Treaty Series No. 51 (1979)

# European Agreement on the Exchange of Tissue-typing Reagents

Strasbourg, 17 September 1974

(with Revised Text of Protocol and Annex)

and

# Additional Protocol

Strasbourg, 24 June 1976

[The Agreement and Additional Protocol entered into force for the United Kingdom on 9 March 1979]

*Presented to Parliament*
*by the Secretary of State for Foreign and Commonwealth Affairs*
*by Command of Her Majesty*
*July 1979*

*LONDON*
HER MAJESTY'S STATIONERY OFFICE
40p net
Cmnd. 7558

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# EUROPEAN AGREEMENT ON THE EXCHANGE OF TISSUE-TYPING REAGENTS

The member States of the Council of Europe, signatory hereto,

Considering that tissue-typing reagents are not available in unlimited quantities;

Considering that it is highly desirable that member States, in a spirit of European solidarity, should assist one another in the supply of these tissue-typing reagents, should the need arise;

Considering that such mutual assistance is only possible if the character and use of such tissue-typing reagents are subject to rules to be laid down jointly by the member States and if the necessary import facilities and exemptions are granted,

Have agreed as follows:

## ARTICLE 1

1. For the purposes of this Agreement, the expression " tissue-typing reagents " refers to reagents of human, animal, plant and other origin, used for the determination of tissue-typing.

2. The provisions of Articles 2 to 6 of this Agreement shall also apply to cells of known antigenic composition to be used for the investigation of typing reagents.

## ARTICLE 2

The Contracting Parties undertake, provided that they have sufficient stocks for their own needs, to make tissue-typing reagents available to other Parties who are in need of them and to charge only those costs of collection, processing and carriage of such substances and the cost (if any) of their purchase.

## ARTICLE 3

Tissue-typing reagents shall be made available to the other Contracting Parties subject to the condition that no profit is made on them, and that they shall be used solely for medical and scientific, i.e. non-commercial, purposes and shall be delivered only to laboratories designated by the governments concerned in accordance with Article 6 of this Agreement.

## ARTICLE 4

1. The Contracting Parties shall certify that the provisions as laid down in the Protocol to this Agreement have been observed.

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

3. All consignments of tissue-typing reagents 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 the Annex to the Protocol.

4. The Protocol and its Annex constitute an administrative arrangement and may be amended or supplemented by the governments of the Parties to this Agreement.(1)

ARTICLE 5

1. The Contracting Parties shall take all necessary measures to exempt from all import duties the tissue-typing reagents placed at their disposal by the other Parties.

2. 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 national and/or regional reference laboratories, empowered to issue certificates as provided in Article 4 of this Agreement and to distribute imported tissue-typing reagents.

ARTICLE 7

1. This Agreement shall be open to signature by the member States of the Council of Europe, who may become Parties to it either by:

(*a*) signature without reservation in respect of ratification or acceptance, or

(*b*) signature with reservation in respect of ratification or acceptance, followed by ratification or acceptance.

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

ARTICLE 8

1. This Agreement shall enter into force one month after the date on which three member States of the Council shall have become Parties to the Agreement, in accordance with the provisions of Article 7.(2)

(1) A revised text of the Protocol and Annex was approved at the 265th Meeting of the Ministers' Deputies held in Strasbourg from 14 to 21 February 1977.

(2) The Agreement entered into force on 23 April 1977.

2. As regards any member State who shall subsequently sign the Agreement without reservation in respect of ratification or acceptance or who shall ratify or accept it, the Agreement shall enter into force one month after the date of such signature or after the date of deposit of the instrument of ratification or acceptance.

ARTICLE 9

1. After the entry into force of this Agreement, the Committee of Ministers of the Council of Europe may invite any non-member State to accede thereto.

2. Such accession shall be effected by depositing with the Secretary General of the Council of Europe an instrument of accession which shall take effect one month after the date of its deposit.

ARTICLE 10

1. Any Contracting Party may at the time of signature or when depositing its instrument of ratification, acceptance or accession, specify the territory or territories to which this Agreement shall apply.

2. Any Contracting Party may, when depositing its instrument of ratification, acceptance or accession or at any later date, by declaration addressed to the Secretary General of the Council of Europe, extend this Agreement to any other territory or territories specified in the declaration and for whose international relations it is responsible or on whose behalf it is authorised to give undertakings.

3. Any declaration made in pursuance of the preceding paragraph may, in respect of any territory mentioned in such declaration, be withdrawn according to the procedure laid down in Article 11 of this Agreement.

ARTICLE 11

1. Any Contracting Party may, in so far as it is concerned, denounce this Agreement by means of a notification addressed to the Secretary General of the Council of Europe.

2. Such denunciation shall take effect six months after the date of receipt by the Secretary General of such notification.

ARTICLE 12

The Secretary General of the Council of Europe shall notify the member States of the Council and any State which has acceded to this Agreement, of:

(*a*) any signature without reservation in respect of ratification or acceptance;

(*b*) any signature with reservation in respect of ratification or acceptance;

(c) the deposit of any instrument of ratification, acceptance or accession;

(d) any date of entry into force of this Agreement in accordance with Article 8 thereof;

(e) any declaration received in pursuance of the provisions of paragraphs 2 and 3 of Article 10;

(f) any notification received in pursuance of the provisions of Article 11 and the date on which denunciation takes effect;

(g) any amendment of or supplement to the Protocol and its Annex under Article 4, paragraph 4 of this Agreement.

In witness whereof the undersigned, being duly authorised thereto, have signed this Agreement.

Done at Strasbourg, this 17th day of September 1974, 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 of the Council of Europe shall transmit certified copies to each of the signatory and acceding States.

## SIGNATURES AND RATIFICATIONS OF THE AGREEMENT

| *State* | *Date of Signature* | *Date of deposit of Ratification or Acceptance(AC)* | *Effective date of Ratification in accordance with Article 8* |
|---|---|---|---|
| Belgium* ... ... | 11 Jan. 1977 | | |
| Cyprus* ... ... | 15 Dec. 1975 | 10 May 1976 | |
| Denmark* ... ... | 17 Oct. 1974 | 5 July 1978 | 6 Aug. 1978 |
| European Economic Community ... | 22 Nov. 1977 | | |
| France* ... ... | 4 Oct. 1976 | 22 Mar. 1977(AC) | |
| Germany, Federal Republic of ... | 18 Feb. 1975 | | |
| Italy* ... ... | 7 Oct. 1977 | | |
| Luxembourg* ... | 17 Sept. 1974 | 12 Apr. 1978 | 13 May 1978 |
| Netherlands* ... | 3 Aug. 1977 | 12 Apr. 1978 | 13 May 1978 |
| Portugal* ... ... | 6 Oct. 1978 | | |
| Switzerland* ... | 17 Sept. 1974 | 21 Nov. 1975 | |
| United Kingdom ... | 8 Feb. 1979 | | 9 Mar. 1979 |

* Subject to ratification or acceptance.

# REVISED TEXT OF THE PROTOCOL TO THE EUROPEAN AGREEMENT ON THE EXCHANGE OF TISSUE-TYPING REAGENTS AND ANNEX TO THE SAID PROTOCOL CERTIFICATE OF THE SECRETARY GENERAL OF THE COUNCIL OF EUROPE

Whereas it is stated in the fourth paragraph of Article 4 of the European Agreement of 17 September 1974 on the Exchange of Tissue-typing Reagents that the Protocol and its Annex may be amended or supplemented by the Governments of the Contracting Parties to the said Agreement;

Whereas the Governments of Cyprus, France and Switzerland, Contracting Parties to the said Agreement, approved the proposal of the European Public Health Committee to replace the units of measurement of haematology by the International System of Units (SI) in the Protocol to the European Agreement on the Exchange of Tissue-typing Reagents;

Whereas, at the 265th meeting of the Ministers' Deputies held in Strasbourg from 14 to 21 February 1977, the representatives to the Committee of Ministers of the Council of Europe of the above-mentioned Governments took note of the revision of the text of the Protocol to the European Agreement on the Exchange of Tissue-typing Reagents;

**The Secretary General hereby certifies as follows :**

The following text constitutes the Protocol to the European Agreement on the Exchange of Tissue-typing Reagents.

## GENERAL PROVISIONS

1. **Specificity**

A. *Tissue-typing reagents to be used in cytotoxic techniques on lymphocytes*

These reagents must, when used according to the technique recommended by the producer, react with all lymphocytes known to contain the antigen(s) corresponding to the specificity (specificities) mentioned on the label. They must not react with any cell known not to contain this antigen (these antigens).

When these reagents are used according to the technique recommended by the producer there must be no evidence of any interfering serological phenomena such as:

(*a*) prozone effect;

(*b*) anticomplementarity.

B. *Tissue-typing reagents for use in a complement fixation technique on platelets*

These reagents must, when used according to the technique recommended by the producer, give complement fixation with all platelets known to contain

the antigen(s) corresponding to the specificity (specificities) mentioned on the label. They must not give complement fixation with any platelets known not to contain this antigen (these antigens).

When these reagents are used according to the technique recommended by the producer there must be no evidence of any interfering serological phenomena such as:

(*a*) prozone effect;

(*b*) anticomplementarity.

2. **Potency**

A. *Tissue-typing reagents to be used in cytotoxic techniques on lymphocytes*

The titre of such a reagent is determined by making successive twofold dilutions of the reagent under study in inactivated AB serum from a donor negative for the antigen(s) corresponding to the antibody (antibodies) in the reagent who should also not have been immunised against tissue antigens by transfusion, pregnancy or other means. Each dilution is then tested with lymphocytes known to contain the corresponding antigen(s) in the reagent, using the technique recommended by the producer. The titre is the reciprocal of the figure representing the highest serum dilution in which a significantly positive reaction occurs, the dilution being calculated without the inclusion of the volume of the corpuscular suspension or any other additive in the total volume.

B. *Tissue-typing reagents for use in a complement fixation technique on platelets*

The titre of such a reagent is determined by making successive twofold dilutions of the reagent under study in a solution containing inactivated AB serum in Veronal ® buffer with a volume fraction of 0.01. Each serum is then tested with platelets known to contain the antigen homologous to the antibodies in the reagent, using the technique recommended by the producer. The titre is the reciprocal of the figure representing the highest serum dilution in which a significantly positive reaction occurs, the dilution being calculated without the inclusion of the volume of the corpuscular suspension or any other additive in the total volume.

Further provisions, for tissue-typing reagents to be used in cytotoxic techniques on lymphocytes as well as for reagents to be used in a complement fixation technique on platelets:

3. **Preservation**

Tissue-typing reagents may be preserved in the liquid or in the dried state. Liquid reagents shall be kept at a temperature not above −70°C, dried reagents at a temperature not above +4°C.

Thawing and refreezing of the reagents during the period of storage must be avoided as much as possible.

Dried reagents shall be kept in an atmosphere of inert gas or in vacuo in the container in which they were dried and which shall be closed so as

to exclude moisture. A dried reagent must not lose more than 0.5% of its weight when tested by further drying over phosphorous pentoxide at a pressure not exceeding 0.02 mm of mercury for 24 hours.

Reagents shall be prepared with aseptic precautions and shall be free from bacterial contamination. In order to prevent bacterial growth the producer may decide that an antiseptic and/or antibiotic shall be added to the reagent. In such cases the reagent must still fulfill the requirements for specificity and potency in the presence of the added substance.

The above also applies to any other additives such as anticoagulants. Reagents, after thawing or after reconstitution, should be transparent and should not contain any sediment, gel or visible particles.

4. **Stability and expiry date**

*Each reagent, when kept under the appropriate conditions of storage,* should retain the requisite properties for at least one year.

The expiry date of a reagent in the liquid state as given on the label shall be not more than one year from the date of the last satisfactory potency test. The expiry date can be extended for further periods of one year by repetition of potency tests.

The expiry date of reagents in the dried form as given on the label shall be in accordance with evidence obtained from experiments on stability.

5. **Dispensing and volume**

Tissue-typing reagents shall be dispensed in such a way and in such volumes that the reagent in one container is sufficient for the performance of tests with positive and negative control corpuscles in addition to the performance of tests with the unknown corpuscles.

The volume in one container shall be such that the contents can, if necessary, be used for the performance of the appropriate tests for potency as described in this Protocol.

6. **Records and samples**

Written records shall be kept by the producing laboratory of all steps in the production and control of tissue-typing reagents. Adequate samples of all reagents issued shall be retained by the laboratory, until it can be reasonably assumed that the batch is no longer in use.

7. **Shipment**

Frozen reagents must be shipped in such fashion that they remain frozen until arrival. Care must be taken to protect reagents against inactivation by the entry of $CO_2$. Dried reagents may be shipped at ambient temperatures.

8. **Labels, leaflets and certificates**

Two labels, one printed in English and one in French, in black on white paper, shall be affixed to each final container and shall contain the following information:

(*a*) name and address of producer;

(*b*) name of the reagent as it appears in the heading of the relevant specification;

(*c*) name and amount of antiseptic and/or antibiotic, if present, or indication of absence;

(*d*) the volume or, where the reagent is dried, the volume and composition of the fluid needed for reconstitution;

(*e*) expiry date;

(*f*) batch number;

(*g*) conditions of storage;

(*h*) results of the test for HB-Ag.

Moreover, these labels or the labels of the carton enclosing several final containers or the leaflet accompanying the containers, shall contain the following information:

(*a*) full name and address of producer;

(*b*) name of the reagent as it appears in the heading of the relevant specification;

(*c*) the volume or, where the reagent is dried, the volume and composition of the fluid needed for reconstitution;

(*d*) date of last potency test;

(*e*) expiry date (if any);

(*f*) batch number;

(*g*) adequate description of the method of use recommended by the producer;

(*h*) conditions of storage of unopened ampoules and precautions to be taken after opening;

(*i*) exact composition, including antiseptic and/or antibiotic if any;

(*j*) statement whether the product contains or does not contain material of human origin.

Each consignment shall be accompanied by a certificate as provided in Article 4 of the Agreement and the Annex to the present Protocol. Examples of label and leaflet are attached to the present Protocol.

## SPECIFIC PROVISIONS *

* *To be completed under Article 4, paragraph 4 of the European Agreement on the* Exchange of Tissue-Typing Reagents.

EXEMPLE D'ETIQUETTE

EXAMPLE OF LABEL

CONSEIL DE L'EUROPE

COUNCIL OF EUROPE

*Accord européen sur l'échange de réactifs pour la détermination des groupes tissulaires*

*European Agreement on the Exchange of Tissue-Typing Reagents*

| | |
|---|---|
| 1. Nom et adresse du producteur | 1. Name and address of the producer |
| 2. Réactif pour groupage tissulaire anti HL-A | 2. Tissue-typing reagent anti HL-A |
| 3. 1 ml | 3. 1 ml |
| ou Reconstituer avec 1 ml d'eau distillée | or To be reconstituted with 1 ml of distilled water |
| 4. Date du dernier contrôle d'activité | 4. Date of last potency test |
| 5. Date de péremption | 5. Expiry date |
| 6. Numéro du lot | 6. Batch number |
| 7. Technique à utiliser: lymphocytotoxicité NIH | 7. Technique to be used: NIH Lymphocytotoxicity |
| 8. A conserver à— ... (temp., etc.) | 8. To be stored at— ... (temp. etc.) |
| 9. Composition | 9. Composition |
| 10. Le réactif contient du sérum humain | 10. The reagent contains human serum |

Cette étiquette sera placée sur le colis renfermant plusieurs récipients définitifs.

This label must be attached to a container enclosing several final containers.

EXEMPLE DE NOTICE

EXAMPLE OF LEAFLET

# CONSEIL DE L'EUROPE
# COUNCIL OF EUROPE

*Accord européen sur l'échange de réactifs pour la détermination des groupes tissulaires*

*European Agreement on the Exchange of Tissue-Typing Reagents*

1. Laboratoire national de référence de groupage tissulaire,
   1 Main Street, Metropolis, Westland
2. Réactif pour groupage tissulaire anti HL-A I
3. $N_3Na$ solution de 1 gramme par litre a été ajouté
4. 1 ml

ou Reconstituer avec 1 ml d'eau distillée

5. Date de péremption le 5 décembre 1975
6. Numéro du lot n° 7257
7. A conserver à −70°C
8. Résultat du test pour dépister le HB-Ag: négatif

1. National Tissue-Typing Reference Laboratory,
   1 Main Street, Metropolis, Westland
2. Tissue-typing reagent anti HL-A I
3. $N_3Na$ solution of 1 g/l is added
4. 1 ml

or To be reconstituted with 1 ml of distilled water

5. Expiry date 5 December 1975
6. Batch number No. 7257
7. To be stored at −70°C
8. Result of the test for HB-Ag: negative

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Cette notice sera fixée sur chaque récipient définitif.

This leaflet must be affixed to each final container.

ANNEXE AU PROTOCOLE

ANNEX TO THE PROTOCOL

# CONSEIL DE L'EUROPE
# COUNCIL OF EUROPE

*Accord européen sur l'échange de réactifs pour la détermination des groupes tissulaires*

*European Agreement on the Exchange of Tissue-Typing Reagents*

Certificat

(*Article 4*)

Certificate

A NE PAS DETACHER DE L'ENVOI

NOT TO BE SEPARATED FROM THE SHIPMENT

.....19...

(lieu) (*place*) (date) (*date*)

| | |
|---|---|
| Nombre de colis<br>Number of packages | Le soussigné déclare que l'envoi spécifie en marge.....<br>The undersigned certifies that the shipment specified in the margin<br>.....<br>..... |
| .....<br>..... | préparé sous la responsabilité de.....<br>prepared under the responsibility of..... |
| Désignation<br>Marked | .....<br>..... |
| .....<br>..... | organisme visé à l'article 6 de l'Accord, est conforme aux spécifications<br>one of the bodies referred to in Article 6 of the Agreement, is in |
| N° des lots<br>Batch No. | du Protocole à l'Accord et qu'il peut être délivré immédiatement<br>conformity with the specifications of the Protocol to the Agreement |
| .....<br>.....<br>.....<br>..... | au destinataire (nom et lieu).....<br>and can be delivered immediately to the consignee (name and place).....<br>..... |

(cachet) (*stamp*) (signature) (*signature*) (titre) (*title*)

Done at Strasbourg, this 7th day of April 1978.

Georg KAHN-ACKERMANN
Secretary General

## ADDITIONAL PROTOCOL TO THE EUROPEAN AGREEMENT ON THE EXCHANGE OF TISSUE-TYPING REAGENTS

The member States of the Council of Europe signatory to the European Agreement on the Exchange of Tissue-typing Reagents (hereafter called the " Agreement ") and to this Additional Protocol,

Having regard to the provisions of Article 5, paragraph 1 of the Agreement, according to which " the Contracting Parties shall take all necessary measures to exempt from all import duties the tissue-typing reagents placed at their disposal by the other Parties ";

Considering that so far as the member States of the European Economic Community are concerned, the undertaking to grant this exemption falls within the competence of the Community, which possesses the necessary powers in this respect by virtue of the Treaty which instituted it;

Considering therefore that for the purpose of the implementation of Article 5, paragraph 1 of the Agreement, it is necessary for the European Economic Community to be able to become a Contracting Party to the Agreement,

Have agreed as follows:

### ARTICLE 1

The European Economic Community may become a Contracting Party to the Agreement by signing it.

### ARTICLE 2

This Additional Protocol shall be open to signature by the States signatory to the Agreement, which may become Parties to the Additional Protocol in accordance with the procedure laid down in Article 7 of the Agreement.

### ARTICLE 3

No State may become a Contracting Party to the Agreement without at the same time becoming a Contracting Party to this Additional Protocol, which forms an integral part of the Agreement;

### ARTICLE 4

This Additional Protocol shall enter into force on the same date as the Agreement.

ARTICLE 5

The Secretary General of the Council of Europe shall notify the member States of the Council and the European Economic Community of:

(*a*) any signature of this Additional Protocol;

(*b*) the deposit of any instrument of ratification or acceptance;

(*c*) the date of entry into force of this Additional Protocol.

In witness whereof, the undersigned, being duly authorised thereto, have signed this Protocol.

Done at Strasbourg, this 24th day of June 1976, in English and in French, both texts being equally authorative, in a single copy which shall remain deposited in the archives of the Council of Europe. The Secretary General of the Council of Europe shall transmit certified copies to each of the signatory and acceding Parties.

## SIGNATURES AND RATIFICATIONS OF THE ADDITIONAL PROTOCOL

| *State* | *Date of Signature* | *Date of deposit of Ratification or Acceptance(AC)* | *Effective date of Ratification in accordance with Article 2* |
|---|---|---|---|
| Belgium* ... ... | 11 Jan. 1977 | | |
| Cyprus* ... ... | 13 Sept. 1977 | 13 Sept. 1977 | |
| Denmark* ... ... | 24 June 1976 | 5 July 1978 | 6 Aug. 1978 |
| France* ... ... | 4 Oct. 1976 | 22 Mar. 1977(AC) | |
| Germany, Federal Republic of * ... | 24 Sept. 1976 | | |
| Italy* ... ... | 7 Oct. 1977 | | |
| Luxembourg* ... | 22 Sept. 1976 | 12 Apr. 1978 | 13 May 1978 |
| Netherlands* ... | 3 Aug. 1977 | 12 Apr. 1978 | 13 May 1978 |
| Portugal* ... ... | 6 Oct. 1978 | | |
| Switzerland ... | 25 Jan. 1977 | | |
| United Kingdom ... | 8 Feb. 1979 | | 9 Mar. 1979 |

* Subject to ratification or acceptance.

Printed in England by Her Majesty's Stationery Office
20972—27 311349 Dd 0593331 K11 7/79

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ISBN 0 10 175580 5