Recommendation No R(93)4 of the Committee of Ministers to member states concerning clinical trials involving the use of components and fractionated products derived from human blood or plasma

(adopted by the Committee of Ministers on 22 March 1993, at the 490th meeting of the Ministers' Deputies)

1. The Committee of Ministers, under the terms of Article 15.b of the Statute of the Council of Europe,

2. Considering that the aim of the Council of Europe is to achieve a greater unity between its members, in particular by the adoption of minimum common rules on matters of common interest;

3. Having regard to the Convention for the Protection of Human Rights and Fundamental Freedoms, in particular its Articles 2.1, 3 and 8; to Article 7 of the United Nations International Covenant on Civil and Political Rights; to the European Convention for the Prevention of Torture and Inhuman or Degrading Treatment or Punishment and to the Declaration of Helsinki, adopted at the 18th World Medical Assembly (1964) and amended by the 29th Assembly in Tokyo (1975), the 35th Assembly in Venice (1983) and the 41st Assembly in Hong Kong (1989), concerning recommendations guiding physicians in biomedical research involving human subjects;

4. Recalling Recommendation No. R (90) 3 of the Committee of Ministers concerning medical research on human beings as well as Resolution (78) 29 on harmonisation of legislations of member States relating to removal, grafting and transplantation of human substances and Recommendation No. R (88) 4 on the responsibilities of health authorities in the field of blood transfusion;

5. Considering the growing importance of blood products in supportive haemotherapy and the need to subject such products to clinical testing and trials to ensure their safety, efficacy and quality as is the case for medicinal products;

6. Considering that such products are of human origin and that hence specific ethical and technical principles have to be taken into account in addition to those, national and international applying to medical research and clinical trials

on human beings;

7. Considering the need for harmonisation of such principles in member States,

Recommends the governments of member States to adopt legislation in conformity with the principles appended to this Recommendation and to take any other measures in order to ensure their implementation.

Appendix to Recommendation No. (93) 4

A. Field of application

1. The following articles apply to:

1.1 the conducting of clinical trials for the purpose of ensuring the safety, efficacy and quality of blood components before their routine clinical use;

1.2 the conducting of clinical trials for fractionated products before obtaining market authorisation;

1.3 the testing of collecting systems involved in the donation of whole blood or apheresis for the purpose of ensuring that these are safe for the donor and that the products are of acceptable safety, efficacy and quality before the marketing of such systems.

2. The recommendations do not apply to the practice of therapeutic apheresis.

B. Ethical principles concerning blood donors and recipients taking part in clinical trials

Article 1

All those responsible for clinical trials of blood components and fractionated products whether they are the investigators in charge of carrying out the trials, or directing the experiment, should take into account the following ethical principles concerning blood donors and recipients as prerequisites to their research activity as blood components and fractionated products differ from other medicinal products in that their source is a human blood donor.

Article 2

Blood donors should be voluntary and non-remunerated. Benefits in cash or kind should not be offered to donors of blood or plasma, although direct expenses of the donor may be reimbursed.

Article 3

Selection of donors should be in conformity with the recommendations of the Council of Europe to ensure that the person is in good health, in order to protect the donor against damage to his/her own health, and to protect the recipient against transmission of diseases or against medicinal products and drugs which could be detrimental to him/her.

Article 4

No clinical trial may be carried out without the informed, free, express and specific consent of the person undergoing it.

In this context, the relevant principles set out in Recommendation No. R (90) 3 should be observed.

The said principles apply also to the donor

- when procedures are to be performed which may have relevance to his/her health and well-being

- when a new procedure is being used to collect his/her blood.

The donor need not be informed when blood or plasma is collected using established procedures and the blood components or fractionated products derived from the donation are being treated in a novel or modified manner to prepare components or products for the purpose of clinical testing or trial respectively.

Article 5

Principle No. 9 (respect of confidentiality) and Principle No. 14 (damages in case of accident) as set out in Recommendation No. R (90) 3 should be applied to recipients, and to donors, under the conditions defined under Article 4 above.

C. Technical principles

1. Principles common to clinical trials of blood components and of

fractionated products

Article 6

Legislation, regulations and both national and international guidelines directed primarily to those who are involved in the generation of clinical data for the purpose of obtaining market authorisation for medicinal products should be applied in clinical trials of blood components and of fractionated products.

Article 7

The preparation of the blood components and fractionated products for the clinical trials should comply with principles of good manufacturing practice and the safety of the components or fractionated products particularly with regard to virology and vis-a-vis transmissible agents, and should be ensured prior to clinical trials; similarly, quality of the product must be ensured prior to the commencement of the trial and throughout the trial.

Article 8

In many instances placebo controlled clinical trials of blood components and fractionated products cannot be undertaken since it is unethical to withhold treatment. In such circumstances the new or modified blood component or fractionated product has to be compared with an existing blood component or

fractionated product. However, with this limitation, clinical trials can be randomised and double blind. An alternative, may be the comparison of a new or modified component or fractionated product with well documented retrospective data obtained using an existing blood component or fractionated product.

Article 9

When a new clinical indication for an existing blood component or fractionated product is proposed, the blood component or fractionated product should be subjected to a clinical trial in the same manner as that for a new or modified medicinal product, keeping in mind the specific characteristics of labile products.

2. Principles applying to clinical trials of blood components

Article 10

When a blood component has been subjected to physical or chemical

modification which may alter its characteristics it should be subjected to a clinical trial (including autologous survival studies where applicable) following approval by an ethical committee, unless the changes are such that secure in vitro tests demonstrate that there has been no biological change; in such a case the person in charge of preparing such a product assumes responsibility for its safety, efficacy and quality and the blood component may be administered to patients only with the authorisation of the physician(s) in charge.

Article 11

Whenever feasible clinical trials should be performed initially by autologous studies to determine adverse reactions and the half-life of the component(s) under test. Group controls should be used.

Article 12

Since each blood component will constitute a batch, a sufficient number of patients must be included in Phase 111 trials to ensure that batch to batch variation can be excluded.

3. Principles applying to clinical trials of fractionated products

Article 13

The presence of contaminants, particularly neo-antigens, which may be relevant to the health of the trial subjects must be assessed prior to the commencement of the clinical trial.

Article 14

In Phase 111 trials, there may be relatively few patients available in a given Centre. In these circumstances, multi-centre trials need to be organised and such trials must be continued for a sufficient period to ensure that all possible factors affecting safety and efficacy of the product have been studied.

Glossary

Blood products
Products derived from whole blood or plasma; these include both cellular

blood components and fractionated products.

Blood component

A labile therapeutic constituent derived by separation from single donation, an apheresis procedure or a small pool of human blood or plasma (ie. 12 or less donations). This will include the cellular components, plasma or simple derivatives derived from plasma, eg. cryoprecipitate.

Fractionated products

A medicinal product derived by fractionation from human plasma. This will include in particular albumin, coagulation factors and immunoglobulins of human origin.

Medicinal product

Any substance or combination of substances presented for treating or preventing disease in human beings or animals. Any substance or combination of substances which may be administered to human beings or animals with a view to making a medical diagnosis or to restoring, correcting or modifying physiological functions in human beings or in animals is likewise considered a medicinal product.

Clinical trial

A clinical trial is any systematic study of medicinal products in human subjects whether in patients or non- patient volunteers in order to discover or verify the effects and/or identity any adverse reaction to investigational products, and/or study their absorption, distribution, metabolism and excretion in order to ascertain the efficacy and safety of the product. For the purpose of this recommendation, the term "clinical trial" includes studies carried out on human blood components, keeping in mind the specific characteristics of labile products. Clinical trials are generally classified into phases 1 to IV. It is not possible to draw distinct lines between the phases and diverging opinions about details and methodology do exist. Definitions (in brief) of the individual phases, based on their purposes related to clinical development of medicinal products, are given below:

PHASE I

First trials of a new active ingredient in man, often healthy volunteers. The purpose is to establish a preliminary evaluation of safety and of the tolerance in respect of the dose and a first outline of the pharmacokinetic/-dynamic profile of the active ingredient in humans.

PHASE II

Therapeutic pilot studies. The purpose is to demonstrate activity and to assess short-term safety of the active ingredient in patients suffering from a disease

or condition for which the active ingredient is intended. The trials are performed in a limited number of subjects and often, at a later stage, in a comparative (eg. placebo-controlled) design. This phase also aims at the determination of appropriate dose ranges/regimens and (if possible) clarification of dose/response relationships, in order to provide an optimal background for the design of wider therapeutic trials.

PHASE III

Trials in larger (and possibly varied) patient groups with the purpose of determining the short and long-term safety/efficacy balance of formulations of the active ingredient, as well as to assess its overall and relative therapeutic value. The pattern and profile of more frequent adverse reactions must be investigated and special features of the product must be explored (eg. clinically relevant drug interactions, factors leading to differences such as age, etc.). The design of trials should preferably be randomised double blind, but other designs may be acceptable, eg. long-term safety studies. Generally the circumstances of the trials should be as close as possible to normal conditions of use.

PHASE IV

Studies performed after marketing of the final medicinal product(s) containing the active ingredient, although definition of this phase is not completely agreed upon.
Trials in phase IV are carried out on the basis of instructions given in the marketing authorisation, including post-marketing surveillance, assessment of therapeutic value or strategies. However, clinical trials (after a product has been placed on the market) exploring eg. new indications, new methods of administration or new combinations, should in practice be considered as trials for new medicinal products having similar objectives as pre-marketing trials. Such studies may consequently - according to the circumstances - require trial conditions as described above for phases I-III