COUNCIL OF EUROPE

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European Agreement on the Exchange of Therapeutic Substances of Human origin [*] and Protocol thereto

Paris, 15.XII.1958

Preamble

The governments signatory hereto, being members of the Council of Europe,

Considering that therapeutic substances of human origin are by their very nature the result of an act of the human donor and therefore not available in unlimited quantities;

Considering that it is most desirable that member countries, in a spirit of European solidarity, should assist one another in the supply of these therapeutic substances, should the need arise;

Considering that such mutual assistance is only possible if the character and use of such therapeutic substances are subject to rules laid down jointly by the member countries and if the necessary import facilities and exemptions are granted,

Have agreed as follows:

Article 1

For the purposes of this Agreement, the expression "therapeutic substances of human origin" refers to human blood and its derivatives.

The provisions of this Agreement may be extended to cover other therapeutic substances of human origin by exchange of letters between two or more of the Contracting Parties.

Article 2

The Contracting Parties undertake, provided that they have sufficient stocks for their own needs, to make therapeutic substances of human origin available to other Parties who are in urgent need of them and to charge only those costs involved in the collection, processing and carriage of such substances.

(*) Text amended pursuant to the provisions of the Additional Protocol to the European Agreement on the Exchange of Therapeutic Substances of Human origin (ETS No. 109) as from its entry into force, on 1 January 1985.
The Treaty of Lisbon amending the Treaty on European Union and the Treaty establishing the European Community entered into force on 1 December 2009. As a consequence, as from that date, any reference to the European Economic Community shall be read as the European Union.

Article 3

Therapeutic substances of human origin shall be made available to the other Contracting Parties subject to the express condition that no profit is made on them, that they shall be used solely for medical purposes and shall be delivered only to bodies designated by the governments concerned.

Article 4

The Contracting Parties shall certify that the minimum requirements with regard to the properties of the therapeutic substances, and the regulations on labelling, packing and dispatch, as laid down in the Protocol to this Agreement, have been observed.

They shall also comply with any rules to which they have subscribed with regard to international standardisation in this field.

All consignments of therapeutic substances of human origin shall be accompanied by a certificate to the effect that they were prepared in accordance with the specifications in the Protocol. This certificate shall be based on the model to be found in Annex 1 to the Protocol.

The Protocol and its annexes may be amended or supplemented by the governments of the Parties to this Agreement.

Article 5

The Contracting Parties shall take all necessary measures to exempt from all import duties the therapeutic substances of human origin placed at their disposal by the other Parties.

They shall also take all necessary measures to provide for the speedy delivery of these substances, by the most direct route, to the consignees referred to in Article 3 of this Agreement.

Article 6

The Contracting Parties shall forward to one another, through the Secretary General of the Council of Europe, a list of the bodies empowered to issue certificates as provided in Article 4 of this Agreement.

They shall also forward a list of bodies empowered to distribute imported therapeutic substances of human origin.

Article 7

The present Agreement shall be open to the signature of members of the Council of Europe, who may become Parties to it either by:

a signature without reservation in respect of ratification, or
b signature with reservation in respect of ratification followed by ratification.

Instruments of ratification shall be deposited with the Secretary General of the Council of Europe.

The European Economic Community may become a Contracting Party to the Agreement by signing it. In respect of the Community, the Agreement shall enter into force on the first day of the month following such signature.[1]

Article 8

The present Agreement shall enter into force on the first day of the month following the date on which three members of the Council shall, in accordance with Article 7, have signed the Agreement without reservation in respect of ratification or shall have ratified it.

In the case of any member of the Council who shall subsequently sign the Agreement without reservation in respect of ratification, or who shall ratify it, the Agreement shall enter into force on the first day of the month following such signature or deposit of the instrument of ratification.

Article 9

The Committee of Ministers of the Council of Europe may invite any non-member State to accede to the present Agreement. Such accession shall take effect on the first day of the month following the deposit of the instrument of accession with the Secretary General of the Council of Europe.

Article 10

The Secretary General of the Council of Europe shall notify members of the Council and acceding States:

a of the date of entry into force of this Agreement and of the names of any members who have signed without reservation in respect of ratification or who have ratified it;

b of the deposit of any instrument of accession in accordance with Article 9;

c of any notification received in accordance with Article 11 and its effective date;

d of any amendment to the Protocol or its annexes under Article 4, paragraph 4.

Article 11

The present Agreement shall remain in force indefinitely.

Any Contracting Party may terminate its own application of the Agreement by giving one year's notice to that effect to the Secretary General of the Council of Europe.

In witness whereof the undersigned, duly authorised thereto by their respective governments, have signed the present Agreement.

Done at Paris, this 15th day of December 1958, in the English and French languages, both texts being equally authoritative, in a single copy which shall remain deposited in the archives of the Council of Europe. The Secretary General shall transmit certified copies to each of the signatory and acceding governments.

(1) Text amended pursuant to the provisions of the Additional Protocol to the Convention (ETS No. 109).

Protocol to the European Agreement on the Exchange of Therapeutic Substances of Human origin *

Part I

General provisions

A. Labelling

A label printed in English and French, based on the appropriate model to be found in Annexe 2 to 10 to the Protocol, shall be affixed to each container or giving-set.

B. Packing and dispatch

Whole human blood shall be dispatched in containers in which a temperature of 4° to 6°C is maintained throughout the period of transport.

This condition is not required for the derivatives mentioned in the Protocol.

C. Products and apparatus

The products and apparatus referred to in Part II of this Protocol shall be sterile, non pyrogenic and non-toxic.

It is recommended that the giving-set, as well as the solvents required for the dried products, be sent with each consignment.

D. Freedom from toxicity of plastic blood transfusion equipment

Equipment shall comply with the provisions set out in Annex 11 to this Protocol.

Part II

Special provisions

I. Whole Human Blood

Whole Human Blood is blood which has been mixted with a suitable anti-coagulant, after collection from a human subject in normal health.

The blodd shall not be obtained from a human subject :

a) who is known to be suffering from or to have suffered from syphyllis or hepatitis,

b) whose blood has bot been tested with negative results for evidence of syphillitic infection, or

(1) Revised text as adopted by the Committee of Ministers at its 318th meeting (28-30 April 1980).

c) who is not, as far as can be ascertained after medical examination and the study of his antecedents, free from disease transmissible by blood transfusion

The blood shall be withdrawn aseptically through a closed system of sterile tubing into a sterile container in which the anticoagulant solution has been placed before the container is sterilised. The equipment used must be pyrogen-free. When withdrawal is complete, the container shall be immediately sealed and cooled up to 4° to 6° C and not opened thereafter until immediately before the blood is to be used.

The blood will be collected into a citrate solution of acid reaction containing dextrose. No antiseptic or bacteriostatic substance shall be added. The volume of the anticoagulant solution must not exceed 220 ml per litre of the Whole Human Blood and the haemoglobin concentration must not less than 97 gram per litre.

Blood group – The blood group under the ABO system shall have been determined by examination of both corpuscles and serum and that under the Th system by examination of the corpuscles, using a separate sample of the donor's blood. When there is a national standard, or nationaly recommended technique of blood grouping, that technique shall be used.

The term Rh negative is only to be used when specific tests have shown the absence of the antigens C, D, D^u and E. All other blood must be labelled Rh positive.

Blood exchange under this agreement should only be used for recipients of the corresponding ABO group.

Storage –Whole human blood shall be kept in a sterile container sealed so as to exclude micro-organisms and stored at a temperature of 4° to 6° C until required or use, except during any period necessary for examination and transport at higher temperatures, any such period not to exceed thirty minutes after which the blood must immediately be cooled again to 4° to 6° C.

Labelling – The label on the container shall give all the information shown on the model label (Annex 2). The Rhesus group shall be written as "Positive" or "Negative" or, in abbreviated form, "POS" or "NEG".

1bis. Human red cell concentrate

A human red cell concentrate is a unit of Whole Human Blood from which most of the plasma has been removed.

It contains most of the red cells of the unit from which it has been prepared ; other cell components may be present or may have been partially removed.

The liquid content of the concentrate will consist either of the residual plasma, or of an appropriate isotonic artificial aqueous solution added after the plasma was removed. The volume of red cells should constitute between 65 and 75 % of the total volume of the product, but if a greater red cell concentration is applied the approximate percentage of erythrocyte volume (haematocrit) shall be indicated on the label.

All operations required in the preparation shall be carried out under aseptic conditions: decantation shall be carried out using a sterile, closed system and by compression only. No antiseptic or bacteriostatic agents should be added.

Blood group and storage – as for Whole Human Blood.

Labelling – The label on the container shall give all the information shown on the model label (Annex 2bis). The Rhesus group shall be written as "Positive" or "Negative" or, in abbreviated form, "POS" or "NEG". If an artificial aqueous solution has been added, the label shall also indicate its volume and composition.

2. Dried Human Plasma

Dried Human Plasma is prepared by drying the supernatant fluids which are separated by centrifuging or by sedimentation from quantities of Whole Human Blood.

During preparation no antiseptic or bacteriostatic or other substances shall be added. Dried Human Plasma shall be obtained by freeze-drying or by any other method which will avoid denaturation of proteins. The dried product shall be readily soluble in a quantity of water equal to the volume of the liquid from which the substance was prepared. The protein concentration of the solution thus obtained must not be less than 45 gram per litre, and must not show visible evidence of the products of haemolysis. The haemaglutinin titre shall not be greater than 1:32.

Dried Human Plasma prepared from one or two donations of blood

Donations shown to contains dangerous levels of iso-haemolysins (determined using a sample of fresh serum) or any immune haemaglutinins shall be excluded. Unless the plasma is pooled and frozen within 48 hours of collecting the blood, the sterility of each unit shall be tested by culturing not less than 10 ml.

Dried Human Plasma prepared from pools of more than two donations

Pools shown to contain dangerous levels of immune haemaglutinis or of iso-haemolysins shall be excluded. To avoid untoward effects due to the products of bacterial growth in the plasma no individual donation shall be used if there is any evidence of bacterial contamination, and the sterility of each pool shall be tested by culturing not less than 10 ml. To minimize the risk of transmitting serum hepatitis, plasma should be prepared from pools which should contain not more than twelve donations, or by any other method that has been shown to diminish the risk in comparative manner.

Solubility in water – Add a quantity of water equal to the volume of the liquid from which the sample was prepared; the substance dissolves completely within 10 minutes at 15° to 20° C.

Identification – Dissolve a known quantity of the product in a volume of water equal to the volume of the liquid from which it was prepared; the solution passes the following tests :

i) by precipitation tests with specific antisera, it must be shown to contain only human plasma proteins;

ii) to 1 ml add a suitable amount of thrombin or calcium chloride; coagulation occurs, which can be accelerated by incubation at 37° C.

Loss of mass on drying – When dried over phosphorus pentoxide at a pressure not exceeding 0.02 mm of mercury for 24 hours, Dried Human Plasma must not lose more than 0.5 % of its weight.

Sterility – The final product, after reconstitution, shall be sterile when examined by a suitable bacteriological method.

Storage – Dried Human Plasma must be kept in an atmosphere of nitrogen or in a vacuum in a sterile container sealed so as to exclude micro-organisms and, as far as possible, moisture, protected from light and stored at a temperature below 20° C.

Labelling – The label on the container shall give all the information shown on the model label (Annex 3).

3. Human Albumin and Human Plasma Protein Fraction

Human Albumin and Human Plasma Protein Fraction are preparations of that protein component which forms about 60% of the total protein mass in the plasma of Whole Human Blood.

The method of preparation used shall be one which produces a material meeting the requirements herein described. Regardless of whether the final product is liquid or dried, the preparation, after the addition of a suitable stabilising agent or agents, must have been heated in the liquid state in the final container at 60° C ± 0.5° C for 10 hours, in order to inactivate the agent causing serum hepatitis. During preparation no antiseptic or bacteriostatic substance shall be addd.

In preparations of Human Albumin, not less than 95 % of the mass of the proteins present shall be albumin. In preparations of Human Plasma Protein Fraction, not less than 85% of the protein shall be albumin. In both preparations, more than 10 milligram immunoglobulin G per gram product shall be present.

When the final product is freeze-dried, it must contain not less than 950 milligram of protein per gram product.

When Human Plasma Protein Fraction is prepared as a solution it shall have a total protein concentration between 45 and 50 grams per litre.

When Human Albumin is prepared as a solution it shall have a total protein concentration not less than 45 gram per litre.

Solubility of the dried product – Add water to the recommended volume; the dried preparation must be completely soluble.

Stability – By comparison of the solutions before and after heat treatment no evidence of significant denaturation of the proteins in solution shall have been detected as estimated by viscosity and turbidity measurements, ultracentrifugation and electrophoresis. The solution shall be substantially free from visible particles after heating at 57° C and after agitation in a mechanical shaker for 6 hours at this temperature.

Identification –

i) By precipitation tests with specific antisera, both preparations must be shown to contain only human plasma proteins.

ii) By electrophoresis, using the moving boundary technique under acceptable and appropriate conditions, it must be shown that the protein fraction having the mobility of the albumin component of normal human plasma, is not less than 95 % of the protein mass in preparations of Human Albumin, or not less than 85% of the protein mass in preparations of Human Plasma Protein Fraction.

Sodium content and sodium concentration – The sodium content of salt-poor Human Albumin must not exceed 0.61 millimole per gram of albumin. In other preparations of Human Albumin and in Human Plasma Protein Fraction, the sodium concentration must not exceed 0.15 mole per litre of solution or reconstituted dried product.

Potassium concentration – The potassium concentration of Human Plasma Protein Fraction must not exceed 2 millimole per litre of solution or reconsituted dried product

Acidity – The pH of either preparation shall be 6.8 ± 0.2 when measured at a temperature of 15 to 25° C in a solution diluted to a protein concentration of 10 gram per litre by means of a solution containing 0.15 mole sodium chloride per litre.

Loss of mass on drying – Dried preparations, when dried over phosphorus pentoxide at a pressure not exceeding 0.02 mm of mercury for 24 hours, must not lose more than 0.5 % of their weight.

Sterility – The final product shall be sterile when examined by a suitable bacteriological method.

Storage – Dried Human Albumin must be kept in an atmosphere of nitrogen or in a vacuum in a sterile container, sealed so as to exclude micro-organisms and, as far as possible, moisture, protected from light and stored at a temperature below 20° C.

Solutions of Human Albumin and Human Plasma Protein Fraction must be kept in sterile containers, sealed so as to exclude micro-organisms, protected from light and stored at a temperature of 4° to 6° C.

Labelling – The label on the container shall give all the information shown on the appropriate model label (Annex 4). For solutions, the date of preparation is the date of heat treatment in the final container.

4. Human Normal Immunoglobulin

Human Normal Immunoglobulin is a preparation of the plasma proteins prepared from Whole Human Blood, containing the antibodies of normal adults. It is obtained from pooled liquid human plasma from not less than 1000 donors.

The method of preparation used should be one which produces a material meeting the requirements herein prescribed and which prevents the transmission of serum hepatitis by the final product. In addition the method of preparation shall be such that the antibodies contained in the starting material shall be concentrated in an adequate amount in the final product. The procedure shall be shown, for each final preparation, to be satisfactory in this respect by titrating in the starting material and in the final product antibodies to at least one virus and one bacterial toxin. The antibodies chosen shall be those for which there are recognised methods of titration.

During preparation no antiseptic or bacteriostatic substance shall be added; a suitable preservative and a stabilising agent may be added to the final preparation to maintain bacterial sterility and stability of the final product.

The final product is issued as a solution in which the immunoglobulin concentration shall be between 100 and 170 gram per litre.

Identification

i) By precipitation tests with specific antisera, it must be shown to contain only human plasma proteins.

ii) By electrophoresis, using the moving boundary technique under acceptable and appropriate conditions, not less than 90 % of the mass of the proteins have the mobility of the gamma component of the globulins of normal human plasma.

Stability – Both before and after heating the final solution at 37°C for 7 days there should be no visible evidence of precipitation or turbidity. It is advisable also to carry out tests using an ultracentrifugation method to determine the extent of degradation of the product to smaller molecular weight components. The method used should be one approved by the national control authority.

Acidity – The pH of the final solution shall be 6.8 ± 0.4 when measured at a temperature of 15 to 25° C in a solution diluted to a protein concentration of 10 gram per litre by means of a solution containing 0.15 mole sodium chloride per litre.

Sterility – The final product shall be sterile when examined by a suitable bacteriological method.

Storage – Human Immunoglobulin solution must be kept in a sterile container, sealed so as to exclude micro-organisms, protected from light and stored at a temperature of 4° to 6° C.

Labelling – The label on the container shall give all the information shown on the model label (Annex 5). The date of preparation is the date of filling the final container.

5. Human Specific Immunoglobulins

Human Specific Immunoglobulins contain antibodies against designated viral or bacterial agents. Therefore they may be prepared from pools of a limited number of donations.

The following human spectific immunoglobulins are included in there requirements:

– Human Immunoglobulin Anti-Tetanus
– Human Immunoglobulin Anti-Vaccinia.

Other specific immunoglobulins may be developed and when the appropriate international standard is in existence, they should be assayed in relation to that standard and their potency expressed in international units.

Human Immunoglobulin Anti-Vaccinia shall contain not less than 500 IU per ml of vaccinia antibody as determined by a neutralisation test on chorio-allantoic membranes or in tissue culture. Human Immunoglobulin Anti-Tetanus shall contain not less than 50 IU per ml of tetanus antitoxin as determined by a neutralisation test in animals.

Human Specific Immunoglobulins must further meet the requirements as described in section 4, Human Normal Immunoglobulin.

Depending on the antibody content, the immunoglobulin concentration of the final solution may vary between 100 and 170 gram per litre.

Labelling – The label on the container shall give all the information shown on the model label (Annex 5). In addition, the label shall state the potency in international units in terms of the appropriate International Standard or International Reference Preparation.

6. Dried Human Fibrinogen

Dried Human Fibrinogen is a dried preparation which contains the soluble constitutent of liquid human plasma which, on the addition of thrombin, is transformed to fibrin. The method of preparation used should be one which produces a material meeting the requirements herein prescribed and which minimieses the risk of transmitting serum hepatitis. Plasma pools used in the preparation of fibrinogen should contain as few donations as possible.

During preparation no antiseptic or bacteriostatic substance shall be added. The final product shall be freeze-dried.

Solubility – Add water to the recommended volume; the dried preparation must be completely soluble. No precipitation shall occur within 60 minutes of reconstitution.

Identification

i) By precipitation tests with specific antisera, it must be shown to contain only human plasma proteins.

ii) The freshly reconstituted product has the property of clotting on the addition of thrombin. When thrombin is added to a solution of Human Fibrinogen of the same concentration as that in fresh normal plasma, clotting shall occur in not more than twice the time taken for clotting to occur in fresh normal plasma after the addition of thrombin.

iii) Clottable protein. Not less than 50% of the total protein shall be clottable by thrombin.

Loss of mass on drying – Preparations, when dried over phosphorus pentoxide at a pressure not exceeding 0.02 mm of mercury for 24 hours, must not lose more thant 0.5 % of their weight.

Sterility – The final product after reconstitution shall be sterile when examined by a suitable bacteriological method.

Storage – Human Fibrinogen shall be kept in an atmosphere of nitrogen or in a vacuum in a sterile container, sealed so as to exclude micro-organisms and, as far as possible, moisture, protected from light and stored at the temperature recommended.

Labelling – The label on the container shall give all the information shown on the model label (Annex 6). The date of preparation is the date of placing into final solution before freeze-drying.

7. Dried or frozen human coagulation Factor VIII

I. Requirements applying to donors

Donors must be in good health and, in particular, free of any communicable disease, in accordance with the criteria adopted for dried human plasma.

II. Requirements applying to preparations

Sterility and atoxicity – The final product must be sterile and pyrogen-free. Where cryoprecipitation is performed in plastic bags, the product must not contain organic solvent or other foreign substances present in the freezing mixture. The passage of such products through the walls of the plastic bag can be prevented by placing the bag in a second impermeable bag during the whole period of immersion. The risk of the plastic bag tearing during storage in the frozen state can be reduced by keeping each bag in a protective box.

Erythrocytes, leukocytes and platelets – Centrifuging should be such as to eliminate the formed elements of the blood as soon and as completely as possible after its collection.

Solubility – The addition of the indicated uantity of appropriate solvent must result in the complete solution of the dry product in less than 30 minutes at 37° C. Small and easily separable aggregates of fibrinogen may persist.

Stability – The preparation conserved at 20° C must not show any sign of precipitation within three hours after it has been dissolved.

Potency – The reconstituted preparation should contain the indicated minimum quantity of factor VIII, one unit corresponding to the potency of 1 ml of average normal fresh plasma, the potency being determined by a method approved by the competent national authority.

Absence of irregular antibodies eand, if the preparation is intended for patients of any ABO group, a titre of anti-A and anti-B antibodies not exceeding 32.

Identification – Precipitation tests with specific antisera shall show that the product contains only human plasma proteins.

Loss of mass on drying – Freeze-dried preparations, when dried ober phosphorus pentoxide at a pressure not exceeding 0.02 mm of mercury for 24 hours must not lose more than 1.5 per cent of their weight.

Storage – Human factor VIII shall be stored in deep frozen state at a temperature under – 30° C, and in the freeze-dried state below 5° C, and protected from light. The dried preparation shall be kept in an atmosphere of nitrogen or in vacuo, in a sterile vial, stoppered so as to exclude all micro-organisms and, as far as possible, all humidity. Storage in the frozen state shall not exceed six months, in the dried state one year, unless the preparation has been retested for minimum required potency.

III. Labelling

The label on the preparation shall give all the information shown on the model label (Annex 7).

8. Dried human coagulation Factor IX

I. Requirements applying to donors

Donors must be in good health and, in particular, free from any communicable disease in accordance with the criteria adopted for dried human plasma.

II. Requirements applying to the concentrate

Sterility and atoxicity – The final product tested by appropriate methods must be sterile, pyrogen-free and free from undesirable vaso-depressor or respiratory effects. The test for absence of vaso-depressor effects should be performed on a dog or cat.

Solubility – The addition of the indicated quantity of the solvent must result in complete solution in 10 minutes at 37° C.

Thromboplastin activity and absence of free thrombin – The recalcification time of a normal plasma measured at 37° C in the presence of an equal volume of various dilutions of the reconstituted product, must not be less than 40 seconds. The reconstituted product, with an equal volume of fibrinogen (3 g/l) added to it, must not coagulate within six hours at 37° C.

Potency – The reconstituted preparation must contain the indicated minimum quantity of factor IX, 1 unit corresponding to the potency of 1 ml of average normal fresh plasma, the potency being determined by a method approved by the competent national authority.

Yield and stability in vivo – The method of preparation must be such that the injection of a dose of 50 units per kg body weight, rapidly administered intravenously, using several batches of material given to several patients, shall cause, in 15 minutes, in the absence of a specific inhibitor and in basal conditions, an average rise of not less than 300 units per litre plasma, and of the persistence, after 24 hours of an average rise of not less than 60 units per litre plasma.

Identification – Precipitation tests with specific antisera shall show that the product contains solely human plasma proteins.

Loss of mass on drying – When dried over phosphorus pentoxide at a pressure not exceeding 0.02 mm of mercury for 24 hours, the product must not lose more than 1.5 per cent of its weight.

Storage – The preparations must be stored dry at a temperature below 5° C. The period of storage must not exceed two years, unless the potency of the preparation has been re-tested.

III. Labelling

The label on the preparation shall give all the information shown on the model label (Annex 8).