccine (inactivated).

44. Requirements for Snake Antivenins

The Committee noted that the Requirements for Snake Antivenins were limited in their scope [2] and was informed that many developing countries had asked for requirements that are appropriate for venins from a greater variety of snakes as well as for those from scorpions and spiders.

The Committee agreed that a revision broadening the scope of these requirements was needed and asked WHO, in consultation with the recently established WHO Collaborating Centre for the Control of Antivenins at the School of Tropical Medicine, Liverpool, to take the necessary steps to draw up such requirements.

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[1] Unpublished working document WHO/BS/77.1153.
[2] Unpublished working document WHO/BS/77.1162.

Annex 1

REQUIREMENTS FOR THE COLLECTION, PROCESSING AND QUALITY CONTROL OF HUMAN BLOOD AND BLOOD PRODUCTS[1]

(Requirements for Biological Substances No. 27)

[1] Prepared by a team of WHO consultants and staff members whose names are given in Appendix 1.

INTRODUCTION

In the past a number of documents of the World Health Organization have been concerned with whole blood and its components, but each one has concentrated on guidelines mainly concerned with blood transfusion services and except for human immunoglobulin none has dealt with the requirements applicable to the quality control of whole blood and blood products.

A WHO Working Group on the Standardization of Human Blood Products and Related Substances [1] considered that there was an urgent need for international requirements for the processing and control of whole human blood and blood products. It emphasized that, as the quality of the source material played an important part in the quality of the final products, such requirements should cover all stages, from the collection of source materials to the quality control of the final product.

In the compilation of these international requirements for human blood products, advice and data from a number of experts have been taken into account. The names of these experts are given in Appendix 2.

GENERAL CONSIDERATIONS

The setting up of an organization for the collection and fractionation of human blood and blood components calls for a great deal of expertise

[1] WHO Technical Report Series, No. 610, 1977, p. 24 (Annex 1).

and considerable investment. Any country contemplating the establishment of such an organization should carry out a careful cost-benefit analysis to determine whether the investment is justified. The collection and distribution of whole blood, the separation of whole blood into components, and the fractionation of plasma batches is a logical developmental sequence for a comprehensive organization. It is not always possible to be specific about the details of the procedures employed, the in-process controls, or the tests applied at each stage of production. This is particularly the case with whole blood and component cells. Although the general principle of fractionation of plasma is well established, there are in practice numerous variations in the details of the various production steps. Therefore, any country wishing to begin the collection and fractionation of blood and blood components should send personnel for training to a plant that is operating successfully. WHO can help in arranging such training.

It would not be possible to rely on any product unless the relevant requirements for each step are complied with, and any attempt to reduce these requirements may have serious consequences for the safety of the final product. It is recommended, therefore, that these requirements be applied as a complete document.

One of the basic questions to be answered in considering whether the fractionation of plasma should be started is whether the country has a suitable donor population of sufficient size to guarantee an adequate supply of source material. It is not possible to set a lower limit for the quantity of source material that would be necessary to make such an operation economic because too many factors are involved. In order to maintain competence in production and to avoid certain contamination risks, it is important to have sufficient source material to maintain the fractionation facility in continual operation. In general it would be difficult to justify setting up a plant unless at least 250 litres or 1000 donor pools of plasma are available for fractionation at regular intervals. Even with this amount the fractionation plant would be working on a small scale, but it could serve as the basis for later expansion to a much larger project. Alternatively it could be used for specialized national services, or it could form part of an integrated service organized on a regional basis with neighbouring countries.

The greatest expense involved is in setting up the fractionation plant, but it would be possible to consider the collection of source material and the fractionation as quite separate operations. A country may wish to establish collection centres to separate the cell components and send the plasma to an established fractionation centre in another country. The

products would then be returned to the original country and the costs involved in this operation might be less than those needed to establish and operate a fractionation plant.

The general prevalence of viral diseases, such as various forms of hepatitis, and of parasitic diseases differs so markedly in different geographical regions that each national authority must decide for itself whether the application of the most sensitive test on each blood donation is cost-effective and whether it is feasible to collect suitable source material. A brief protocol of the collection of source material is in any case mandatory (see Appendix 3). In countries where the prevalence of hepatitis B virus (HBV) and parasitic diseases is so high that the supply of the most suitable source material is markedly restricted, greater emphasis should be placed on the production of fractions made by a process that experience has shown causes the least risk of contamination. For example, immunoglobulin prepared by the cold ethanol fractionation method of Cohn has a well established reputation of being free from contamination with HBV, as have albumin products prepared by the same method and heated for 10 hours at 60°C.[1] Nevertheless, the assurance of freedom of these products from infectious viruses requires extreme care in manufacture and cannot be assumed when new fractionation methods are introduced.

When source material with a high risk of contamination is handled, special care should be given to the protection of the health of the staff and appropriate protective measures approved by the national control authority insisted upon.

The transport of source materials from blood collecting centres and hospitals to the fractionation facilities requires special consideration. Thus refrigeration at the temperature range appropriate for the product must be efficient and reliable and proved to be so by monitoring. Thermal insulation must be adequate as a safeguard against a temporary failure of refrigeration. Containers of liquid source material should be filled so as to diminish frothing due to shaking. Because of the potentially infective nature of these biological materials, suitable safeguards should be taken in the event of breakage, spillage, or leakage of containers.

In this document the qualifying word " human " has been dropped from the names of the products derived from human blood. Blood products of animal origin are immunogenic, and their administration to man should be avoided wherever an equivalent product of human origin

[1] WHO Technical Report Series, No. 602, 1977, p. 45.

could be used in its place. Any such products of nonhuman origin should now carry the species of origin in its proper name. In order to avoid confusion while the recommendation is being implemented, it is advised that for an interim period national authorities introduce the animal species in the proper names of animal products before the qualification " human " is dropped.

These requirements have been formulated in the following five parts.

A. Requirements for the collection of source materials.
B. Requirements for single-donor and small-pool products.
C. Requirements for the manufacturing of human blood products.
D. Requirements for the control of plasma fractions.
E. National control requirements.

Each deals with a separate part of the whole process but all the parts taken together are intended to make a composite document.

The parts are divided into sections, each of which constitutes a recommendation. Text printed in type of normal size is written in the form of requirements so that, if a health administration so desires, these parts as they appear may be included in definitive national requirements. Paragraphs printed in small type are comments and recommendations for guidance.

Should individual countries wish to adopt these requirements as the basis for their national regulations concerning blood products and related substances, it is recommended that a clause be included that would permit manufacturing requirements to be modified on the condition that it be demonstrated, to the satisfaction of the national control authority, that such modified requirements ensure a degree of safety and efficacy of the products at least equal to that provided by the requirements formulated below. It is desirable that the World Health Organization should then be informed of the action taken.

The terms " national control authority " and " national control laboratory " as used in these requirements, always refer to the country in which the product is collected, manufactured or used, as appropriate.

Rapid technological developments in the measurement of biological activity of blood products and related substances require the establishment of international biological reference materials. The first two international reference materials (for anti-A and anti-B blood typing sera) were established in 1950, and a further six reference materials have been established in the last seven years. There are a number of materials currently under investigation for the preparation of new standards.

Furthermore, the increased demand for the use of blood products is resulting in the extensive movement of such products between countries. Internationally accepted requirements are therefore necessary in order that countries without any regulations concerning blood products and related substances may refer to these requirements when importing such products.

International standards and international reference preparations

The activity of blood and blood products shall be expressed in international units where an international standard or international reference preparation exists.

A list of international standards and international reference preparations appropriate for the control of blood products and related substances is given in Appendix 4.

These standards are in the custody of the laboratories in Copenhagen, London, Amsterdam and Bilthoven mentioned in Appendix 4.

Samples are distributed free of charge on request to national control laboratories. The international standards are intended for the calibration of national standards for use in the manufacture and laboratory control of human blood and blood products.

PART A:

REQUIREMENTS FOR THE COLLECTION OF SOURCE MATERIALS

A.1. DEFINITION OF CENTRES, ACTIVITIES AND SOURCES

A.1.1 Centres for the collection of source material

The following definitions are intended for use in this document and are not necessarily valid for other purposes.

Blood donor centre : an establishment in which blood and/or blood components are obtained from donors.

Placenta collecting centre : an establishment in which placentas and/or retroplacental blood or parts of either are received from hospitals, accumulated and stored.

A.1.2 Activities of collection centres

Blood collection : a procedure by which a single donation of blood is collected either in an anticoagulant and stabilizing solution or in a container of a kind that permits the separation of serum from coagulated blood.

Processing : any procedure used after collection and before compatibility testing with a prospective recipient.

Plasmapheresis and cytopheresis : procedures by which whole blood is separated by physical means into components and one or more of them returned to the donor.

A.1.3 Donors

Blood donor : a suitable person who gives blood.

A.1.4 Single-donor materials

Whole blood (sometimes referred to as " blood ") : the blood collected in an anticoagulant solution with or without the addition of nutrients such as glucose or adenine.

Whole blood, plasma-reduced (sometimes referred to as " plasma-reduced blood ") : the whole blood in which the erythrocyte volume fraction (" packed cell volume ") has been elevated to approximately 0.6 by the removal of plasma.

Whole blood, modified : the whole blood from which plasma has been separated for the purpose of obtaining cryoprecipitate, platelets, or leukocytes and the plasma returned to the blood cells.

Blood component : any part of blood separated from the rest by physical procedures.

Plasma : the liquid part of blood collected in a receptacle containing an anticoagulant.

Plasma, fresh frozen : a plasma frozen within 6 hours of donation and stored below −20°C (and preferably below −30°C).

Plasma, frozen : a plasma obtained from whole blood within a specified short time (but longer than 6 hours) of collection and maintained in the frozen state below −20°C (and preferably below −30°C).

Plasma, platelet-poor : a plasma from which most platelets have been removed.

Plasma, specific immune : a plasma that can be used either for passive immunization or for the manufacture of specific immunoglobulins.

Plasma, freeze-dried : any of the above forms of plasma that have been freeze-dried for preservation.

Plasma, recovered : a plasma that does not meet the requirements of " plasma, fresh frozen " or " plasma, frozen " and is intended for further processing.

Plasma, platelet-rich : a plasma containing at least 70% of the platelets of the original whole blood.

Cryoprecipitated Factor VIII : a preparation of Factor VIII that is obtained either from plasma from whole blood or by plasmapheresis, through a process involving chilling and precipitation.

Serum : the liquid part of coagulated blood or plasma.

Specific immune serum or plasma : a serum that can be used either for passive immunization or for the manufacture of specific immunoglobulins.

Red cell concentrate : whole blood from which most of the plasma has been removed and having an erythrocyte volume fraction (" packed cell volume ") greater than 0.7.

Red cell concentrate, washed : a red cell concentrate from which most of the plasma, leukocytes and platelets have been removed by one or more stages of washing with an isotonic solution.

Red cell concentrate, leukocyte-poor : a red cell concentrate containing at least 80% of the red cells and less than 25% of the leukocytes of the original whole blood.

Red cell concentrate, frozen : a frozen red cell concentrate to which a cryoprotective agent such as glycerol has been added prior to freezing.

Red cell concentrate, deglycerolized : a red cell concentrate, frozen, that has been thawed and has had the glycerol removed by washing.

Platelet-concentrate : platelets obtained either by separation of whole blood or by pheresis and suspended in a small volume of autologous plasma.

Leukocyte concentrate : a concentrate of leukocytes obtained either by the separation of whole blood or by pheresis and suspended in autologous plasma.

A.1.5 Postpartum source materials

Placenta : the placenta with or without the retroplacental blood from a single delivery.

Placental blood : the blood expressed from the placenta.

Retroplacental blood : uterine blood collected during and after delivery.

Retroplacental serum : the liquid part of the coagulated retroplacental blood.

A.2. PREMISES

The premises shall be of suitable size, construction, and location to facilitate their proper operation, cleaning, and maintenance in accordance with accepted rules of hygiene. They shall comply with the revised Requirements for Biological Substances No. 1 (General Requirements for Manufacturing Establishments and Control Laboratories) [1] and in addition provide adequate space, lighting, and ventilation for the following activities where applicable :

(1) Medical examination of individuals to determine their fitness as donors of blood and/or blood components.

(2) Withdrawal of blood from donors and, where applicable, reinfusion of the components with minimum risk of contamination and errors.

(3) Care of donors, including the treatment of those who suffer reactions.

(4) Storage of whole blood and blood components in quarantine pending completion of processing and testing.

(5) Laboratory testing of blood and blood components.

(6) Processing and distribution of whole blood and blood components in a manner that prevents contamination, loss of potency, and errors.

(7) Performance of all steps in pheresis procedures.

(8) Labelling, packaging, and other finishing operations in a manner that prevents errors.

(9) Storage of equipment.

(10) Storage of finished products prior to distribution.

(11) Documentation and recording of data on the donor, the donated blood, and the ultimate recipient.

[1] WHO Technical Report Series, No. 323, 1966, p. 13.

The collection of blood can be achieved by mobile teams. Although the premises used by such teams may not comply with the more stringent requirements for centres built specially for the purpose, the facility must be adequate for the safety of both the donor and the collected blood or blood components.

A.3. EQUIPMENT

Equipment used in the collection, processing, storage, and distribution of blood and blood components shall be kept clean and shall be maintained and checked regularly. The revised Requirements for Biological Substances No. 1 (General Requirements for Manufacturing Establishments and Control Laboratories) [1] shall apply in every particular.

Equipment employed to sterilize materials used in blood or blood component collection or for the disposal of contaminated products shall ensure the destruction of contaminating microorganisms. The effectiveness of the sterilization procedure shall be not less than that achieved by a temperature of 121.5°C maintained for 20 minutes by saturated steam at a pressure of 103 kPa (1.05 kgf/cm^2 or 15 lbf/in^2) or by a temperature of 170°C maintained for two hours with dry heat.

Tests for sterility are indicated in the International Pharmacopoeia.[2]

The disposal of contaminated material should comply with the local by-laws controlling such procedures.

A.4. PERSONNEL

A blood or blood component collection organization shall be under the direction of a designated qualified person who shall be responsible for ensuring that all operations are carried out properly and competently. The director shall have an adequate knowledge and experience of the scientific and medical principles involved in the procurement of blood and, if applicable, the separation of blood components and the collection of plasma by plasmapheresis.

The director shall be responsible for ensuring that employees are adequately trained and acquire practical experience and that they are

[1] WHO Technical Report Series, No. 323, 1966, p. 13.

[2] *Specifications for the quality control of pharmaceutical preparations ; second edition of the International Pharmacopoeia.* Geneva, World Health Organization, 1967, p. 747.

aware of the application of accepted good practice to their respective functions.

The director should have the authority to enforce or to delegate the enforcement of discipline among employees.

The persons responsible for the collection of the blood and blood components shall be supervised by licensed physicians who shall be responsible for all medical decisions.

The personnel responsible for the processing, storage, distribution, and quality control of blood, blood components, and plasma shall be adequate in number, and each shall have a suitable educational background and training or experience to assure competent performance of assigned functions so that the final product has the required safety, purity, potency, and efficacy.

A.5. THE COLLECTION OF BLOOD AND BLOOD COMPONENTS

A.5.1 The selection of donors

Source materials for further processing are obtained from donations of blood or its components. The medical criteria for accepting donors—criteria relating to the safety, purity, potency, and efficacy of the final products—must be the same for donors of whole blood and of cellular components or blood components collected by pheresis.

Blood from donors with glucose-6-phosphate dehydrogenase deficiency, sickle-cell trait, or other inherited erythrocyte abnormalities may give rise to transfusion reactions under certain circumstances. Decisions regarding the suitability of such donors should be made by the national control authority.

A.5.2 Donors of whole blood

The physical fitness of a donor shall be determined by a licensed physician or a person under the direct supervision of a licensed physician. Donors shall be healthy persons of either sex between the ages of 18 and 65 years. The frequency of donations shall not exceed one every two months, with a maximum volume in any consecutive 12-month period of 2 litres.

The recruitment of volunteer (non-remunerated) donors should be the aim of any national blood programme. In some countries

the upper and lower age limits of the donors may differ from 18 and 65 years.

The frequency of donation may have to be modified on an individual basis, and, in general, premenopausal female donors may be bled less frequently than males. Donors should be within normal weight limits (see section A.5.4).

A.5.3 Medical history

A.5.3.1 *General*

Before each donation questions shall be asked to determine that the donor is in normal health and has not suffered, or is not suffering, from any serious illness, e.g., malignant disease, diabetes, epilepsy, hypertension, renal disease.

Any donor who appears to be suffering from symptoms of acute or chronic disease or who is receiving oral or parenteral medication, with the exception of vitamins or oral contraceptives, may not be accepted for donation unless approved by a physician.

Any donor who appears to be under the influence of alcohol or any drug or who does not appear to be providing reliable answers to medical history questions shall not be accepted.

A.5.3.2 *Infectious diseases*

Donors shall have a negative history of viral hepatitis, of close contact with an individual with hepatitis within the past six months, of receipt within six months of human blood or any blood component or fraction that might be a source of transmission of viral hepatitis, or of tattooing within six months.

Acupuncture within six months may also present a risk.

In some countries donors with a history of viral hepatitis or of a positive test for hepatitis B surface antigen are permanently excluded. In other countries such donors are accepted providing that recovery occurred longer than one year previously and that the reaction for hepatitis B surface antigen is negative when tested by a sensitive technique.

Any donor shall be permanently excluded if a previous blood donation given by him was the only unit of whole blood or of a blood component administered to a patient who developed hepatitis within six months and who received no other blood fractions capable of hepatitis transmission during this period.

Donor populations showing a prevalence of acute or chronic hepatitis higher than that found in the general population should be avoided for collection both of single donor products (whole blood and its components) and of plasma for pooling for the manufacture of plasma fractions known to be capable of transmitting hepatitis, such as clotting factor concentrates.

Countries with a low incidence of hepatitis should not use whole blood or blood products obtained from source material collected from an area in which there is a high incidence of hepatitis.

The testing of blood or plasma for the presence of hepatitis B surface antigen shall be done by methods described in section B.1.

National health authorities shall develop policies designed to prevent the transmission of other infectious diseases based on the prevalence of these diseases in the donor population and the susceptibility of recipients to the same diseases.

In countries where malaria is not endemic, donors should have a negative history of malaria exposure during the past six months and a negative history of clinical malaria or malaria prophylaxis while residing in an endemic area within three years of donation. Such restrictions may be less important in countries where a high level of endemic malaria is present in both donors and recipients, except when blood products are required by visitors from non-endemic areas.

Other diseases that can be transmitted by blood include syphilis, brucellosis, trypanosomiasis (Chagas' disease), infectious mononucleosis, and cytomegalovirus infection. Precautions should be taken to avoid blood collection from persons known to have suffered acute or chronic brucellosis or trypanosomiasis in areas where these diseases are prevalent. Spread of herpes viruses (Epstein-Barr virus and cytomegaloviruses) by blood transfusion is a hazard not easily avoided owing to the high prevalence of asymptomatic chronic infection with these agents in the general population.

A.5.3.3 *Minor surgery*

Donors shall have a negative history of tooth extraction or other minor surgery during a period of 72 hours prior to donation.

A.5.3.4 *Pregnancy*

Pregnant women shall be excluded from blood donation. In general, mothers shall also be excluded for the period of lactation and for at least six months after full-term delivery.

The interval following pregnancy may be shorter in some cases—e.g., six weeks following an abortion during the first trimester.

In some countries donors are accepted when pregnant or during the period of lactation when the blood contains rare blood group antibodies. The volume to be taken should be determined by the physician responsible.

A.5.3.5 *Immunization*

Symptom-free donors who have recently been immunized may be accepted with the following exceptions.

- Those receiving smallpox vaccine shall be excluded until the scab has fallen off or until two weeks after an immune reaction.
- Those receiving attenuated vaccines for measles (rubeola), mumps, yellow fever, or poliomyelitis shall be excluded until two weeks after the last immunization or injection.
- Those receiving attenuated rubella (German measles) vaccine shall be excluded until eight weeks after the last injection.
- Those receiving rabies (therapeutic) vaccine or immunoglobulin shall be excluded until one year after the last injection.
- Those receiving passive immunization using animal serum products shall be excluded until four weeks after the last injection.

A.5.4 Physical examination

Donors shall have a weight, blood pressure, pulse rate, and temperature within normal limits. Donors with any measurements outside the established normal limits of weight, blood pressure, and pulse rate may be accepted only if approved by the responsible licensed physician.

The following recommendations may be useful for guidance:

(1) Blood pressure. Systolic blood pressure between 12 and 24 kPa (90 and 180 mmHg); diastolic blood pressure between 6.67 and 13.3 kPa (50 and 100 mmHg).

(2) Pulse. Between 50 and 100 beats per minute and regular.

(3) Temperature. Oral temperature not exceeding 37.5°C.

(4) Weight. Donors weighing less than 50 kg may be bled proportionately less than 450 ml in an appropriate volume of anticoagulant, provided all other donor requirements are met.

In some countries it is not required to take the body temperature but such decisions should be made by the national control authority.

Donors shall be free from any infectious skin disease at the venepuncture site and of skin punctures or scars indicative of addiction to narcotics.

A.5.5 Haemoglobin or haematocrit determination

The haemoglobin shall be not less than 125 g/l of blood for women and 135 g/l of blood for men or the haematocrit, if substituted, shall be not less than 38% or 41% respectively.

These limits are not universally accepted, and national control authorities should raise or lower them when appropriate.

A.5.6 Donors for plasmapheresis

All phases of plasmapheresis, including explaining to donors what is involved in the process and obtaining their informed consent, shall be performed under the direct supervision of a licensed physician.

There are two groups of plasmapheresis donors : those who donate at a frequency comparable to that allowed for whole blood donations and those who donate more frequently. The former group shall be accepted on the basis of the above criteria for donors of whole blood.

In addition to these criteria, donors participating in a more frequent plasmapheresis programme shall be examined by a licensed physician on the day of the first donation, or no more than one week prior to the first donation. This examination shall include urine analysis and blood sampling for liver function tests, a serological test for syphilis, and determination of plasma proteins by electrophoresis or another suitable method.

On the day of each donation, in addition to meeting the requirements for whole blood donors, plasmapheresis donors shall be shown to have a total serum protein of no less than 60 g/l.

The medical evaluation of plasmapheresis donors shall be repeated at regular intervals, as specified by national control authorities. The interval between physical and laboratory examinations shall not exceed four months.

Whenever a laboratory value is found outside the established normal limits or a donor exhibits any important abnormalities of history or on physical examination, the donor shall be removed from the programme. The donor shall not return to the programme until the abnormal finding has returned to normal and the responsible physician has given approval.

In the event that a plasmapheresis donor donates a unit of whole blood or does not have the red blood cells returned from a unit taken

during the procedure, the donor shall be deferred for eight weeks unless special circumstances warrant approval by the responsible physician of earlier plasmapheresis.

In general, plasma collected by therapeutic plasmapheresis shall not be used for fractionation.

There may be individual exceptions to this last requirement—e.g., plasma collected by intensive plasmapheresis during pregnancy of patients with high levels of anti-Rh_0 (anti-D) immunoglobulin.

It is difficult to state the maximum volumes of plasma that can be safely collected from donors until more definitive data are available on the effects of plasmapheresis on donors. In 1967 the Subcommittee of Specialists on Blood Problems, of the Council of Europe, recommended that no more than 8 single units of plasma (each of approximately 300 ml) should be removed in one month, and not more than 50 single units should be removed in one year.[1] However, different limits are imposed in certain countries, e.g., USSR and France : 10 litres per year ; USA : 50 and 60 litres per year for donors weighing respectively below and above 80 kg.

A.5.7 Donors for plateletpheresis and leukopheresis

In general, plateletpheresis and leukopheresis donors shall meet the criteria for whole blood and plasmapheresis donors.

The optimum conditions for performing plateletpheresis and leukopheresis to assure donor safety and satisfactory quality of the products are under active investigation in many countries. The following recommendations may be useful for guidance.

On the day of each donation, plateletpheresis donors should have an absolute platelet number concentration (" count ") of not less than 100×10^9/l and leukopheresis donors should have an absolute granulocyte number concentration of not less than 1.5×10^9/l. Both types of donor should have a normal leukocyte type number fraction (" differential count ").

Recovery of circulating platelet and leukocyte levels occurs promptly in donors, but data are not at present available to define the maximum numbers of platelets and leukocytes that can be safely collected from donors.

Leukopheresis may entail the administration of drugs to donors and their exposure to colloidal agents in order to enhance the yield of granulocytes. Appropriate precautions should be taken to protect the donors, such as investigation for latent diabetes by a glucose tolerance test on those who are to be given corticosteroids.

[1] WHO Technical Report Series, No. 468, 1971, p. 11.

Where leukopheresis is carried out for the treatment of a patient with chronic myeloid leukaemia it should be done only if approved by his attending physician. It is generally considered inadvisable to use the leukocytes from such patients.

A.5.8 Donors for immunization

Immunization of donors shall be carried out only when sufficient supplies of material of suitable quality cannot be obtained by selection of appropriate donors or from donations selected by screening. Donors must be fully informed of the risk of any proposed immunization procedure, and pressure shall not be brought to bear on a donor to agree to immunization. Donors of blood and those undergoing plasmapheresis shall if necessary undergo investigations that may reveal hypersensitivity to a proposed antigen.

When immunization is intended, the donor should be :

(1) informed of the procedures by a licensed physician and encouraged to take part in a free discussion, which in some countries is achieved by informing potential donors initially in small groups of people ;

(2) encouraged to seek advice from his family doctor before agreeing to immunization ;

(3) informed that any licensed physician of his choice will be sent all information about the proposed immunization procedure ; and

(4) required to indicate his agreement by signing an informed-consent form.

A.6 COLLECTION OF BLOOD

In the collection of blood several precautions must be taken, as described in the following sections.

A.6.1 The taking of the blood

The skin of the donor at the site of venepuncture shall be prepared by a method that has been shown to give reasonable assurance that the blood collected will be sterile. The collection of blood into a container shall be done using an aseptic method. The equipment for collecting the sterile blood may be closed or vented provided that the vent is designed to protect the blood against microbial contamination (see section B.1.1).