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SCIENTIFIC COMMITTEE ON MEDICINAL PRODUCTS AND MEDICAL DEVICES

Opinion
On
Quality and Safety of Blood

Adopted by
The Scientific Committee on Medicinal Products and Medical Devices
On 16 February 2000

1.1.1.1.Introduction

The quality, safety and effectiveness of blood and blood products are the subject of on-going concern among the general public, underlining the Community's need for a coherent and evolving range of legal instruments in this field.

A number of initiatives have been taken at Community level with the aim of ensuring a high level of quality and safety throughout the transfusion chain and promoting self-sufficiency in the Community, the most recent being Council Recommendation 98/79/EC of 29 June 1998 on the suitability of blood and plasma donors and the screening of donated blood in the European Community.[1]

The entry into force of the Treaty of Amsterdam, and in particular Article 152 (4) (a) and (5), has given an opportunity for the Commission to propose binding measures laying down high standards of quality and safety of blood and blood derivatives, in so far as these do not affect national provisions in force in the field of donations or of the medical use of blood and blood components.

There is, therefore, a need to establish at Community level sound scientifically-based safety and quality requirements for the collection, processing, storage and distribution of blood, blood components and blood precursors, and to fill in existing gaps in order to establish a high level of quality and safety throughout the transfusion chain.

In view of the above, former DG V/F had asked the Scientific Committee for Medicinal Products and Medical Devices (SCMPMD) to express its opinion on what are the key scientific elements for establishing high standards of quality and safety for the collection, processing, storage and distribution of whole blood, blood components and blood precursors.

In response to this request the SCMPMD has identified the following key elements:

Inclusion of the complete transfusion chain into the consideration

Quality and safety for the patient in the context of transfusion of labile blood components is the cumulative result of the different activities of the blood transfusion chain, stretching 'from vein to vein', including recruitment of donors, collection of donations, processing of units, testing of blood samples, storage of finished products, distribution of them to hospitals, testing in the hospital laboratories, handling in the hospital wards and finally transfusion and follow-up of the patient. Therefore, it is not sufficient to focus solely on certain aspects like collection, processing, storage and distribution of whole blood and blood components. Instead, only harmonised and widely accepted regulations which cover all elements of the transfusion chain will lead to high standards in transfusion medicine. Otherwise, there will be the risk that efforts in some areas will be undermined by weaknesses in others A chain is only as strong as its weakest link.

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[1] O.J. L203 21.7.98 p.14

For many years a number of recommendations and guidelines increasing the standards of the first part of the transfusion chain (from donor recruitment to the storage of finished products) have been issued by international (World Health Organization, Council of Europe) and national bodies. Less attention has been given to the rest of the chain. Therefore, it is important to the SCMPMD to emphasise the need also to set up detailed rules covering the clinical part of blood transfusion undertaken within the hospitals.

Based on the experience in some Member States it is highly recommended to require transfusion committees in every hospital, to set standards for blood transfusion, review patient files in relation to haemotherapy in order to ensure optimal use of blood, audit practices connected to blood component therapy and organising haemovigilance within the hospital.

Establishment of a Quality System

Although still to be supported up by scientific evidence, it is assumed that the introduction of a Quality System according to international standards will contribute to an increase in quality and safety in the blood transfusion setting. The issue of a Quality System for Blood Services was discussed at the "Vienna Forum" held July 13 to 15, 1998, in Baden/Vienna, with the support of the European Commission. The results have been published by the Austrian ministry of Health ("Quality Management for Blood Collection, Processing and distribution in the European Community: A Way Forward"). The following comments are based on the conclusions and recommendations of this conference.

A Quality System should be in agreement with scientific principles and should facilitate and not hinder further improvement of evidence-based medical practice. Elements of such principles are:

- evidence-based quality standards
- common critical quality system essentials
- education/training programs in transfusion medicine
- inspection/licensing
- quality audits/accreditation
- haemovigilance

A Quality System should ensure that no part of the transfusion chain is lacking in quality. Therefore, it seems to be scientifically justified to include the 'vein to vein' concept in the Quality System perspective.

Organisations and responsibilities of blood establishments vary between Member States. Activities may be restricted to blood donations, they may include diagnostic laboratory activities like blood group serology and antibody screening, include immunohaemotherapy units with therapeutic apheresis and stem cell transplantation centres, include research and education activities, be large or small blood component or product manufacturing sites where pharmaceutical rules and regulations must, to varying degrees, be adhered to, or even include all of the mentioned activities. All these activities have to be included in the Quality System.

Technical standards or guidelines are present in many Member States as well as systems for constant improvement of such documents. These standards are fitted to the situation in the Member States where they are produced and contribute to good medical practise. It seems scientifically justified, however, to define the most critical elements at the European level. As an example, it could be stated that the Quality System must include reference to written standards for all methods and that such standards must be based on validated methods. This will allow transparency and encourage the use of evidence based procedures.

It is essential that the core elements of a common Quality System are selected so as to be applicable throughout the European Community. This will facilitate benchmarking and other types of quality comparisons within and between Member States. Such activities may be essential to achieve mutual trust and recognition.

The selection of critical Quality System essentials is not a task of the SCMPMD. There are, however, some basic requirements which may be expected to add to quality and thus to trust between Member States. Such critical Quality System essentials are listed in the following table.

ORGANISATION	Localisation and premises / responsible person / management / personnel / authority / education and training / responsibilities
DOCUMENTATION SYSTEM	Quality master file or quality manual / organisation / prescriptive as well as postscriptive documents / record keeping / responsibilities / equipment / product identification and traceability / standard operating procedures (SOPs) with reference to published methods, guidelines etc. /
MANUFACTURING	Identification of products / contracts / storage / labelling provisions / hygiene control / proficiency testing / internal and external quality control / validation / calibration / incident-error-accident reporting and review
LICENSING / AUTHORISATION	To get started and then maintained / performed by the National Regulatory Authority / based on the presentation of the above Quality System essentials presented in a quality master file or manual and inspection / maintained licensing could require accreditation
ACCREDITATION / AUDITS	Updated regularly (yearly?) by an accreditation body / based on the above mentioned Quality System essentials as described (recognised essentials) / based on audits including compliance with the evidence based quality standard essentials as well as the critical quality system elements / correction of deviations and faults required to maintain accreditation (and licensing, where applicable)

The critical essentials discussed above are common elements in several internationally recognised quality standards like GMP, ISO 9000 series (9004:2000) with the revised ISO Guide 25 and EN 45000 series (ISO 17025), to which reference could be given in the common core Quality System (see references).

Implementation of quality management will take place at three levels; the European Community, the Member States and the Institutions. It is therefore essential that :

The European Community

- defines the core essentials of a common quality system as well as the critical elements of quality standards.
- establishes an expert committee for ongoing revision
  - of the elements of the core quality standards on a scientific evidence base
  - of the contribution of the QS to safety, efficacy and availability of blood and blood products

The Member States

- adopt and implement the core elements of the EC common quality system
- provide, publish, and maintain technical standards and clinical transfusion guidelines fulfilling the core requirements.
- adopt and publish inspection and audit criteria
- establish competent licensing authorities to conduct inspections and authorise blood establishments
- establish accreditation bodies acknowledged by the other Member States, basing their audits on recognised essentials as well as the core Quality System elements
- ensure the implementation of the core quality standard in clinical transfusion practise

Need for a haemovigilance system.

In order to continuously improve safety in blood transfusion, the administration of blood products should be covered by constant and efficacious vigilance. Therefore efficient haemovigilance systems should be introduced and maintained. By those systems

- data should be collected on serious adverse reactions in recipients, during and after transfusion of blood and blood components,
- data should be gathered on serious incidents in donors, during and after donation, as well as epidemiological data on donors (especially in relation with incidence and prevalence rates of infectious diseases markers).

Rapid Alert / Early Warning should be incorporated in the haemovigilance system to allow instant reaction in case of emerging threat to the blood supply, of any kind.

Collection of data in relation to the use of blood and blood components in the hospitals is highly desirable.

Haemovigilance systems should cover all the above mentioned areas and should be designed in a way to allow exchange of information relevant to haemovigilance between Member States.

In order to operate in an efficient way, haemovigilance within each Member State should have a clearly defined and transparent structure, starting at the ward level in the hospitals and making its way up to an institution at national level, centralising and evaluating the data collected, ensuring feed-back and having direct access to the competent authorities in case of emerging threat to the blood supply. The responsibilities in relation to haemovigilance should be clearly defined at each level of the system.

It should be recognised that heamovigilance will not be the only system in the field of medical care in which data on adverse reactions and unwanted events are collected and evaluated, possibly resulting in, sometimes immediate, measures. Other systems are pharmakovigilance, toxicovigilance and the collection and evaluation of unwanted events in the area of medical devices. It should be ensured that these systems are of similar structure, that interfaces for the exchange of data, where necessary, are well defined and that they can be easily handled by the health care personnel as the same person may have to submit observations to all these systems.

Blood donor recruitment and retention policies

Blood and products derived from it are life saving in many circumstances. At the same time they can cause harmful and, as the experience taught during the last decades, life threatening diseases if they carry infectious agents like HIV, HBV and HCV. It is therefore of paramount importance to minimise the potential bioburden of the donated blood. This goal is not completely achieved by simply testing blood donations for the presence of infectious agents. An additional and irreplaceable element is the exclusion of donors at risk which is based on the answers of donors to a number of relevant questions. It is obvious that the effectiveness of this exclusion mechanism depends on the reliability of the answers. It is therefore necessary to avoid circumstances in which potential donors may not tend to give the correct answers.

A crucial step to reduce the potential risk in the starting material is, therefore, to avoid to a maximum any pressure or any inducement for the donors at the medical interview and during the selection process before donation. All efforts must be undertaken to ensure that donors intending to donate blood give any relevant information pertaining to their health and disclose any information in relation with possible risk activities that could jeopardise the safety of the blood donation.

Educational efforts are necessary to encourage the donors to withdraw before, during and after blood donation, when the donor recognises that his blood may bear a potential risk for the future recipient when his blood is used for transfusion.

In the scientific literature, the effect of a payment to donors on the risk of transmitting infectious diseases by blood has been extensively discussed. After a preliminary review, it appears that voluntary, non-remunerated donations have the lowest residual risk. Therefore voluntary, unpaid donations seem to offer a higher margin of safety than paid donations. On request, the SCMPMD could deliver a critical review of published information pertinent to the role of payment or remuneration.

Need for criteria for the suitability of the donor and for his protection.

Disparities in policies and practices were reported to exist in the member states with regard to the selection of blood and plasma donors and the screening of their donations. The Commission carried out a survey of current regulations and practices in the Spring of 1997 with the view of proposing common criteria for the European Community (SEC(97) 2298: the suitability of blood and plasma donors and the screening of their donations).

The suitability and the protection of donors depend on several parameters: physical condition, medical history, frequency and volume of donation. For all these criteria, there is a permanent evolution in the scientific knowledge. Criteria must be adaptable to this evolving scientific knowledge. This adaptation could be proposed by a scientific committee.

Eligibility criteria for the acceptance of donors of whole blood and donors of components by apheresis are described in the recommendation 98/463/EC. Nevertheless the following should be kept in mind :

- Physical condition: age, body weight, blood pressure, pulse, haemoglobin or haematocrit and total serum protein. For all these characteristics acceptance criteria are established, based on long-time experience, but not on scientific data.

  Deviations of these criteria must be possible for specific cases (e.g.: autologous blood donations, need for exceptional and rare blood groups etc). These exceptions should be at the discretion of the responsible physician.

  Before donating blood or plasma the general appearance of the donor should also be evaluated.

- Medical history: for the permanent and temporary deferral criteria of donors, both for protection of the donor himself and for the protection of the recipient, there are also evolving new scientific data. The lists of diseases which lead to deferrals should be revised regularly on the basis of this new scientific data (e.g. fainting spells (syncope) or convulsions are not always a reason for exclusion).

- Drug use: As drugs (prescribed, non prescribed) taken by the donor and contained in his donations may cause adverse reactions in the recipient regulations have to be set up which contribute to minimising this risk.

- Frequency and volume of donations: again, available figures are not supported by scientific data. On the occasion of the presentation of the recommendation (98/463/EC) scientific research on these donation criteria was announced: "existing guidelines at international level in the area of blood recommended 15 litres as the maximum annual volume of plasma to be collected via automated plasmapheresis; there is no scientific evidence of whether or not adverse health effects result from higher volume collection; this area should be a priority area for scientific studies." Indeed studies in this field should be undertaken. The figures for frequency and volume of donations will depend on the evolution of collection techniques.

- The criteria for suitability of donors are not fully applicable when autologous donations are intended where donor and recipient are the same person. Therefore, these criteria have to be drafted in a way which does not unnecessarily impede autologous donations.

- The possibility of a scientific committee in charge of the adaptation of the requirements should be envisaged.

Testing requirements

To prevent adverse reactions in recipients of blood components or plasma derivatives it is necessary to perform a number of blood group tests and microbiological assays on each donation of whole blood or plasma. The testing requirements may be more restricted or adapted (e.g. HCV NAT-testing) for plasma which is only used for fractionation. Specific products/indications may require additional testing.

All tests or reagents have to comply with the EU Directive on Medical Devices for In-vitro Diagnosis 98/79/EC. A quality system to monitor performance of the employed tests should be in place. The test results should be interpreted according to the manufacturer's instructions, as this is the method which was accepted for licensing according to the fore-mentioned EU Directive. With regard to sensitivity and specificity, all tests should comply with state of the art standards.

1.1.2. Testing requirements for all donations currently performed in all member states

As is defined in Council Recommendation 98/436/EC ("On the suitability of blood and plasma donors and the screening of donated blood in the European Community" - O.J.No.L203.21/07/98 p.14) all donations (including autologous predeposit blood units) are tested for blood group ABO and Rhesus (D). In some Member States these tests should be performed twice for new donors using two different samples (for example obtained by taking blood from the vein of the donor respectively from the blood unit). In repeat donors the blood group results should be compared with historical blood group data from the donor.

The following serological screening tests are applied to detect the presence of the respective blood borne viruses:

- HBsAg (for hepatitis B virus), minimal 1 ng/ml;

- anti-HCV antibodies (for hepatitis C virus), employing a multi-antigen test;

- anti-HIV 1 and anti-HIV 2 or combined testing of anti-HIV-1/2 antibodies (for Human Immunodeficiency Virus (HIV)1/2, including HIV-1 subtypes E and O).

For autologous predeposit transfusions these screening tests should be included to limit exposure of personnel of blood centres and hospital staff to infectious agents and to comply with GMP regulations.

Microbiological screening tests should be repeated in duplicate if the initial test is reactive (initially reactive). When one or more of the latter two test results is reactive (repeatedly reactive), the screening test is considered positive and the donation and related products are not

to be used for transfusion or fractionation. If none of the latter two duplicate tests is reactive, the screening test is considered negative and the donation and related products may be released. A supplementary assay, preferably using a different method, should be employed to confirm a repeatedly reactive screening test result. Supplementary assays should preferably be as sensitive, but more specific than the screening test.

If a new virus infection of a donor is detected donations given during a defined period of time before this detection should be identified (Look-back procedure). If they are still available they should be withdrawn. If they have already been administered the recipient should be informed that he might be infected. A test for the detection of this infection as well as medical counselling should be offered. The details of such a look-back procedure have to be defined in writing and should be updated in the light of new scientific evidence. In addition, there is a need for a well defined procedure which is followed in the communication of such new infections to companies which have obtained plasma or other components for further processing.

The CPMP requires that all (pooled) plasma used for fractionation is tested for HCV using NAT (Nucleic Amplification Technology).

Note: although at present testing of vCJD (variant Creutzfeldt-Jakob Disease) in blood donors is not possible, it is likely that once a sensitive and specific test for this disease is available such a test will be implemented in all member states.

1.1.3. Testing requirements for specific products and/or indications used in all member states

For specific clinical conditions it may be necessary to use only blood donations which are typed for red cell antigens (other than ABO / Rhesus(D)), as well as Human Leukocyte Antigens (HLA) and Human Platelet Antigens (HPA). All member states should therefore have a base of donors, which are typed accordingly.

Testing of anti-CMV (Cytomegalovirus) antibodies is considered necessary for (non-leukocyte depleted) blood components when transfused to patients at risk of CMV-infection, such as CMV-seronegative bone marrow and organ transplant recipients as well as neonates with a birth weight below 1500 g when the mother is anti-CMV seronegative.

For medicinal products derived from plasma or blood, specific requirements as defined by the CPMP are applied, including HCV NAT of manufacturing pools of plasma for fractionation.

1.1.4. Additional tests employed by some member states

In addition to the previously described tests, a variety of assays for blood group typing and antibodies to blood cells as well as microbiological tests and surrogate tests are used in a number of member countries. For a variety of reasons all countries do not uniformly use these tests. In some instances the scientific evidence for such testing is considered to be insufficient or disputed (e.g. ALT, neopterin). Some tests are felt to be not sensitive or specific enough to identify donors with certain blood borne diseases (e.g. malaria). Furthermore cost/benefit considerations (e.g. Rh-phenotyping) and epidemiological data (e.g. anti-HTLV-I/II) may have led in some countries to their implementation for all donations or only for new donors, while in others such testing is not performed.

Rhesus C-, c-, E-, and e-phenotyping and determination of K-antigens of all blood donations is required in some member countries. The scientific evidence for routine testing of these antigens is weak and its costs are significant. It may argued that blood group K should still be included in the testing requirements to prevent allo-immunisation in female recipients (notably women in the pre-menopausal period) which may lead to haemolytic disease of the new-born.

Testing of antibodies to red cell antigens, so-called irregular antibodies, is performed in some member countries. There is as yet no consensus that such testing should be routine or only performed in specific situations such as in donors with previous pregnancies and/or transfusions. It should be emphasised that only clinical important antibodies should be included and that the criteria for testing (e.g. titre and type of antibodies) should be defined. It may be argued that for certain products (e.g. platelet concentrates) which contain plasma, such testing is of benefit.

For many years ALT has been used in a number of member countries as a surrogate marker for the prevention of posttransfusion-hepatitis. More recently, the need for such testing has been questioned as routine testing of hepatitis C has been implemented throughout the Community. In 1999 the CPMP has decided that ALT testing is not required for plasma derivatives (CPMP/BWP/385/99).

In the past the presence of anti-HBc-antibodies in blood donations was used as a surrogate marker for prevention of transfusion transmitted hepatitis. Testing of anti-HBc-antibodies in blood donors is not required in most member countries and in some only for new donors. In contrast to previous epidemiological data from the USA, three prospective studies carried out in Europe failed to show a preventative effect on posttransfusion hepatitis (Reesink, 1988, Aymard, 1986, Widell, 1988).

Through the use of NAT-methods it is possible to shorten the "open window" period of infection through a number of blood borne viruses. HCV- NAT-testing in manufacturing pools is required by the CPMP for the preparation of medicinal products derived from blood or plasma. In some member countries this technology has recently been introduced for the detection of HCV (and occasionally for HIV) in minipools of whole blood donations and the outcome of such testing is used for the release of cellular blood components. Several other countries have made preparations for the implementation of NAT in the near future. It is expected that in time other blood born viruses such as Parvo B19 and hepatitis A (HAV) will be included for the testing of plasma for fractionation.

Routine testing for antibodies to Human T-cell-Lymphoma/leukaemia Virus (HTLV)-I/II is required only in some member countries. As there is no evidence that this virus is transmitted through plasma, it may be argued that plasma donors need not to be tested for this virus. There is discussion about the effectiveness of this testing for all donors in stead of only first time donors.

Although syphilis testing (Treponema pallidum) of blood donors is performed by most member countries already for many years, there are some countries where only new donors are tested (Sweden) or testing is not mandatory (Finland). Again, the testing of plasma donors for syphilis may be questioned, as there is no evidence for transmission through plasma products.

There is no common policy among the member states with regard to malaria testing. As potential donors who have visited endemic areas are usually excluded for three years in case of

specific immunity (residents) or for shorter periods in case of tourism by non-immune persons (non-residents), blood centres may face problems when there are shortages in the supply of blood products. Through the use of tests for malaria the exclusion period may be shortened. However, the currently used malaria tests are not yet validated for general use or found to be of insufficient quality.

In one country an additional surrogate test, i.e. Neopterin, is required for all donations. Other countries have decided not to include this test which is a non-specific marker of immune reactivity.

It may be worth to pose questions to the SCMPMD to elaborate opinions on the different microbiological assays mentioned in this section.

1.1.5. Tests for bacteria

Transmission of bacteria through the transfusion of blood components may cause severe risks for the recipient(s). Recent haemovigilance studies have demonstrated the significance of such risk. New automated techniques which allow the early detection of bacterial contamination of blood are needed. More research is needed to decide if these methods should be introduced for routine screening of all donations or only for specific products e.g. platelet concentrates.

Storage conditions.

Current recommendations regarding storage conditions for blood components for transfusion are mainly based on long-standing experience. However, the storage conditions may have to be changed with technical progress made in this field, and may have to be adjusted for new products involving e.g. apheresis or leukodepletion techniques. Such fine-tuning of storage conditions would have to be based on measurements of stability and integrity of the product, as well as assessment of potential bacterial contamination.

In some countries, e.g. Germany, blood components are regarded as medicinal products and therefore dossiers and marketing authorisations exist. In these dossiers, also the licensed storage conditions are contained. The marketing authorisation holder is required to demonstrate the quality of his product by suitable laboratory measurements. He also has the possibility to claim a certain shelf life for his product, if he is able to provide stability data. Several marketing authorisation holders, for instance, were able to demonstrate that under optimal and well-controlled conditions fresh frozen plasma is sufficiently stable at –30°C for more than two years. Such data supporting a certain shelf life, however, could not be easily generalised.

Thus, it is proposed to list general recommendations for storage conditions, as requirements which should be adhered to, unless justified by valid laboratory measurements approved by a competent authority. Such general recommendations are already existing on national and European levels. It appears desirable to harmonise these existing guidance documents. It is also recommended, especially for new products, to develop and improve laboratory methods, which would provide meaningful information on the quality, safety, and clinical efficacy of such products in correlation to the storage period.

It could be discussed whether or not maximum times between collection and freezing of certain products have to be fixed. The SCMPMD, however, believes, that this aspect pertains to the Good Manufacturing Practice (GMP) and should be covered by the Quality System, mentioned

above. In some member states (Germany, Austria), these aspects are determined by the Marketing Authorisation.

Requirements for labelling.

The labelling is a typical item to be regulated in a legally binding way. However, blood components are licensed as medicinal products in same Member States (Germany, Austria), where the labelling is already determined by legislation (e.g. German Drug Law). Such already existing regulations should be taken into account.

Any new regulatory document dealing with labelling should take into account the limited space on the labels and the necessary links to electronic data systems. For discussion, it is important to decide, whether it is intended to have further literature ("package leaflet"), which is provided to the users (treating physicians, possibly also patients) as a further information. Such literature is required e.g. by the German drug law, and gives the opportunity to provide much more detailed information.

Introduction of new preparations and products

The way by which the introduction of new preparations and products for transfusion is regulated differs widely between Member States. The extremes are no regulation at all on one hand and a licensing procedure as for medicinal products on the other hand. The SCMPMD recommends that new preparations and products are checked by a body independent from the producer. This procedure should ensure that the final preparation is of high quality, is produced by validated methods and is effective and safe as revealed from clinical trials. This procedure should be designed not to impede the evolution of the products and the timely adaptation to the state of the art.

Importance of a common terminology.

It is a general principle that any kind of prescription needs to be clear and unambiguous in order to fulfil its purpose. This is particularly true for scientific work and legislation.

Concise definitions are clearly needed. This poses several problems. Several terms have been used by those who are working in the transfusion sector for a long time, and have been influenced by the specific medical practice and tradition within a country or area. Thus a term may have a variable meaning. Items in new and developing fields like the use of haematopoietic cells, are first named by researchers according to specific aspects they are interested in, but may be subject to revised nomenclature with increasing use. Scientific terminology is often very specific, but for the purpose of regulatory documents more general and comprehensive terms are needed.

Considering the terminology in an official document intended to regulate aspects of the transfusion sector, both the addressees of the document and the items which are to be regulated, as well as the precautions and measures to be implemented have to be clearly defined. In particular, the following requirements can be identified:

- The terminology should be unambiguously understandable both for the workers in the transfusion sector and the regulatory bodies.

- It is necessary to identify the items which need to be defined considering the purpose of the regulatory document to be drafted.

- It is important that the terminology is coherent with definitions in previous regulatory documents.

- The definitions should be scientifically sound and correct, and avoid unnecessary circumscriptions.

- The terms should be specific enough to clearly meet the intended meaning, and comprehensive enough to cover the entire item to be addressed.

- As far as possible, the terminology should incorporate the terms which have evolved and are accepted in the field, particularly those incorporated in existing guidance documents.

- The terminology should take into account differences in the medical practice and traditions in the member states, and should provide harmonised definitions where necessary and feasible.

The positive effects of a common terminology can be exemplified by the accurate and unambiguous set of definitions of the status of donors (first time, repeat, regular, etc.) given in the Council Recommendation of June 29, 1998, on the suitability of blood and plasma donors and the screening of donated blood in the European Community. As a consequence, comparisons of donor policies and donor populations between Member States, which were difficult and always methodologically questionable due to the lack of common terminology, are now easily possible and may be a tool of high value for the European Community. Such a common terminology should be expanded to all the other aspects of the transfusion chain.

Mechanism for establishing and maintaining harmonised Quality Standards.

The guidelines for component manufacture and quality monitoring, currently in use in the member states (either as national, regional/local, or published by the Council of Europe), could be drawn on by the Community to derive a common set of quality standards for blood component manufacture and quality monitoring. These documents in general represent a valid interpretation of the current state of knowledge. The standards they contain have small variations one from the other, and seem to be convergent on most points. Important differences in approach do exist, reflecting different historic positions rather than different approaches to quality of patient care. However, there does not seem to be a scientific basis for a strong challenge to the different positions.

These Guideline documents do not exist as stand alone documents: they are essentially part of a process of constant development and review by focussed groups of experts meeting year after year: they should not be frozen in time. In particular they were not designed to be enshrined in a legislative process. It is very unlikely that the Community could do as well or better without setting up a similar dynamic process of regular review and feedback process. Guidelines formulated by the Commission without such a process would be unlikely to be valued by Inspectorates in Member States or indeed by Transfusion Services.

There is no reason why the Community could not put together its own Working Group to produce a single harmonised Guideline, or to standardise areas of discrepancy in the current

guidelines. However, it would be necessary to put in place a dynamic process whereby that Group would regularly review and update the Guideline. It would take them at least a year of work to produce the first edition. They would have to start on the second edition almost immediately, and so forth.

The SCMPMD recommends that

Blood Establishments should prepare and monitor all blood components collected, processed, stored and distributed, according to specifications and quality parameters that reflect current best practice and the state of the art. The specifications and quality parameters in use must be subject to a formal process of regular review and update at timely intervals. Member States must ensure that that this process is conducted by qualified experts in the relevant areas of transfusion practice, and that it is subject to inspection by the national competent body. At present, national competent bodies are free to choose the Quality Standard for blood products that they consider appropriate.

The Commission could review the standards currently in use throughout the Community, and in particular the process by which they are brought into being and maintained.

Annex

List of blood components

Blood components are defined according to the Council Recommendation of June 29, 1998, on the suitability of blood and plasma donors and the screening of donated blood in the European Community as "therapeutic components of blood (red cells, white cells, platelets, plasma) that can be prepared by centrifugation, filtration and freezing using conventional blood bank methodology".

A complete list taking into account all possible preparations would be extremely tedious, and not be easily updated. A more comprehensive approach is based on defining two different steps in the preparation of blood components:

- Basic blood components prepared through very simple processes from whole blood or apheresis donation;

- Additional procedures, that can be applied to several basic blood components.

In addition, some biological characteristics of the donor may also contribute to the definition of blood components, e.g. CMV status, phenotype of red cells, HLA or platelet antigens, as well as a known negative compatibility test with the intended recipient. These aspects have not been taken into consideration in this list.

The following three tables provide

1. definitions of **basic blood components** (homologous, autologous and hematopoietic stem cell concentrates) ;

2. definitions of additional **procedures**;

3. the possible **associations between basic blood components and additional procedures**.

1. BASIC BLOOD COMPONENTS

HOMOLOGOUS BASIC BLOOD COMPONENTS

1	Whole blood	collected directly from the donor in a plastic bag with an anticoagulant solution, without any further manipulation
2	Red cell concentrate	prepared from whole blood after centrifugation and elimination of a major part of plasma
3	buffy-coat depleted Red cell concentrate	prepared from whole blood after centrifugation and elimination of plasma and buffy-coat

4	apheresis Red cell concentrate	red cells collected by apheresis with a minimum amount of plasma
5	platelet concentrate (PRP method)	prepared from whole blood after a two step separation procedure : preparation of PRP by a low g centrifugation and separation of platelets by a high g centrifugation
6	platelet concentrate (buffy-coat method)	prepared from whole blood after a two step separation procedure : preparation of buffy-coat by a high g centrifugation and separation of platelets by a low g centrifugation
7	apheresis platelet concentrate	platelets collected by apheresis
8	apheresis granulocyte concentrate	granulocytes collected by apheresis
9	fresh frozen plasma (from whole blood)	plasma prepared either by a single high g centrifugation or by two consecutive centrifugation steps (preparation of PRP by a low g centrifugation and plasma extraction after a high g centrifugation of the PRP)
10	apheresis fresh frozen plasma	plasma prepared by apheresis
11	peripheral blood hematopoietic stem cell concentrate	hematopoietic stem cells collected by apheresis
12	cord blood hematopoietic stem cell preparation	hematopoietic stem cells collected from umbilical cord blood
13	bone marrow hematopoietic stem cell preparation	hematopoietic stem cells collectes by bone marrow aspiration

AUTOLOGOUS BASIC BLOOD COMPONENTS

1	Whole blood	consists in whole blood collected directly from the donor in a plastic bag with an anticoaguant solution, without any further manipulation
2	Red cell concentrate	prepared from whole blood after centrifugation and elimination of a major part of plasma
3	apheresis Red cell concentrate	red cells collected by apheresis with a minimum amount of plasma
4	apheresis platelet concentrate	platelets collected by apheresis
5	fresh frozen plasma (from whole blood)	plasma prepared either by a single high g centrifugation or two consecutive centrifugation steps (obtention of PRP by a low g centrifugation and plasma extraction after a high g centrifugation of the PRP)

6	apheresis fresh frozen plasma	plasma prepared by apheresis
7	peripheral blood hematopoietic stem cell concentrate	hematopoietic stem cells collected by apheresis
8	bone marrow hematopoietic stem cell preparation	hematopoietic stem cells collected by bone marrow aspiration

2. ADDITIONAL PROCEDURES

1	additive solution	any solution added to a blood component that contributes to minimise storage lesions
2	paediatric preparation	consists in preparing several units from a single blood component that will be available for sequential use in the same patient
3	volume reduction	elimination of the supernatant of a given blood component
4	pooling	consists in mixing several blood components for clinical use
5	leukoreduction	reduction of leukocyte content of a given blood component below a specified threshold, eg 10e6
6	plasma depletion	elimination of the major part of plasma with a procedure ensuring that the initial plasma protein concentation is reduced below a specified threshold, eg .5g/L
7	cryopreservation	preservation of a cellular blood component in the frozen state
8	gamma irradiation	irradiation by gamma rays with a procedure ensuring that the irradiation dose is between specified minimum and maximum values , eg above 3.5Gy and below 5Gy
9	virus inactivation	any treatment (physical, chemical or physico-chemical) that ensures a significant reduction of viral load, eg log depletion >6
10	immunologic selection	positive or negative selection by immunological means leading to a higher degree of purity of hematopoietic stem cells or a reduction of unwanted cell populations
11	chemical (drug) selection	use of drug to eliminate undesirable cells from a hematopoietic stem cell concentrate

12	in vitro expansion	use of growth factors during in vitro cultivation in order to obtain a significant expansion of haematopoietic stem cells

3. POSSIBLE ASSOCIATIONS BETWEEN BASIC BLOOD COMPONENTS AND ADDITIONAL PROCEDURES

HOMOLOGOUS BASIC BLOOD COMPONENTS	additional preparations											
	1	2	3	4	5	6	7	8	9	10	11	12
Whole blood		x	x		x	x	x	x				
Red cell concentrate	x	x	x		x	x	x	x				
buffy-coat depleted Red cell concentrate	x	x	x		x	x	x	x				
apheresis Red cell concentrate	x	x	x		x	x	x	x				
platelet concentrate (PRP method)			x	x	x	x	x	x				
platelet concentrate (buffy-coat method)	x		x	x	x	x	x	x				
apheresis platelet concentrate	x	x	x	x	x	x	x	x				
apheresis granulocyte concentrate			x			x		x				
fresh frozen plasma (from whole blood)				x	x				x			
apheresis fresh frozen plasma				x	x				x			
peripheral blood haematopoietic stem cell concentrate			x			x	x			x		x
cord blood haematopoietic stem cell preparation			x			x	x			x		x
bone marrow haematopoietic stem cell preparation			x			x	x			x		x

AUTOLOGOUS BASIC BLOOD COMPONENTS												
Whole blood					x		x					
Red cell concentrate	x				x		x					
apheresis Red cell concentrate	x				x		x					
apheresis platelet concentrate	x				x		x					

fresh frozen plasma (from whole blood)												
apheresis fresh frozen plasma												
peripheral blood haematopoietic stem cell concentrate			x			x	x			x	x	x
bone marrow hematopoietic stem cell preparation			x			x	x			x	x	x

1 = additive solution

2 = paediatric preparation

3 = volume reduction

4 = pooling

5 = leukoreduction

6 = plasma depletion

7 = cryopreservation

8 = gamma irradiation

9 = virus inactivation

10,= immunologic selection

11 = chemical (drug) selection

12 = in vitro expansion