HEALTH

Treaty Series No. 41 (1985)

Revised Text

of the Protocol to the European Agreement on the Exchange of Tissue-typing Reagents and Annex to the said Protocol

Strasbourg, 28 March 1985

Presented to Parliament
by the Secretary of State for Foreign and Commonwealth Affairs
by Command of Her Majesty
August 1985

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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 on the Exchange of Tissue-typing Reagents, signed at Strasbourg on 17 September 1974,[1] that the Protocol and its Annex may be amended or supplemented by the Governments of the Parties to the said Agreement;

Whereas, at the 378th meeting of the Committee of Ministers of the Council of Europe at Deputies level, held in Strasbourg from 26 November to 7 December and on 13 December 1984, the representatives of the Governments of Belgium, Cyprus, Denmark, France, Ireland, Italy, Liechtenstein, Luxembourg, the Netherlands, Switzerland and the United Kingdom, Parties to the said Agreement, approved the revised Protocol to the European Agreement on the Exchange of Tissue-typing Reagents;

Whereas, by letter of 7 September 1984, the European Economic Community, Party to the Agreement, made known to the Secretary General its agreement to the draft revised Protocol,

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(ies) mentioned on the label. They must not react with any cell known not to contain this antigen (these antigens). If a sole reagent does not satisfy these conditions, a combination of four sera of the same specificity must be used together. In this case, at least three sera must react with each lymphocyte sample containing the corresponding antigen and, inversely, not more than one should react with cells not containing this antigen.

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 effects,

(*b*) anticomplementarity.

B. *Tissue-typing reagents for use in 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

[1] Treaty Series No. 51 (1979), Cmnd. No. 7558.

the antigen(s) corresponding to the specificity(ies) mentioned on the label. They must not give complement fixation with any platelets known not to contain this antigen (these antigens). If a sole reagent does not satisfy these conditions, a combination of four reagents of the same specificity must be used together. In this case, at least three sera must react with each platelet sample containing the corresponding antigen and, inversely, not more than one should react with cells not containing this antigen.

Where 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 effects,

(*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 serum under study in inactivated AB serum or in another appropriate medium from a donor who is negative for the antigen(s) corresponding to the antibody (antibodies) in the reagent and 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 serum under study in a solution containing inactivated AB serum in Veronal (R) 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 −40°C and 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 fulfil 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.

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 reageents 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*) the specificity of the reagent,

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

(*d*) the volume or, when the reagent is dried, the volume and composition of the fluid needed for reconstruction.

(*e*) expiry date,

(*f*) identification,

(*g*) conditions of storage,

(*h*) results of the test for HB_sAg.

Moreover, the leaflet accompanying the containers shall include the following information:

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

(*b*) the recognised specificity of the reagent,

(*c*) the volume or, when 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*) identification and (if possible) the name of the reagent,

(*g*) adequate description of the method of use recommended by the producer including technique, volume and dilution to be used,

(*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,

(*k*) the reaction score ++,−+,+−,−−, and the values of coefficient r (serum/antigen).

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

EXEMPLE D'ÉTIQUETTE
EXAMPLE OF LABEL

COUNSEIL 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

a. Laboratoire national de référence pour le groupage tissulaire: 1 Main Street, Metropolis, Westland	*a.* National Tissue-typing Reference Laboratory: 1 Main Street, Metropolis, Westland
b. Réactif pour groupage tissulaire: anti-HLA-A1	*b.* Tissue-typing reagent: anti-HLA-A1
c. Une solution de N_3Na à 1 g/l a été ajoutée	*c.* N_3Na solution of 1 g/l has been added
d. Volume: 1 ml	*d.* Volume: 1 ml
ou: Reconstituer avec 1 ml d'eau distillée	or: To be reconstituted with 1 ml of distilled water
e. Date de péremption: 5 décembre 1985	*e.* Expiry date: 5 December 1985
f. Identification	*f.* Identification
g. A conserver à: −40°C	*g.* To be stored at: −40°C
h. Résultat de l'épreuve $AgHB_s$: . . .	*h.* Result of the test for HB_sAg: . . .

Cette étiquette sera apposée sur chaque récipient définitif.
This label must be affixed to each final container.

EXEMPLE DE NOTICE
EXAMPLE OF LEAFLET

COUNSEIL 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

a. Nom et adresse complets du producteur	*a.* Full name and address of the producer
b. Réactif de groupage tissulaire: anti-HLA-A1	*b.* Tissue-typing reagents: anti-HLA-A1
c. Volume: 1 ml	*c.* Volume: 1 ml
(ou: reconstituer avec 1 ml d'eau distillée)	(or: to be reconstituted with 1 ml of distilled water)
d. Date du dernier contrôle d'activité:	*d.* Date of last potency test:
e. Date de péremption:	*e.* Expiry date:
f. Identification et (si possible) nom du réactif:	*f.* Identification and (if possible) name of the reagent:
g. Mode d'emploi; technique à utiliser: Lymphocytotoxicité NIH, etc.	*g.* Methode of use; technique to be used: NIH Lymphocytotoxicity, etc.
h. A conserver à: (température, . . .)	*h.* To be stored at: (temperature, . . .)
i. Composition	*i.* Composition
j. Le réactif contient du sérum humain	*j.* The reagent contains human serum
k. Résultats de réactions: ++ −+ +− −− 30 0 1 300 Sérum/antigène r=0.90	*k.* Reaction score: ++ −+ +− −− 30 0 1 300 Serum/antigen r=0.90

Cette notice accompagnera le colis renfermant plusieurs récipients définitifs.
This leaflet must accompany a container enclosing several final containers.

ANNEXE AU PROTOCOLE
ANNEX TO THE PROTOCOL

COUNSEIL 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 de l'Accord)
Certificate (Article 4 of the Agreement)

A NE PAS DÉTACHER DE L'ENVOI
NOT TO BE SEPARATED FROM THE SHIPMENT

..... 19.....
(lieu) (date)
(place) (date)

Nombre de colis Number of packages .... Marqué(s) Marked .... Identification Identification	Le soussigné déclare que l'envoi cité en marge ..... The undersigned certifies that the shipment specified in the ..... margin ..... préparé sous la responsabilité de ..... prepared under the responsibility of .... l'un des organismes visés à l'article 6 de l'Accord, est one of the bodies referred to in Article 6 of the Agreement, conforme aux spécifications de l'Article 5 is in conformity with the specifications of Article 5 du Protocole á cet Accord et doit être délivré immédiate- of the Protocol to the Agreement and must be delivered ment au destinataire (nom et lieu) ..... immediately to the consignee (name and place) ..... (nom et lieu) ..... (name and place) ..... (cachet) (signature) (qualité) (stamp) (signature) (title)

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