BLOOD, TISSUES AND CELLS FROM HUMAN ORIGIN

the European Blood Alliance Perspective

TABLE OF CONTENTS BOOK I–II

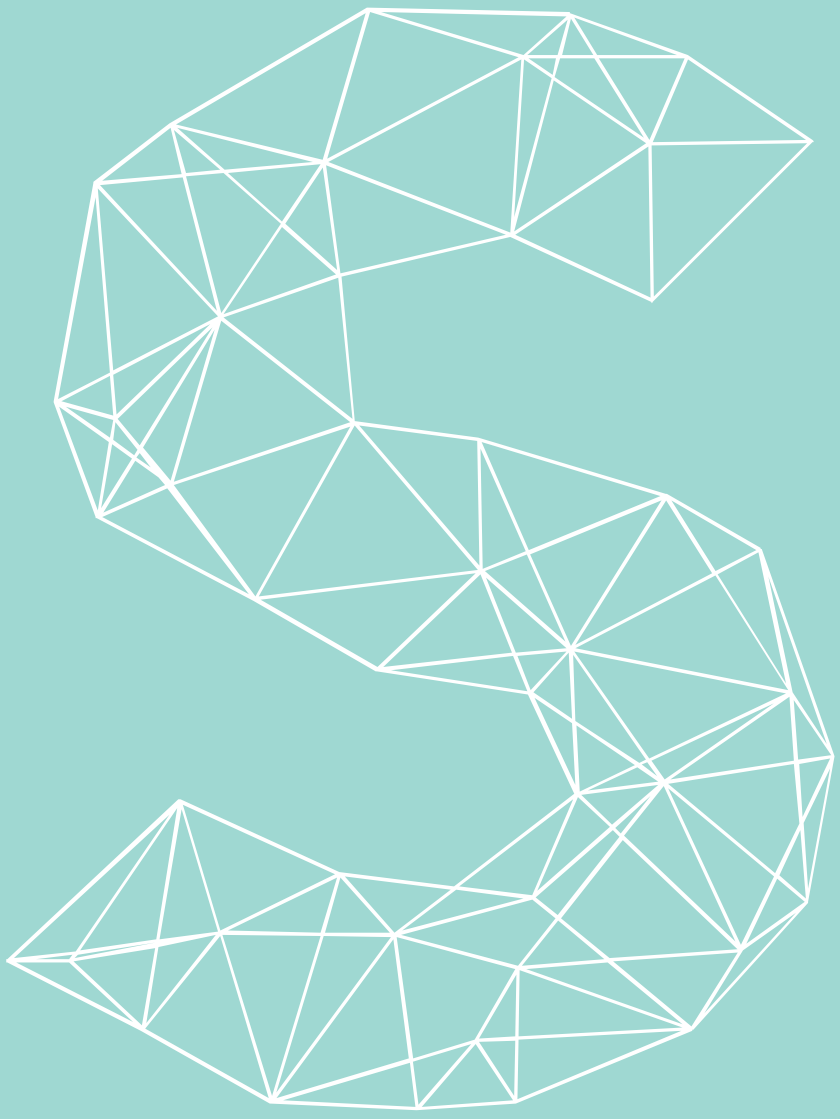
BOOK I · SAFETY BY REGULATION
Legislation and challenges

BOOK II · SAFETY BY VNRD
Legislation and challenges

TABLE OF CONTENTS BOOK III–IV

BOOK III · SAFETY BY MANAGEMENT
Blood and Blood components of Human origin

BOOK IV · SAFETY BY MANAGEMENT
Tissues and Cells of Human origin



BY REGULATION

Legislation and challenges

Blood, tissues and cells from human origin: the European Blood Alliance Perspective

SAFETY BY REGULATION

Legislation and challenges

Corresponding address
European Blood Alliance (EBA)
Plesmanlaan 125
1066 CX Amsterdam
tel: +31 20 512 3291
fax: +3120 512 3755
eba@sanquin.nl

English revision
Mary Condren

Graphic Design
Studio Duel

Printing
Ando bv

ISBN
9789082031003

Transparency Register
EBA is registered in the EU Joint Transparency Register. More information and a link to this register: www.europeanbloodalliance.eu/TR

e-pub / pdf

EDITORS

AUTHORS & CONTRIBUTORS

Authors

David Allan
Canadian Blood Services
Canada

Georges Andreu
Institut National de Transfusion Sanguine (National Institute of Blood Transfusion)
France

Jolanta Antoniewicz-Papis
Institute of Hematology and Transfusion Medicine Warsaw
Poland

Alex Aquilina
Maltese National Blood Transfusion Service
Malta

Kari Aranko
Suomen Punainen Risti Veripalvelu (Finnish Red Cross Blood Service)
Finland

Halvard Bönig
Deutsches Rotes Kreuz -Blutspendedienst Baden Württemberg - Hessen (German Red Cross Baden Württemberg – Hessen)
Germany

Olivia Ligia Burta
Centrul de Transfuzie Sanguina, Oradea (Blood Transfusion Centre, Oradea)
Romania

Yves Charpak
Établissement Français du Sang (French Blood Establishment)
France

Dana Devine
Canadian Blood Services
Canada

Rich Feliciano
American Red Cross
USA

Gilles Folléa
European Blood Alliance
The Netherlands

George Galea
Scottish National Blood Transfusion Service
Scotland

Andrew Hadley
National Health Service: Blood and Transplant (NHSBT)
United Kingdom

Reinhard Henschler
Institute for Transfusion Medicine and Immune Hematology, German Red Cross Blood Service, Goethe University, Frankfurt, Germany
Germany

Keld Homburg
Clinical Immunology Region Zealand Transfusion and Tissue Services, Hospital South
Denmark

Wim de Kort
Stichting Sanquin Bloedvoorziening (Sanquin Blood Supply Foundation)
The Netherlands

Laurence Le Texier
Établissement Français du Sang (French Blood Establishment)
France

René van Lier
Sichting Sanquin Bloedvoorziening (Sanquin Blood Supply Foundation)
The Netherlands

Lisa McLaughlin
American Red Cross
USA

Markus Müller
Deutsches Rotes Kreuz -Blutspendedienst Baden Württemberg - Hessen (German Red Cross Baden Württemberg – Hessen)
Germany

Veřa Novotný
Sichting Sanquin Bloedvoorziening (Sanquin Blood Supply Foundation)
The Netherlands

Jukka Partanen
Suomen Punainen Risti Veripalvelu (Finnish Red Cross Blood Service)
Finland

Joanne Pink
Australian Red Cross Blood Service
Australia

Liz Pirie
Scottish National Blood Transfusion Service
Scotland

Primož Rožman
Zavod Republike Slovenije za transfuzijsko medicino (Blood Transfusion Centre of Slovenia)
Slovenia

Michael Schmidt
Deutsches Rotes Kreuz -Blutspendedienst Baden Württemberg - Hessen (German Red Cross Baden Württemberg – Hessen)
Germany

Christian Seidl
Deutsches Rotes Kreuz -Blutspendedienst Baden Württemberg - Hessen (German Red Cross Baden Württemberg – Hessen)
Germany

Erhard Seifried
Deutsches Rotes Kreuz -Blutspendedienst Baden Württemberg - Hessen (German Red Cross Baden Württemberg – Hessen)
Germany

Ruth Sylvester
America's Blood Centers
USA

Karen van der Toren
Stichting Sanquin Bloedvoorziening (Sanquin Blood Supply Foundation)
The Netherlands

Philippe Vandekerckhove
Rode Kruis Vlaanderen (Red Cross Flanders)
Belgium

Claudio Velati
SIMTI - Sociata Italiana di Medicina Transfusionale e Immunoematologia (Italian Society of Transfusion Medicine and Immunohematology)
Italy

Cees Verhagen
Stichting Sanquin Bloedvoorziening (Sanquin Blood Supply Foundation)
The Netherlands

Elze Wagenmans
Stichting Sanquin Bloedvoorziening (Sanquin Blood Supply Foundation)
The Netherlands

Lee Ann Weitekamp
Michigan Blood
USA

Jeroen de Wit
Stichting Sanquin Bloedvoorziening (Sanquin Blood Supply Foundation)
The Netherlands

Günther Wittauer
Österreiches Rotes Kreuz (Austrian Red Cross)
Austria

Gilles Folléa
Jeroen de Wit

FOREWORD

For many decades, the transfusion of blood components and plasma derived medicinal products has been established as a lifesaving therapy. However, the risks of this therapy were highlighted when many transfused patients were contaminated by infectious transmissible agents, mainly before the 1990s. For this reason, the preparation of blood components and plasma derived medicinal products, from collection to distribution, is now highly regulated.

For blood components, the current Blood Directives, issued and enforced between 2003 and 2005, describe the basic regulatory requirements and standards of quality and safety for the collection, testing, processing, storage and distribution of human blood and blood components. They also provide the regulatory bases of haemovigilance requirements for traceability and notification of serious adverse reactions and events.

Nonetheless, transfusion medicine is evolving fast and the European Commission initiated in 2012 the process of revising the current Blood Directives, by consulting the Competent Authorities for blood and blood components in the EU Member States. This has offered a unique opportunity to contribute to the reflection needed for this revision process, starting with the following question: how can these Directives be updated, with the aim of improving patient and donor safety, and healthcare efficiency?

The use of tissues and cells of human origin has also become an important therapeutic resource for many patients. The preparation of human tissues and cells, from donation or procurement to distribution, is also highly regulated. The current Directives on human tissues and cells, issued and enforced between 2004 and 2006, describe the basic regulatory requirements with standards of quality and safety for the donation, procurement, testing, processing, preservation, storage and distribution of human tissues and cells. They also provide the regulatory bases of human tissue and cell vigilance, with basic requirements for traceability and notification of serious adverse reactions and events.

The European Commission also initiated the process of revising the current Directives on human tissues and cells, by requesting the EU Parliament to produce a report on voluntary and unpaid donation of tissues and cells. The final report, voted at the EU Parliament in September 2012 with a vast majority, strengthened the EU political willingness to further promote voluntary and unpaid donation of tissues and cells. Similar to the Blood Directives, this offers a unique opportunity to contribute to the reflection needed for this revision process, starting with the basic question: how can these Directives be updated, with the aim of improving patient and donor safety and healthcare efficiency?

The European Blood Alliance (EBA) is an association of non-profit Blood Establishments collecting, processing and distributing blood and blood components from voluntary non-remunerated donors, and has 25 members throughout the European Union and European Free Trade Area States. Its mission is threefold:

- To contribute to the availability, quality, safety and cost-effectiveness of the blood and tissue and cell supply for the citizens of Europe by developing and maintaining an effective and efficient collaboration amongst European blood and tissue and cell services.

- To increase public and professional awareness of voluntary non-remunerated donation of blood and blood components, as the basis for preparation of blood components, which are an indispensable therapeutic means of saving patients.

- To assist European blood establishments to continuously improve their performance, based on scientific and ethical principles, for the benefit of patients.

Given the forthcoming revision of both the Blood Directives and the Directives on human tissues and cells, this book aims at presenting the European Blood Alliance perspective on blood, tissues and cells from human origin.

The book identifies some of the major challenges, in particular, the development of voluntary non-remunerated donors and donations and the prevention of potential negative consequences of unregulated competition between blood component suppliers, both of prime importance. Expertise on key subjects concerning blood and blood components, and human tissues and cells is derived from the leading practitioners on these subjects throughout Europe, and for cellular therapies, also from Australia, Canada and the United States. Their expertise focuses first on patient safety, and leads to final recommendations, most of which should be at least discussed and seriously considered in the revision process of the Directives concerned.

For the benefit of patients, donors, healthcare providers and stakeholders, we hope that this book will assist policy and decision makers, and the regulators involved in these important domains.

Philippe Vandekerckhove

01. THE ENVIRONMENT OF THE EUROPEAN BLOOD ESTABLISHMENTS: NEW SCENE AND CHALLENGES

This chapter describes the overall environment within which European Blood Establishments (BEs) and their stakeholders (hospitals, policy-makers, regulators and suppliers) must operate today, and plan for the future.

1.1 HISTORICAL CONTEXT

For anybody connected with blood transfusion at that time, the 1980s and early 1990s were dominated by the disastrous impact of the transmission of HCV and HIV to thousands of recipients of blood transfusions and plasma-based treatments. In many countries, this led to a decline in public and governments' confidence in the safety of the blood supply.

Conversely, for the last 15 years, in Western Europe and in other parts of the developed world, in spite of continuing challenges, impressive levels of continuity and sufficiency of blood supply have been maintained, and consistently high levels of safety of the product to the patient have been achieved.

Throughout this period, in the face of an ageing European population and rapidly developing medical treatments for such ailments as heart disease, cancer and tissue deterioration, blood transfusion has remained a vital clinical intervention. Data from haemovigilance systems that monitor untoward events involving blood transfusion shows that in these countries the greatest danger by far to blood recipients lies, not in the quality of the products issued to hospitals by BEs, but from problems arising in hospitals from their procedures. The main hospital based problem is that the wrong product is transfused to the patient.

Significant contributors to this strong performance on the part of BEs have included the level of sustained additional investment in blood and blood product safety, improved management of BEs and increased regulatory scrutiny: these all comprised responses by national governments to the HCV and HIV disasters. In addition to national government action in many European states, the EU implemented directives setting standards for both plasma derived products and blood components. These set the minimum requirements for blood related activities in all EU Member States.

BEs and Plasma Derived Medicinal Product (PMDP) manufacturers in the EU and in many other parts of the world now find themselves operating within a much stricter legal and regulatory framework than was imaginable 25 years ago. Nonetheless, at the time of writing, the achievement of equivalent standards across the EU, driven by the EU Blood Safety Directive 2002/98/EC *(See Chapter 2)* and its 'daughter' directives, has still to be completed, as it relies on two things to achieve this equivalence of standards:

1. The required funding in all EU Member States to introduce all steps necessary for equivalence across the EU
2. Equivalence of inspection regimes to enforce these standards

Despite major efforts, the safety of the product persistently raised considerable challenges in the very recent past.

In Europe, in the 1990s and the early 21st Century, vCJD threatened to become as big an issue as HCV and HIV had been in the preceding decades, which actually precipitated the current EU directives on blood. However, the outbreak has been isolated almost entirely to the UK where the problem originated, and, to date, the number of cases has been small.

There now appear to be reasonable hopes that the spread of vCJD via blood transfusion, tissue and organ transplants and the use of certain problematic surgical equipment will be limited.

There have been differing views about the range of precautionary measures taken by the UK Government to minimise the secondary transmission of vCJD, and by many other governments and regulatory authorities to limit the risk of importing vCJD via UK citizens and residents. So far, the risk of the outbreak developing into an epidemic has been avoided.

New diseases continue to emerge and known diseases re-emerge in Europe, including West Nile Virus (WNV), Chikungunya, Severe Acute Respiratory Syndrome, Chagas disease, dengue fever, babesiosis [1]. In Spain alone, it has been suggested that there may be some 15,000 carriers of the Chagas parasite amongst travellers and immigrants from South America. There is also a significant increase in global cases of dengue fever and in October 2012, this concerned an EU country with an outbreak in Portugal (two isolated cases had been reported in France in 2010).

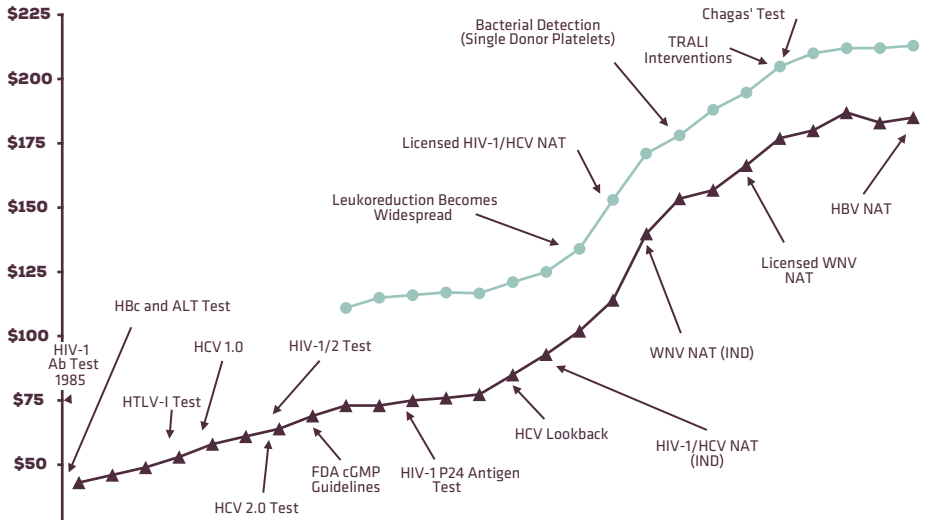
In 2011, a new virus, xenotropic murine leukemia virus-related virus (XMRV) – that could be transmissible via blood – was initially linked to chronic fatigue syndrome and prostate cancer, before important scientific studies brought evidence to preclude these links. This virus arose as a result of laboratory contamination and, so far, has had no consequences for blood safety [1].

In North America, the greatest perceived threat during this period has been WNV. This was dealt with effectively and its spread through blood transfusion was reduced by the rapid and coordinated actions by the regulators (FDA and Health Canada), the test manufacturers and the BEs. They had the advantage that the virus had already been characterised and the risk of transmission through blood transfusion could be managed using conventional blood safety strategies: donor screening, testing and, where appropriate, exclusion. This will not be the case for all emerging diseases.

In Europe, the threat of WNV, concerning thousands of donors returning from affected areas (e.g. Greece and Italy), has been mainly addressed by deferring these returning donors. Only in 2012, was donor testing for this virus officially accepted in principle by the European Commission because of the threat to blood supply [2].

Widespread problems for patients arising from blood transfusion in Europe and other developed countries have largely been avoided over the last 15 years. This has not been achieved either easily or cheaply. Significant sums have and continue to be invested in research relating to blood safety: management teams in blood transfusion services have been strengthened; expensive new safety interventions have been implemented and great emphasis has been given to strengthening the sustainable relationships between reliable and safe donors and BEs.

The chart below illustrates the last point. It has been first created by H. Alter to assess effectiveness of main interventions in donor selection and screening that resulted in decreasing incidence of transfusion associated hepatitis in blood recipients, since the 1970s [3]. It has been adapted to assess the impact of such measures on red blood cell prices, and then regularly updated by America's Blood Centers (ABC). Reproduced below with their kind permission, it maps the median price for Red Blood cells against the new safety interventions introduced since 1985. While this is USA data, a similar pattern would be seen from European data. After stripping out inflation, the price of red cells has more or less doubled in the same period.



	1986	1987	1988	1989	1990	1991	1992	1993	1994	1995	1996	1997	1998	1999	2000	2001	2002	2003	2004	2005	2006	2007	2008	2009	2010	2011
RBCs	43,06	46	49	53	58	61	64	69	73	73	75	75,94	77,37	85	93	102	114	139,88	153,5	156,8	166,45	177	180	187	183	185
RBCs, LR									111	115	116	117	116,69	121	125	134	153	171	178,06	188	194,75	204,88	210	212	212	213

LR = Leukoreduced

Figure 1: Blood safety measures and median Red Cell Service Fees 1986 – 2011
(courtesy America's Blood Centers)

Although not strictly a European problem, we should remember that there remains much to do to improve blood supply and safety in many less developed countries. It is a sad fact that in these countries significant numbers of avoidable deaths results from lack of blood for transfusion or from lack of availability of plasma products. BEs in Europe, North America and elsewhere, collectively and individually, regard making a contribution to improving this situation an important part of their mission.

1.2 LEGAL FRAMEWORK WITHIN THE EU

Pan-EU law continues to become an increasingly important influence on BEs' decision-making, as is described in detail in Chapter 2. To summarise briefly the main aspects: the context is set by the European Treaty objectives which are to foster four freedoms of movement: people, goods, services, and capital. These freedoms reflect the origins of the EU as an economic community and it is no accident, therefore, that another major principle of the EU is fair competition.

For much of the life of the EU, the provision of health services has been excluded from its declared realm of competence, and consequently, such provision is largely left to the individual member states. However, as discussed in Chapter 3, the fact that plasma derived medicinal products are treated as pharmaceuticals which are traded on the open market (to standards required by the European Plasma Directive of 1989) has been in stark contrast with the position for blood components, which, with few exceptions, have been, and still are, universally supplied by domestic, not-for-profit BEs, many of which are government-owned, and rely exclusively on domestic donors.

As set out above, HCV, HIV and vCJD caused the EU to expand its interest in issues affecting European-wide public health. The European Blood Directive and its daughter directives (passed and implemented in the first decade of the 21st Century) sought to ensure minimum standards for labile blood components throughout the expanding EU, but did not seek to interfere with the existing structure of supply. Nonetheless, the directives, and the efforts to ensure common inspection standards throughout Europe have the effect of making it easier to move components between EU Member States.

BROADER EU LAW

There have been two specific occasions in the last 10 years where the provision of labile blood products has been subject to broader aspects of European Law.

Burton Case: The so-called 'Burton Case' (named after the judge who heard it) concluded in England in 2001, and was brought against the National Blood Authority (NBA) on behalf of about 100 plaintiffs. These plaintiffs had been infected by HCV via blood transfusion in the period after a test had become available but before the National Blood Service (NBS, as it then was) began to use it.

Before the case came to court, the Department of Health conceded that, for the purposes of this case, blood could be regarded as a product. Consequently, the case was considered under the European Consumer Protection Directive (CPD), and not under medical negligence legislation. The purpose of the CPD is to protect the consumer from, or compensate them for, the consequences of a defective product, without the need to demonstrate that the producer has acted negligently: 'The producer shall be liable for damage caused by a defect in his product…'.

The effect of this was that those BEs providing blood components within the EU/EEA, in all cases where disease transmission could be demonstrably linked to blood transfusion,

were now potentially exposed to the 'strict liability' regime of the CPD ('The injured person shall be required to prove the damage, the defect and the causal relationship between the defect and the damage....') rather than the more limited liability implied by negligence regimes ('to take reasonable care').

At the time, not all BE leaders in Europe accepted that blood for transfusion was correctly regarded as a product in this context, and there have been no further cases involving EU BEs heard under the CPD. However, the judgement has certainly encouraged BEs to avoid making statements that blood transfusion presents 'zero risk' to recipients, and to ensure that their decision-making processes around whether or not to introduce new safety interventions are both transparent and well-documented. In the UK and many other EU member states, BEs now actively publicise statements that having a blood transfusion is not without risk.

European Court of Justice: In 2010, the European Court of Justice reached a preliminary ruling in the case brought by Humanplasma GmbH, a German for-profit blood service, against the Austrian Government. The case *(considered in more detail in Chapters 2 and 4)* arose because Humanplasma considered that it had been unfairly excluded from a tendering process for supply of blood components to the Vienna Hospital Association as the Austrian Government passed legislation that banned any payment at all to blood donors after the tender had been issued.

The preliminary ruling concluded that member states were entitled, in the interests of public health, to make requirements over and above the standards required in the Blood Directives. However, on this occasion, the requirement to exclude all payment, including compensation for expenses incurred by donors, "went beyond what is necessary to attain the objective pursued, that is, to ensure the quality and safety of the blood and of the blood components", and was, therefore, hindering intra-Community trade.

This latter case illustrates the fact that there can be tensions between various aspects of EU legislation. It is likely, particularly if borders continue to open up for healthcare in the EU, that there will be more recourse to the courts to clarify and resolve these issues.

DIFFERENCE IN LEGISLATION ACROSS THE EU

Another issue worth mentioning is the differences in legislation applying to blood components and to plasma derived medicinal products (PMDP) across the EU and European Economic Area (EEA). A recent survey of EBA members revealed that, for the 20 Member States covered by the responses, 18 have specific national legislation for labile blood components; two cover blood components only in legislation for medicinal or pharmaceutical products; another two cover blood components both in specific blood component legislation and legislation for medicinal products. Of the four EU/EEA Member States that cover blood components in medicinal product legislation, three have special sections in this legislation dealing with blood components.

Six Member States have specific legislation for PMDPs. Thirteen cover these products in general medicinal and pharmaceutical product legislation (one did not answer this question). Of these thirteen states, seven have special sections in their general medicinal legislation for PMDPs.

These findings demonstrate two points. First, labile blood products are generally distinguished from traditional pharmaceutical products, whereas PMDPs are all treated in a way identical to traditional pharmaceutical products.

Second, variations in national legislation make it possible that identical products are treated differently in different Member States. It may, for instance, result in the odd fact that a blood product is recognised in one individual member state as a pharmaceutical product, and henceforth can also be sold in all other EU Member States, even if those states would not accept the product for recognition and reimbursement under their own blood laws.

1.3 DEMOGRAPHICS AND DONORS

There are three major demographic trends that affect the management and regulation of BEs in Europe: an ageing population, both absolutely and as a proportion of the total population [4, 5]; a combination of the expansion of the EU and increased movement of people between countries and continents; and improved electronic communication that has given global coverage to news that was only local until recently.

Ageing Population: The ageing of the EU population has two major effects on BE's management of blood supply [6]:

1. An ageing population is more likely to suffer from chronic diseases and more likely to require medical treatments that may involve having a blood transfusion. Yet, there are fewer people of donor age, as currently defined, as the demand for blood potentially increases.
2. Treatments have become more complex, so the drive to save and improve more patients' lives demands globally more blood (red cells and particularly platelets).

EU Expansion: The expansion of the EU, combined with the increasing movement of people between countries and continents, has three major effects on BEs:

1. The increasing number of people going on holidays to countries where malaria and other transmissible diseases are endemic both reduces the number of available donors and potentially reduces the frequency of donation by otherwise regular donors.
2. Travellers from wealthy countries expect to be able to access the standards of healthcare they enjoy at home. This increases awareness of the historical variation in standards of healthcare, both within the EU and across the world and results in pressure to reduce those variations.
3. Diseases can spread between countries and continents more quickly and affect more people than hitherto.

Global Communication: Improved electronic communication and huge growth in global news coverage has made the world very small and exerted pressure on policy makers and regulators to respond quickly in their countries to incidents and news stories that arise in other countries and continents. This has led to a converging of regulation and also, to some extent, of standards, although this is constrained by different economic and legal circumstances. A number of BEs worldwide, including EBA's members, have responded to this by co-operating in the Alliance of Blood Operators' (ABO's) Managed Convergence Project that is mentioned in paragraph 1.5 of this chapter.

BEs and increase in supply: BEs have responded to the need to maintain and expand the numbers of regular donors in a number of ways. Current best practice is well described and considered in the manual [7] produced by DOMAINE (Donor Management in Europe), an EU co-funded project led by Sanquin Blood Supply Foundation and supported by the EBA.

Major developments have included the introduction of modern marketing techniques to attract and retain donors, including television advertising and, more recently, the use of new media – text messages, internet, – particularly to attract and retain younger donors; the creation and use of sophisticated donor databases; accepting both younger and older donors (some EU BEs no longer have an upper age limit for donation); and changing the timings, locations and structure of donation sessions.

The fundamental objective of all these initiatives is to ensure that sufficient safe and reliable donors enter into sustainable relationships with their BE. It is worth noting that the cost of achieving this has been considerable.

Hospitals and decrease in utilisation: The picture across Europe is mixed. Many clinicians are working with their BEs to use less blood in particular interventions where this is appropriate for clinical reasons. Nonetheless, some of the Member States in Europe that have already achieved much in this direction – sometimes precipitated by a national blood scandal – are now seeing their demand starting to rise again. The preliminary evidence suggests that the ageing population is the principal cause. Conversely, others who have made less progress in previous years still experience falling demand, despite ageing populations.

Ongoing donor controversies: Unsurprisingly, the donor field attracts a number of controversies. There is a broad consensus in Europe (and elsewhere), set out by the Council of Europe and captured in the Preamble of the European Blood Safety Directive, that the recruitment of voluntary non-remunerated donors for labile blood products for transfusion makes a significant contribution to the safety of the final product. Conversely there are those, including some representatives of the patients who rely on the products, who argue that fractionated plasma products can safely be derived from raw material supplied by properly managed compensated donors *(See Chapter 4)* to guarantee supply. Others would prefer to rely on fractionated plasma products sourced solely from non-remunerated donors.

The other main controversy has been around the acceptance of donations from men who have had sex with men (abbreviated as MSM). Most developed countries have excluded MSM from blood donation for life. This exclusion is seen as a great affront by gay rights activists and their sympathisers, who argue that it is both contrary to their human rights and an unnecessary and discriminatory precaution when BEs have sophisticated testing regimes.

BE orthodoxy has maintained that blood donation is not a right, and, in any event, is subordinate to the recipients' right to safe blood. Epidemiological data continues to support the view that MSM display a much greater incidence of HIV and other STD prevalence than the general population accepted for donation.

Consequently, relying exclusively on testing (however effective it might be) still increases the risk of transmitting one of these diseases to a recipient. In some countries where the exclusion of MSM has been considered by the courts, the findings generally have been that, insofar as the exclusion is based on consideration of scientific data in the interests of blood safety, it is not discriminatory at all. A number of BEs, supported by their governments, have sought to reduce the exclusion from donation to a specified period (for instance one year) rather than a lifetime ban. The EBA keeps the situation in Europe and around the globe under constant review (including the recently released EDQM report TS057 on "Risk behaviours having an impact on blood donor management"), so that it can readjust its position (supporting permanent deferral) if and when necessary.

1.4 TECHNOLOGY

1.4.1 SAFETY OF BLOOD PRODUCTS

The chart of *Fig.1* indicates the main interventions (excluding donor deferrals) to improve blood safety that have been introduced in North America, the EU and other economically developed countries since 1985. In some cases they have been introduced as additional safety measures against established risks (e.g. nucleic acid testing -NAT- for HCV and HIV); in other cases they have been measures to combat emerging or new risks (e.g. NAT for WNV and Trypanosoma cruzi in North America and other regions with significant prevalence).

Testing technologies: Testing technology now plays a major role in combating the major transmissible pathogens and, used in tandem with rigorous donor screening, the residual risks of a HCV or HIV transmission through blood transfusion are now typically one per several million donations. However, there are no perfect technical solutions to emerging risks. NAT can be introduced as a response but there is an inevitable delay between the emergence of the pathogen and the introduction of a specific test; and, once introduced, it has a window period, allowing some cases to go undetected. For reducing the risk of bacterial contamination, many BEs have adopted bacteria detection technology for platelets. Looking ahead, novel technologies such as micro-array testing systems potentially allow further improvements to the testing supply chains.

Pathogen inactivation: Pathogen inactivation techniques for plasma have been in widespread use for a number of years. There has been substantial trialling and piloting and some adoption in the EU and around the world (but notably not in the US) of innovative pathogen inactivation technologies for platelets (and similar technologies are being tested for red cells). Pathogen inactivation provides pre-emptive action against many of transfusion transmissible viruses, parasites and bacteria, but is currently available only for platelets and plasma. In addition, it can be overwhelmed by high microbial loads, and its clinical efficiency and efficacy (platelet functionality, coagulation factor levels) is still debated.

Cost: Either technical step involves adding significant cost to blood components submitted to this treatment. Many countries use 'cost per additional Quality Adjusted Life Year (QALY)' to assess the cost-effectiveness of proposed new health or safety interventions. The generally accepted maximum level to demonstrate cost effectiveness in developed economies is between €20,000 to €100,000 per additional QALY. As comparison, a 4-yearly Pap-smear costs about €20,000/QALY, as does coronary bypass surgery. Haemodialysis comes in at about €30,000/QALY.

First generation testing for HIV, at about €5,000 per QALY, clearly falls into this range. Second generation testing (P24 antigen and NAT testing) is, in practice, costing more than €2,000,000 per QALY. HBV NAT testing costs a whopping €66 million/QALY, whereas WNV NAT testing costs more than €500,000/QALY.

Additional safety measures that are currently being considered – such as pathogen inactivation for platelets – are estimated to have similarly high costs per additional QALY (until a new virus comes along, at which time its cost/QALY would drop dramatically).

It is quite clear that governments in the developed economies are prepared to accept and fund interventions to achieve extremely high levels of blood safety that are much less cost effective than they would accept elsewhere in their health services. There is no consensus as to what this level should be, though a first attempt was made at achieving such consensus at the Toronto's 'Risk-Based Decision Making for Blood Safety' consensus conference held in 2010 *(see paragraph 1.6)*.

1.4.2 TRACEABILITY

Another specific use of technology is to assist the tracking and tracing of each unit of blood from the donor, through the BE process, to issue to the hospital and then onto the recipient patient. It is no accident that the EU blood safety directives placed such a strong emphasis on traceability. It is vital to ensure that the component that is issued is indeed derived from the donation that arrived at the blood centre, in order that any contaminated unit can be traced to a particular patient. In the event of a significant transmissible pathogen coming to light in future years, 'look-back' can be facilitated.

Barcoding of blood donations and of the components manufactured from them (at a cost of €15.000/QALY, much lower than that of many other blood product safety measures) is a well-established technology in developed BEs. In recent years, the use of barcoding right through the hospital supply chain to the recipient has been piloted and promises to reduce the risk of wrong transfusions. In many EU countries, such wrong transfusions represent one of the greatest residual risks faced by a patient receiving a blood transfusion.

RFID (at a cost of €200.000/QALY) is being explored as an alternative means of achieving the same results. It is also now technically possible to link the unit of blood cross-matched for a particular patient to that patient by using a tracing device that will only allow the unit to be transfused into the intended patient. This potentially would virtually eliminate cases where blood is given to the wrong patient.

The systematic recording of the use of each unit has the additional benefit of helping the BE and the hospital to evaluate how much blood is used for each procedure. Comparisons of this type have been shown to be effective in assisting clinicians not to over-use blood components, thereby both reducing the risk, however small, that inevitably arises from having a transfusion and ensuring that donors are not bled unnecessarily.

Linking BE and hospital IT systems (rather than using manual systems) makes this possible. The Scottish BE (SNBTS) worked closely with its Ministry of Health and hospitals to link information from IT systems and facilitate comparisons of blood usage by procedure and clinician. More recently, ABC's web-based AIM system, which builds on systems that have been developed and brought into use by NHSBT in England and by the Finnish Red Cross BTS, collects and analyses data relating to every unit of blood transfused. This allows hospitals to manage their blood usage much more effectively; and to compare, on an anonymised basis, their usage with other similar hospitals. Similar IT "vein to vein" systems, intending to help blood supply management from donors to patients are being developed by several other manufacturers as well.

The EU Optimal Blood Use Project [8], led by SNBTS, supported by EBA, and including over 20 participants from across Europe *(Report published 2010 and referred to in*

Chapter 10), describes European good practice in this whole field, including tracking of components, procedures in hospitals and training of staff.

1.4.3 MANAGEMENT

Another way in which technology has been exploited by BEs is in assisting the management of the organisation more effectively and thereby improving productivity. Many BEs now have integrated IT systems that link the core BE operational IT system with stock management, costing, financial and HR systems to enable decision-making to be based on current and consistent information. More recently, BEs have started using customer-relations systems to improve the targeting and timeliness of communications with donors.

1.5 MANAGEMENT OF BLOOD TRANSFUSION SERVICES, GLOBALISATION, CO-OPERATION AND CONVERGENCE

1.5.1 MANAGEMENT OF BEs

A significant development increasingly apparent in the last 20 years has been the professionalisation of the management of BEs. This has been a response to the increasing scale and complexity of BE activities and to the demands made on them by their sponsors and funders. Freestanding BEs handle substantial amounts of public money (for example, one of the largest, England's NHSBT, has an annual turnover in excess of €0.5 billion) and performs a vital high profile service to healthcare. Consequently, they are required to meet contemporary high standards of governance and public accountability and they need to benefit from a full range of management skills.

Many European BEs experienced major restructurings in the 1990s and early 21st century. This involved consolidating sites and activities, introducing new technologies, bringing new skills to their workforces and sometimes replacing skills no longer required. In addition to the clinical, scientific and technical skills that are central to its mission, the following skills have also been identified as essential to the success of a contemporary BE, whether they are provided in-house or supplied by external partners.

- Expertise in HR
- Expertise in IT
- Risk management
- Financial management and cost control
- Supply chain management
- Logistics
- Efficiency improvement
- Effective public relations and communications

In parallel with this strengthening and professionalisation of BE management, and possibly partially as a consequence of it, there has been a great increase in the extent to which BEs seek to collaborate and co-operate with each other on organisational issues. The development of a lively and productive global community of blood transfusion clinicians, scientists and technical experts long predates this, as witnessed by the history and current strength of International Society of Blood Transfusion and of regional scientifically and technically based organisations.

1.5.2 STRUCTURED COLLABORATION BETWEEN BEs

The emergence of structured collaborations dealing with organisational aspects of blood transfusion is much more recent. Setting aside the special case of America's Blood Centers (ABC), having celebrated its 50th anniversary at the beginning of 2012, the first multi-national organisation specifically focussed on this aspect of blood transfusion was the European Blood Alliance, founded in 1998, and stimulated by the emergence of the European Blood Safety Directive.

The number of members, originally nine, has now increased to 23. EBA has extended its range of activities from its original concern primarily with regulatory issues to include, amongst many other concerns, benchmarking, standardisation and training. EBA has actively sponsored four important EU co-funded projects, each led by an EBA member, covering SOPs, inspections, optimal use of blood and donor management.

More recently, new regional blood transfusion networks, primarily concerned with organisational rather than scientific and technical issues, have been created such as the Asia Pacific Blood Network (APBN), or are in the process of being set up, such as the Alianza Latino Americana de Sangre (ALAS).

BEs have also responded to the increased globalisation of the environment in which they operate. Many of their suppliers are multi-nationals, and their regulators, while primarily responsible for safeguarding their home populations, routinely discuss issues in international fora. These considerations have led to the foundation of the Alliance of Blood Operators (ABO) early in the 21st Century, focussing its efforts on major, long-term issues that could not be resolved either nationally or even regionally.

The managed convergence of regulatory regimes has been one of its main projects. It consists of developing a collaboration between BEs, suppliers of medical devices (MDs) and blood and MD regulators upstream of innovations, to help making available new MDs for patients and donors more quickly and at lower cost, in the interests of providing continuous improvement of patients' and donors' safety. A pilot project of this managed convergence to improve the safety of apheresis connectors for donors and patients is currently underway. It was activated in 2009 after the tragic death of a donor from a misconnection of anticoagulant and saline during an apheresis donation *(see also paragraph 1.6 of this chapter)*.

1.5.3 INTERNATIONAL ORGANISATIONS AND BLOOD BANKING

Furthermore, international organisations also have made efforts to improve global blood safety. WHO, as mandated by successive World Health Assembly resolutions, has made a priority of establishing global blood safety and availability [9]. The findings of the WHO Global data base on blood safety report 2011 [10] are sobering:

- 48% of all blood donations are made in high-income countries, home to just 15% of the world's population.
- 82 countries, on a total of 164 having provided 2008 data to WHO, report fewer than 10 donation per 1,000 population (the minimum needed to meet basic needs in a country). All are low- or middle-income countries.
- 40 countries collect less than 25% of their blood supplies from voluntary unpaid blood donors, which is the safest source.
- In 39 countries blood donations are not routinely tested for transfusion-transmissible infections (TTIs), including HIV, hepatitis B, hepatitis C and syphilis.

The flip-side of this situation is that perhaps the greatest challenge facing blood supply and especially the stable plasma product supply lies in the future. At present, most of the economically developing world is undersupplied with, or cannot afford, coagulation products and immunoglobulins. The resolution of this major issue will require a huge increase in supply. And once large countries such as China, India, and Brazil start using products at the same level at which the EU and the US do today, we may be faced with global shortages of certain products, price wars, etc. that will also affect the "rich" countries.

The Red Cross/Red Crescent national societies involved in blood collection and transfusion have created the "Global Advisory Panel (GAP) on Corporate Governance and Risk Management of Blood Services in Red Cross and Red Crescent Societies", with the main aim of transferring know-how and expertise, in particular, in the field of donor management.

Of the 187 Red Cross/Red Crescent national societies in existence, 23 are the national blood service; 21 have some responsibility for blood collection; 117 focus on blood donor recruitment or advocacy/promotion of VNRBD, whereas only 26 have no involvement at all. European Red Cross Blood Services such as those of Finland, Switzerland, and Germany have been deeply engaged in these efforts.

All of this seems a far cry from the European norm of 25 years ago when individual blood centres in neighbouring cities operated in splendid isolation from one another, and it seems highly likely that the trend towards global convergence of regulatory requirements and of standards and ever-increasing communication and co-operation between BEs will continue. If the borders between countries in Europe for healthcare and/or blood products continue to open up (*see paragraph 1.7 below and Chapter 3)*, it will be interesting to see how the tensions between collaboration and competition are reconciled.

1.5.4 MANUFACTURING MOVING?

A further development that may well occur over the next few years is that the focus of manufacturing of equipment and reagents for Western BEs, and of fractionation of plasma products, even from European or US donors, may move from its traditional loci in Europe and North America to the major developing economies such as China, India and South East Asia. If this were to occur, it would follow the trend already set in many manufacturing industries. It could come about either because the existing suppliers chose to move their manufacturing bases to countries with lower labour costs, possibly by going into partnership with enterprises already established in those countries; or as a result of enterprises in the developing economies introducing products, which are able to compete successfully on both quality and price with products produced in Western economies.

1.6 FUNDING AND COST PRESSURES

1.6.1 RISK-BASED DECISION MAKING FOR BLOOD SAFETY

BEs in the EU gain most of their funding from public funds. This can be directly from national or regional taxation; or from government sponsored health insurance schemes. In some cases, the BE is directly funded; in others, it charges its customer hospitals. All EU BEs are now expected to meet the minimum requirements set out in the Blood Directives. In many EU Member States, expensive new safety interventions over and above those required by the directives can be introduced only with the explicit agreement of the relevant Ministry of Health; and in some cases, the Ministry of Health may instruct a BE to introduce specific safety interventions.

Everyone involved in providing blood components for patients is committed to maximising their therapeutic benefit and minimising risk. The fall-out from the HIV and HCV disasters pushed BEs and their sponsors towards a conservative reading of the Precautionary Principle. The UK's Government's experience with vCJD further reinforced this approach in the later 1990s. The cost benefit ratio of additional blood safety interventions became much lower than that of other health-related activities and, for a time, the view that zero risk for the patient should be achieved at any cost was predominant.

However, as governments regained confidence in BEs' ability to provide both security of supply and safety of the product, attitudes began to change. The view started to reassert itself: that extra euros should be invested in a particular blood safety project only where it would provide a greater health benefit than if it were spent on another blood project or on a project in another area of medicine.

Many professionals working in blood transfusion shared this latter view and the Canadian Blood Services took the initiative to organise a consensus conference in Toronto in October 2010 on 'Risk-Based Decision Making for Blood Safety'. The consensus statement [11, 12] identified the five following critical requirements.

1. A comprehensive approach to blood safety, with the development of an integrated risk management framework that encompasses 'vein to vein', and beyond.
2. Decision-making based on transparent principles of risk management.
3. A system that balances risks, costs and benefits in a sustainable manner.
4. Meaningful engagement with interested and affected parties throughout the process of risk decision-making.
5. Adherence to well-established ethical principles, including autonomy, beneficence, non-maleficence and justice to ensure that the rights of both donors and recipients are respected.

To fully implement these five principles, the consensus statement recommended the following concrete steps:

1. Commitment by all the leaders in the blood system to implement a risk-based decision-making framework.
2. Agreement on governance structures.
3. Definition of objectives and priorities.
4. Investment in assessment, evaluation and monitoring, such as an expanded system of haemovigilance.
5. A commitment to investment in research, innovation and education, staff training and infrastructure.

Although succeeding conferences could help resolving questions such as acceptable cost/QALY, two additional points emerged clearly: 1) there was a clear consensus amongst the participants that zero risk is an unattainable aspiration; 2) in developed countries the greatest danger by far to blood recipients today lies, not in the quality of the products issued to hospitals by BEs, but from problems arising in the procedures within hospitals – the main one being the wrong product being transfused to the patient. On this point, the conference concluded that more effort (and paradoxically at a much lower cost/QALY than in further product improvement) should be put into improving process safety within hospitals.

In practice, a combination of factors, not least the rising cost of healthcare and the global economic crisis, was already making BE funders less able and more reluctant to fund further expensive innovations when blood was already seen as very safe. However, BEs and their sponsors need to remain vigilant to emerging threats to blood safety and it seems likely that any substantial new threat will be met with the proactive response that has characterised the last 15 years.

1.6.2 MANAGED CONVERGENCE

The cost pressures discussed above, linked to increasingly onerous regulatory and validation procedures have combined to make it more difficult for the test and device manufacturing industries to develop new products for the blood transfusion market. Relative to the total market for healthcare-related products, however, the cost of these procedures for new product development is both small and diverse. This difficulty is potentially damaging to the ability of the BEs and all their stakeholders to respond quickly, should a new virus become widespread in Europe or elsewhere.

Some consider that it will take a radical streamlining of the way in which new testing and device products are trialled, validated and marketed to resolve this issue. This remains primarily a matter for the regulatory authorities and the manufacturers. Nevertheless, EBA is working with suppliers' associations (Eucomed and Edma) and regulators (SANCO, Competent Authorities in the EU) to try to achieve this new streamlining in Europe, and with their partners in the Alliance of Blood Operators to achieve a broader convergence of international regulatory requirements.

This 'Managed Convergence' is currently tested in a pilot to develop harmonisation of apheresis connectors to prevent adverse serious reactions in donors and patients. This was initiated by a death of a donor in 2009 having resulted from a misconnection of anticoagulant and saline during an apheresis donation. The collaborative work organised

with BEs, apheresis set manufacturers and regulators (including SANCO and FDA), is expected to lead to a standardisation of apheresis connectors, at a global level, by the end of 2014. Two new ISO standards are currently prepared. This should allow to prevent any misconnection and related serious adverse reaction in donors and patients in whom apheresis sets are used. When the proof of concept has been established for managed convergence, other projects could be implemented, as developing dialogue between haemovigilance and medical device vigilance, which is presently missing or insufficient in many EU countries.

Furthermore, in order to get an acceptable balance between cost effectiveness and safety, it may be necessary for BEs, policy-makers and regulators to examine all therapeutic and safety measures, those already in place and potential new ones, on the same basis of cost-benefit. This holistic approach might be the best way of ensuring that scarce resources are being optimally used to treat and protect patients. Here again, the managed convergence could help.

1.7 COMPETITION

As set out in Chapter 3, competition may become a more prominent aspect of the environment for at least some EU BEs. Historically, across the EU, the blood components used in hospitals have been collected, tested, processed and delivered to the hospitals by not-for-profit organisations. Many of these have a or monopoly of supply of blood for transfusion, but are territorially constrained to their own country. This is either for obvious reasons if they are state-owned or state-instituted, or, as laid out in the statutes of the International Red Cross/Red Crescent in the case of Red Cross organisations. However, the recent entry into the market in Germany of a commercial company which compensates donors for giving blood, and its attempt to enter the market in Austria, has caused EBA to consider the implications of increased competition for the security and safety of the blood supply throughout Europe.

Already before this legal discussion, BEs in the EU recognised that they operate within the context of EU principles, law and regulations, and have no problem with the principle of competition. However, they also recognise the important proviso that there needs to be effective regulation to guarantee a level playing field, avoid cherry-picking, and thus protect public health. This regulation probably has to be both at Member State and at EU level as some of the competition is within the State and some involves trade across State borders. This is reflected in EBA's Position Paper [13], which was drawn up after consideration of some of the difficulties caused by unregulated competition in the USA and the emerging situation in Germany and Austria. Of particular concern was the potential impact on donors.

The main recommendations in the EBA are as follows:

I. Donors providing blood from which labile blood components are derived, for use in an EU State, must not be paid (i.e. they must be voluntary and non-remunerated, as defined by the Council of Europe).
II. There should be no unregulated competition for donors.
III. Any new labile blood component supplier to an EU State (i.e. a supplier of red cells, platelets or fresh frozen plasma) must comply with all the terms of the Blood Directive.
IV. Any blood establishment collecting, testing or processing blood for use in an EU State (even if the establishment is situated outside the EU) should be subject to regular inspections by the regulator in the receiving State.
V. Any new blood component supplier to an EU State should be required to take its share of high cost customers and products and meet the full obligations of a normal not-for-profit blood service (e.g. meeting peak demand; providing the full range of blood components, including specialist products; providing an advice service on product use, delivering service 24/7, etc.).
VI. Any blood service operating within the EU should provide an enforceable guarantee (with redress from its parent company or a bank in the event of default), to ensure the following: that it could meet any legal claims found against it; or to fund the cost of disruption caused if it were to withdraw abruptly from the market (e.g. to fund the cost of finding new donors, etc.).
VII. Most importantly, the authorities at EU and State levels should examine the advantages and disadvantages of various types of competition before they occur, since once a national blood service and its donor base have been eroded or destroyed, it would take years to re-establish them.

EBA and its members consider it vital for the appropriate regulation to be put in place to protect public health, before further competition develops.

1.8 SUMMARY – WHAT DOES THE FUTURE HOLD?

It is, of course, impossible to predict the future and unwise to do so in print. Nonetheless, reviewing the ways in which the environment in which European BEs has changed over the last 30 years, and particularly the last 10 years, it is possible to discern some trends that seem likely to continue:

I. The attraction and retention of adequate numbers of voluntary donors willing to donate regularly will continue to be a major challenge for BEs, demanding both hard work and ingenuity. This will be a greater challenge in Europe with its ageing population than in some other parts of the world.
II. BEs and their public health partners will need to remain vigilant in their awareness of new and emerging threats to the safety of the blood supply, whatever forms these threats may take.
III. New technology will allow further improvements both in safety and in efficiency, but this will need to be facilitated by access to funds to research and develop new interventions, and by convergence and streamlining of BE and regulatory requirements to enable new products to get to market more quickly and at lower cost.
IV. Global collaboration and co-operation between BEs will continue and strengthen, both to address the issues discussed and to continue the support given by BEs in wealthy countries to colleagues in less wealthy countries.
V. The cost of health services in general and BEs in particular will remain a major challenge for governments in many countries. Consequently, BEs will expend considerable effort in continuing to deliver high quality services at lower cost. Innovative ideas and improved productivity exemplified in BEs in other parts of the world may increase the pressure to improve productivity in Europe.
VI. BEs in some EU Member States may find their established market position challenged at some point, and all BEs will need to continue to develop their management skills, as well as maintaining their clinical, scientific and technical expertise.
VII. The application of EU law and regulation to BEs is likely to increase. This concerns both the general principles and laws such as the open market principles and the Consumer Protection Directive and regulation aimed specifically at BE activities.
VIII. In parallel, increased travel and improved communications will lead to a converging of global regulation and standards. This will be limited by economic disparities but initiatives will increasingly come from outside America and Europe.

REFERENCES

1. Glynn SA, Busch MP, Dodd RY, Katz LM, Stramer SL, Klein HG, Simmons G, Kleinman SH, Shurin SB for the NHLBI Emerging Infectious Disease Task Force convened November 7, 2011. Emerging infectious agents and the nation's blood supply: responding to potential threats in the 21st century. Transfusion 2012. http://dx.doi.org/10.1111/j.1537-2995.2012.03742.x
2. European Commission's Directorate General for Health and Consumer Policy (DG SANCO). West Nile virus and blood safety. Introduction to a Preparedness Plan in Europe. 2012. Document circulated to Competent Authorities for blood of EU Member States on June 6th 2012. http://ec.europa.eu/health/blood_tissues_organs/docs/wnv_preparedness_plan_2012.pdf
3. Alter HJ, Klein HG. The hazards of blood transfusion in historical perspective. Blood 2008, 112: 2617-26. http://dx.doi.org/10.1182/blood-2008-07-077370
4. Ali A, Auvinen MK, Rautonen J. The aging population poses a global challenge for blood services. Transfusion 2010, 50 (3): 584-8. http://dx.doi.org/10.1111/j.1537-2995.2009.02490.x
5. Greinacher A, Fendrich K, Brzenska R, Kiefel V, Hoffmann W. Implications of demographics on future blood supply: a population-based cross-sectional study. Transfusion 2011, 51: 702-9. http://dx.doi.org/10.1111/j.1537-2995.2010.02882.x
6. Seifried E, Klueter H, Weidmann C, Staudenmaier T, Schrezenmeier H, Henschler R, Greinacher A, Mueller MM. How much blood is needed? Vox Sang 2011, 100: 10-21. http://dx.doi.org/10.1111/j.1423-0410.2010.01446.x
7. De Kort W, Veldhuizen I for the EU Donor Management in Europe Project Partners. Donor management manual. 2010. ISBN 978-90-815585-1-8. www.domaine-europe.eu
8. McClelland DBL, Pirie E, Franklin IM for the EU Optimal Use of Blood Project Partners. Manual of Optimal Blood Use. Scottish National Blood Transfusion Service ed. 2010, p. 1 – 64. ISBN 978-0-9564680-0-0. www.optimalblooduse.eu
9. World Health Assembly. Resolution WHA 63.12 on Availability, safety and quality of blood products. 21 May 2010. http://apps.who.int/gb/ebwha/pdf_files/WHA63/A63_R12-en.pdf
10. World Health Organization. Global data base on blood safety. Summary Report 2011. http://www.who.int/bloodsafety/global_database/GDBS_Summary_Report_2011.pdf
11. Stein J, Besley J, Brook C, Hamill M, Klein E, Krewski D, Murphy G, Richardson M, Sirna J, Skinner M, Steiner R, van Aken P, Devine D. Risk-based decision-making for blood safety: preliminary report for a consensus conference. Vox Sang 2011, 101: 277-81. http://dx.doi.org/10.1111/j.1423-0410.2011.01526.x
12. Leach Bennett J, Blajchman MA, Delage G, Fearon M, Devine D. Proceedings of a Consensus Conference: Risk-Based Decision Making for Blood Safety. Transfus Med Rev 2011, 25: 267-302. http://dx.doi.org/10.1016/j.tmrv.2011.05.002
13. http://ebaweb.files.wordpress.com/2012/08/eba-position-paper-competition-in-european-blood-component-market-final.pdf

ACKNOWLEDGEMENTS

The author acknowledges the contribution of Martin Gorham and Angus W. Macmillan Douglas (DGP) in preparing parts of the manuscript.

Philippe Vandekerckhove

02. IMPACT OF EUROPEAN DIRECTIVES ON HUMAN BLOOD AND BLOOD COMPONENTS AS FROM 2003

2.1 INTRODUCTION

This chapter aims at describing the current relevant EU legislation on human blood and its components, and focuses on issues and legal unclarities that have arisen because of this legislation, or because of conflicts with other EU legislation. The main lack of clarity pointed out deals with the question as to whether blood and blood components should be treated as "goods" regulated by internal market principles, or "medical services" regulated by considerations of public health. The inconsistencies may also, in future, pertain to the circulation of human tissues and organs.

Some relevant case law is described and analysed. Topics are identified to which legislators involved in the process of revision of the blood directives, initiated in 2012, need to give urgent attention.

2.2 HISTORICAL BACKGROUND OF EU BLOOD LEGISLATION

Within the European Union (EU), the following hierarchy of law exists:

- **Primary Law (EC-treaties):** Treaties of Rome (1957), Maastricht (1992), Amsterdam (1997), Nice (2000).
- **Secondary Law:** Directives that are binding for the Member States as to the result to be achieved, e.g. minimum standards of safety for medical devices, blood, etc...).
- **National Law:** National Law of the Member States.

The EU has no "general" competences, only "derived" competences given to it by the Member States through primary EU law. Most EU competences are economic (i.e. to create an internal market). Almost no EU social/health competences exist, as these remain Member State competence, i.e. the national law of the respective states.

2.2.1 BLOOD REGULATION BEFORE 1990s

Prior to the late 1980s, the European institutions had little to do with the regulation of blood components and plasma derivatives. Regulation and standards had been developed on a national basis, by each Member State. Therefore, there were differences between the rules and inspection regimes across the EEC. And Europe itself looked quite different then, as a significant part of it still lay inside the Warsaw Pact and was allied to the Soviet Union. The EEC itself only had 12 Members at this time.

For standards in producing blood components and plasma derivatives, the common criteria used across Europe and further afield derived from the Council of Europe's "Guide to the preparation, use and quality assurance of blood components" first published in 1995 [1]. That guide is currently used by some of the leading specialists in the field and is updated each year to provide recommendations on good practice.

2.2.2 ORIGINS OF EU BLOOD LEGISLATION: 1990s

The collapse of communism changed the political map of Europe and enabled the creation and subsequent expansion of the EU. However, the devastating spread of HIV and HCV through the use of plasma derivatives and the transfusion of blood components in the 1980s and early 1990s changed the world of blood transfusion and created the motivation to introduce Europe-wide regulation.

Directive 89/381/EEC of 14 June 1989 [2], which passed into European Law in 1989 (and which was subsequently transposed into the law of each Member State) ruled that stable plasma derivatives would be treated as pharmaceutical products. This made the manufacturers of plasma derivatives subject to licensing and inspection on a Europe-wide basis, and made them subject to EEC liability and competition law as already applied to any other manufacturer. It put plasma derivatives on a quite different legal and regulatory position to that of blood components.

The fact that the regulation of blood components was not similarly placed on a Europe-wide basis at that time was, in part, the result of the phase of development that the EEC (and later on the EU) itself had reached. It did not have the authority to legislate on most matters covered by national health services and this included most of the activities of blood transfusion services.

From the mid 1990s, because of the Bovine Spongiform Encephalopathy (BSE)-crisis, the European Commission worked to try and change this situation; and, at the Treaty of Amsterdam (1997) an exception was formulated for veterinary and phytosanitary measures and for blood and blood products, in which harmonisation henceforth was allowed. The EU thus was granted the competency to 'adopt measures that set high standards of quality and safety of organs and substances of human origin, blood and blood derivatives'. Importantly, this competency was not extended further into the clinical activities of health services, so management of the supply chain between a hospital blood bank (HBB) and the patient, and the optimal use of blood components could not be covered by EU legislation.

Treaty of Amsterdam: The Treaty of Amsterdam allowed the European Commission to develop what became the Blood Directive and its supporting technical directives. The objective of these directives is "public health" (safety of blood and self –sufficiency within the EU), rather than creating an internal market. This is in contrast to the pharmaceuticals & medical devices directive.

Quality and safety minimal standards were defined as a compromise between Member States; e.g. voluntary and non-remunerated donations (VNRD) are encouraged, but not made mandatory, due to lobbying of the commercial plasma fractionation industry and support of a few member states. However, Member States may maintain or introduce more stringent protective measures than those of the directive while ensuring compliance with the treaty's provisions.

In the first report on the application of the directives (COM/2006/313), we read that "Ten Member States avail of this option with measures that ranged from designating blood preparations as medicinal products, requiring additional testing for viruses [...] to imposing more stringent measures for donor selection, biological control of donations and haemovigilance." However, the directive as a side-effect has implications for the internal market because common (minimum) safety standards make cross-border movement possible and more likely to occur.

2.2.3 DEVELOPMENT OF EU BLOOD DIRECTIVES: 2000s

By the early 2000s, the Draft Directive had been through rigorous consultation with experts from the member states and the Council of Europe and, after debates within the European Parliament and subsequent compromise and revision. Then, the legislation passed into European Law in 2003 as Directive 2002/98/EC [3], known as the Mother Directive. This was followed over the next few years by the passing into European Law of three technical and supporting Directives, known as the Daughter Directives:

- Directive 2004/33/EC: dealing with technical requirements for blood and blood components [4].
- Directive 2005/61/EC: dealing with traceability requirements and notification of serious adverse events and reactions [5].
- Directive 2005/62/EC: dealing with a quality system for Blood Establishments (BEs) [6].

In retrospect, there were probably three factors that made the passing of EU-wide legislation on the licensing, inspecting and quality systems of what became defined as a BE so important:

- HIV/HCV: The horror caused by the transmission of HIV and HCV by plasma derivatives and blood components had to be addressed. The European public increasingly showed zero tolerance of such disasters. Against this background, national governments were content to have the responsibility for safe blood shared with their EU partners. However, as a result of having the need for the Directive to be driven by problems with the quality of the product, this led to the legislation focussing on the quality of the product, rather than the quality of the process (i.e. the transfusion process from the vein of the donor to the vein of the patient in the hospital).
- EU commitment to freedom of movement: The EU's commitment to the free movement of persons within its borders meant that there was a public expectation of being able to receive similarly safe blood components in all member states. This became particularly important as the EU increased its membership to 27 member states, with inevitably very different histories and traditions of BE operations and regulation.
- Travel and migration: The greatly increased travel and migration of people led to the more rapid and wide transmission of different diseases across Europe and beyond. This required an ability to respond quickly and in a coordinated way and led to increased convergence of regulation and of standards internationally.

2.3 SCOPE OF THE BLOOD DIRECTIVE AND ITS DAUGHTER DIRECTIVES

The primary (Mother) Directive 2002/98/EC [3] passed into European Law on January 27th, 2003. The last of the Daughter Directives passed into European Law on September 30th, 2005. They all apply to the 27 Member States of the EU (15 states at the time of the Directive's adoption) plus the three members of the European Economic Area (Iceland, Liechtenstein and Norway). Each state then had two years in which to transpose the Mother Directive and approximately one year in which to transpose the Daughter Directives into the laws of its own country. It could transpose the Directive(s) in original form or it could add to the provisions in each Directive, but it could not adopt lower standards than those laid out in Directive 2002/98/EC and its Daughter Directives.

The scope of the Directive is explicitly curtailed by the provisions of the Treaty of Amsterdam. This treaty makes clear that the responsibility for the 'organisation and delivery of health services and medical care' lies with the Member State. The EU authority to legislate for the collecting, testing, processing, storing and distributing of blood and blood components 'shall not affect National provisions on donations or medical use of organs and blood.' In this way the Treaty on the Functioning of the European Union (TFEU), recycling the foregoing provisions of the Treaty of Amsterdam, restricts the EU's responsibilities to safeguarding the quality of the whole blood and component in the bag. It clearly excludes responsibility for donor welfare and the clinical use to which the components are put.

The Mother and Daughter Directives mainly apply to the activities carried out within a BE. They apply to a lesser extent to activities carried out within an HBB. A BE is defined within the Mother Directive as '*any structure or body that is responsible for any aspect of the collection and testing of human blood or blood components, whatever their intended purpose, and their processing, storage and distribution when intended for transfusion*'. An HBB is defined as a '*hospital unit which stores and distributes and may perform compatibility tests on blood and blood components exclusively for use within hospital facilities, including hospital based transfusion activities*.'

Therefore, the provisions of the directives apply not only to the traditional blood transfusion service, whether organised on a national, regional or hospital basis; but also to the collection and testing activities of facilities that collect plasma for fractionation.

The Directives cover all the activities of a BE: collection, testing, processing, storage, distribution to hospitals and traceability of the blood components. Some blood transfusion services have wider responsibilities than just those of a BE. For example, some carry out hospital blood banking, and these activities will be covered by the parts of the Directives that cover HBBs. Some are responsible for or assist in management of the supply chain from the HBB to the patient and/or optimal use of blood programmes; these fall outside the remit of the Directives, as do any responsibilities for HLA-typing, blood and umbilical stem cells, and tissue and organ management, etc.

2.3.1 BLOOD ESTABLISHMENTS

The following specific functions of a BE are covered:

Products concerned: The blood directive 2002/98/EC [3] states in article 2 that it concerns i) the collection and testing of human blood and blood components, whatever their intended purpose, and ii) their processing, storage, and distribution when intended for transfusion. It further defines in article 3: i) **blood:** whole blood collected from a donor and processed either for transfusion or for further manufacturing; ii) **blood component:** a therapeutic constituent of blood (red cells, white cells, platelets, plasma) that can be prepared by various methods; iii) **blood product:** any therapeutic product derived from human blood or plasma.

Licensing: The Mother Directive requires that each Member State sets up a Competent Authority (CA), to which the BE must provide defined information on an annual basis. The CA has the authority to grant and withdraw a licence from a BE. The BE cannot operate without that licence. As BEs are part of governmental administration in many EU states and, thereby responsible to Ministers, a formal licensing system was not always in place; nor was a CA, as specified in the Mother Directive.

Inspection: The national CA must organise inspections of the BE(s) that are within its jurisdiction to take place at least once every two years. This inspection process must ensure that the provisions of the Directives are being met by the BE concerned. Most importantly, it must check that the quality system, made mandatory by the Directives, is being applied. This quality system must reflect Good Manufacturing Practice (GMP). The existence of formally qualified inspectors and a practical inspection process was not in place in all member states. Also, there existed an inconsistency in the standards insisted upon within different member states.

EuBIS (EU-Blood Inspection System): The Directives created the basis for resolving these inconsistencies, but the implementation of consistent inspection outcomes has been greatly facilitated by an EU co-sponsored project, called EuBIS. This project has been led by the German Red Cross Baden Württemberg – Hessen, supported by the European Blood Alliance (EBA) and has comprised BEs, a number of national regulators and CAs plus advisory bodies such as the Council of Europe and the Pharmaceutical Inspection Cooperation Scheme (PICS).

This Project was completed in 2010. It aimed to build on the work done in EUSTITE (European Union Standards and Training in the Inspection of Tissue Establishments), which was a collaboration between EU and WHO with regards to tissue vigilance and training of external inspectors (mostly CA). Their work resulted in the "Guideline for the Inspection of Tissue and Cell Procurement and Tissue Establishments" and a training course (including some e-learning modules). The main outcome from EuBIS was the development of a good practice manual for the inspection of blood establishments in Europe [7,8]. Currently the manual and training guide have been disseminated to more than 530 institutions from 70 countries, in Europe and worldwide. EuBIS has also developed training material and courses, to give practical assistance to CAs and BEs in implementing the Directives' requirements. These activities have been coordinated since 2010 by the EuBIS Academy.

CATIE (Competent Authority Training of Inspection in Europe): Is a more recent initiative that follows up EuBIS. The objective of the CATIE project [9] is to develop an inspector training programme in the field of blood and blood components and to conduct training sessions for a defined number of inspectors from CAs. The project seeks to reinforce the twofold responsibility of inspectors – to ensure the quality and safety of blood and blood components so as to protect public health and to ensure compliance with EU and national regulatory requirements.

Quality system: This is a core theme running through the directives. It is defined as the organisational structure, responsibilities, procedures and resources required for quality management. Its objective is to ensure that the final blood components consistently meet the defined specifications and comply with regulations. It requires that a BE appoints the post of Responsible Person, as has long been required in a pharmaceutical establishment. This post is responsible for ensuring that the BE operates in accordance with the directives and laws of the Member State, and that all the required information is provided in a timely way to the CA. Prior to the directives, this post did not exist in many BEs. Its responsibilities, in so far as they existed, would have been shared amongst the management of the BE.

European Standard Operating Procedures (EU-Q-Blood-SOP) / EQUAL: At the time that Directive 2005/62/EC [6] was being finalised, the EU co-sponsored an initial project, led by the German Red Cross Baden Württemberg – Hessen, supported by EBA comprising some 18 European BEs that was aimed at using European good practice to assist BEs to develop standard operating procedures (as required by the EU directives and based on GMP). The Project developed a SOP methodology in order to assist BEs services to implement or expand their standard operating procedures (SOPs) and assist blood establishments in preparing for the inspection of their services by CAs. The aim of the EU-Q-Blood SOP project was not to provide an operating procedure to be used in an institution. Rather it was to provide the tools through which each institution can build its standard operating procedures and translate it into a formal document. The EU Blood SOP manual contains therefore also a common basic EU-SOP formats (master SOP format) and special formats for testing, equipment and processing that can be used as templates. In this context, the manual has been used by partners to consolidate or modify their existing SOPs system. The manual has been distributed to more than 414 institutions, blood establishments, competent authorities, pharmaceutical industries from more than 62 countries in Europe and World-wide. This project was finalised in 2008 and is continued under the coordination of the EuBIS Academy with the revised name Equal [10]. Since 2010, the English version of the manual is available on-line as an e-book (www.eubis-europe.eu).

Personnel: There must be sufficient personnel in the critical posts and they must be qualified and trained to carry out the tasks for which they are responsible. This is critical to having an effective quality system. These requirements will have been in place in most member states prior to the Mother Directive but implementation may have been mixed.

Haemovigilance: This term is generally used to cover the safety of the process from donor to patient (vein to vein) and the optimal use of blood components. However, for reasons given above, it is limited within the directives to covering the tracing of each component from donor to patient and to the reporting of any serious event or any serious reaction.

The former covers any event related to the collection, testing, processing, storage and distribution of blood and blood components that may have an influence on their quality and safety. The latter covers any reaction during or after transfusion that may be attributed to the quality and safety of the blood or blood component.

In either case, the BE must inform the CA and provide an annual report summarising the information. The information on traceability (which unit went to which patient and vice versa) must be kept by the BE for 30 years. The traceability has, in practice, been of uneven quality throughout the EU. The requirement for a combination of BEs and hospitals to keep the data for 30 years creates a challenge.

EU Optimal Blood Use Project (EUOBUP): Because of the way that the EU's authority is prescribed, the important aspects of haemovigilance covering the quality system from the HBB to the patient and covering the most beneficial prescribing of blood components to the patient are left as the responsibilities of the Member State. However, an EU co-sponsored project, led by the Scottish Blood Transfusion Service, supported by EBA and including blood transfusion services and others from across the EU has done much to develop and codify good practice in this area. This Project, called the EU Optimal Blood Use Project (EUOBUP) was completed in 2010, with the publication of a manual [11].

Donors: The directives specify the information that should be given to and received from donors. It also specifies minimum specifications for the main components. Much of this replicates existing good practice. However, as with any prescriptive legislation, an issue may arise when good practice changes, although this potential problem may be alleviated as the directives set only minimum standards.

DOMAINE (Donor Management in Europe): Perhaps the main issue with regards to donors is what is not included. The directives do not mandate the exclusive use of voluntary and unremunerated blood donations. But the Mother Directive does state that *'Member States shall take the necessary measures to encourage voluntary and unpaid blood donations with a view to ensuring that blood and blood components are in so far as possible provided from such donations.'* The EU has subsequently followed up the directives by co-sponsoring a project, led by Sanquin, supported by EBA and comprising BEs from across the EU and some other organisations with the objective of developing European best practice in blood donor management. This project, called DOMAINE (Donor Management in Europe), was completed in 2010 with the publication of a manual [12].

2.3.2 HOSPITAL BLOOD BANKS (HBB)

A limited number of the directive's requirements that apply to a BE also apply to an HBB. The critical ones that do not apply to the HBB are those relating to licensing and inspection. This is consistent with the emphasis of the directive on the component in the bag, not on the process of transfusion, but it does potentially weaken the assurance of safety to the patient as more than 90% of reported incidents concern the process not the product. The main requirements of the Directives that do apply to the HBB are: i) Quality System; ii) Traceability and notification of serious adverse events and reactions; iii) Personnel qualifications and training.

2.4 ISSUES THAT HAVE ARISEN DURING THE IMPLEMENTATION OF THE BLOOD DIRECTIVES AND ITS IMPACT ON BEs AND HBBs IN EUROPE

2.4.1 COMPETENT AUTHORITIES

In most of the long-standing members of the EU, prior to the Blood Directive coming into Law, a regulatory system existed that included a body that resembled a CA, and also mandated licensing the BE and the carrying out of regular inspections.

Sometimes the responsibilities of the CA are divided between the Ministry of Health and a medicines agency (with the latter typically being responsible for licensing and inspection). In many of the newer EU members, the CA and the licensing and inspection system had to be established or an existing system had to be modified in a major way.

The establishment of CAs has now taken place across the EU. Sometimes in these new systems, responsibilities were also divided between the MoH and an agency responsible for licensing, inspection and compliance. In the early years after the directive was transposed into national law there were reports of this division in the responsibilities of a CA causing some confusion. But, if this caused some problems initially, the author did not have such issues reported to him as still being of major concern.

The BT sector is tiny, compared to the pharmaceutical sector and the healthcare sector as a whole. It is, therefore, not easy, certainly for smaller countries, to find and maintain the necessary independent competence for their CA. Because of this, and especially in those countries where the CA is the medicines agency, inspections and regulation are sometimes based on a "copy and paste" approach from the pharmaceutical sector.

The lack of knowledge of the unique link between BEs and the hospitals they service (which does not exist in the traditional pharmaceutical sector) can be a problem, especially for the many functions BEs perform for the hospitals but that fall outside the scope of the Blood Directive (such as cross-matching, HLA-typing, stem cell and cord blood activities). Despite the stricter inspections this – paradoxically – has sometimes reduced the overall vein-to-vein safety because of fragmented approaches, although the medicines agencies in most Member States seem to be learning quickly.

2.4.2 LICENSING AND INSPECTION

For those Member States that already had a licensing and inspection system in place, the Blood Directives do not appear to have required major changes to that system. However, where the system had to be introduced or where an existing system had to be substantially revised major changes were often required for both the regulatory authority and the BE. In a number of these latter cases, the agency carrying out inspections has had to take time to recruit and train staff and some states have used foreign inspectors both for training and for carrying out inspections in the early years.

There has been a major challenge to achieve consistency across the EU in inspection standards and, therefore, in achieving the overarching objective of the Blood Directive to improve the level of quality and safety of blood and blood components across the EU. In order to meet this challenge, the EU co-sponsored several initiatives which were described above such as the EUSTITE (www.sohovs.org), EuBIS, and CATIE Projects.

In some Member States, some HBBs have had to be licensed as BEs because some of the activities that they undertake, for example, irradiation of red cells or platelets, could be considered to be processing under the terms of the directive.

There was also reportedly some confusion over whether a bone marrow transplant unit that carries out lymphocyte infusions should be licensed under the Blood Directive or the Tissues and Cells Directive. There now appears to be widespread agreement that it should be the latter. But this emphasises the close interface between regulation in the whole area of organs and substances of human origin. This is particularly the case as BEs in an increasing number of member states become responsible for managing the processing, storing, and distributing of organs, tissues and stem cells.

2.4.3 QUALITY SYSTEM

Again, in the long-standing EU states, changes to a BEs quality system as a result of the directive have been limited and, while they may have been resource-consuming, they have not generally caused problems. Most of these BEs already followed the Council of Europe Guide [1], and many had already adopted quality systems such as ISO or local healthcare quality norms.

However, this was not true for all (and not only the younger) member states. Typical systems that had to be introduced or changed included the following:

- Validation of new equipment
- Writing and agreeing organisation charts that clearly identified lines of responsibility throughout an organisation
- Agreeing and writing job descriptions
- Introducing regular staff reviews
- Ensuring that proper training was in place
- Improving documentation.

One of the issues that Project Equal [10] demonstrated was the uneven use of standard operating procedures (SOPs) across the BEs in the EU. Project Equal helped the 18 participating BEs develop SOPs by providing a template and providing examples of how to develop SOPs and flow charts and how to use these to strengthen a quality system. Similarly, the EuBIS Project [8] lays out a template and detailed instructions for carrying

out internal audits. This both helps a BE to develop a strong quality system and to audit it in practice.

The concepts of good practice and good manufacturing practice are key to developing quality systems. However, there is a lack of clarity in the directives as to what this actually means. This initially caused some problems within some BEs but cooperation between BEs (in part facilitated by EBA), the Equal and EuBIS Projects and the existence of the Council of Europe Guide have all helped to spread an understanding of what good practice means and how it can be implemented. A number of BEs have adopted ISO as part of their response to the Directive, as GMP can be quite abstract (ISO 9001 as a general system; ISO 15189 for diagnostic and testing labs).

The picture of how HBBs have responded to the requirement of the directive on quality systems is not so clear, because there are many more of them and it is difficult to obtain all the information. However, it appears that the challenges facing HBBs have been at least as great as those facing BEs and that these challenges have been more equally shared across the EU. In at least the older member states, BEs have been inspected rigorously and in great detail for many years. This has not always been the case with HBBs.

2.4.4 REPORTING OF SERIOUS ADVERSE EVENTS (SAEs) AND SERIOUS ADVERSE REACTIONS (SARs)

As a result of the directive, a number of BEs have had to adapt their existing SAE and SAR reporting systems or introduce systems. In some cases, the previous system only covered donor problems or the reporting was voluntary. There has been some criticism that the new system is too complicated.

But the main criticism is that, because of the directive's limited scope, the events and reactions to be reported are not all of those that may exist from the entire process comprising retrieving blood from one vein to transfusing it into another. This is a very important issue, as in many Member States the main risk to a patient due to receive a blood transfusion comes, not from the quality of the component in the bag, but from a failure in the process of getting the blood from the HBB to the (right) patient.

In fact, a number of the existing systems within the Member States provide much fuller information in this respect than is required by the directive. Transparent reporting of serious incidents provides an essential start to taking appropriate action to resolving these problems. However, it appears that close cooperation between the European Commission, EBA, the Council of Europe's expert panel and the International Haemovigilance Network is helping to resolve this issue. In addition, the Optimal Blood Use Project [11] has consulted widely to define European good practice in this area.

A number of BEs have mentioned that a key requirement to achieving progress on both reporting of SARs and providing traceability of the blood and component from donor to patient is the awareness and commitment of clinical staff in the hospitals. In this respect, in a number of the Member States, the existence of the directive has been of great help.

2.4.5 TRACING BLOOD AND COMPONENT FROM DONOR TO PATIENT AND RETAINING INFORMATION FOR 30 YEARS

No BE reported problems with tracing the component from donor to patient and vice versa. However, keeping information over such a long period and being able to access it quickly, when required, relies on both the BEs and hospital's information systems being efficient and fully maintained. A switch from paper to IT is essential. In this respect, in some countries, the legal requirement with regard to the signature of the donor on the medical questionnaire poses a problem. It is clearly vital that staff across the supply chain from donor to patient be aware of the importance of traceability.

2.4.6 FINANCIAL CONSTRAINTS

A number of BEs from the newer member states have mentioned that the existence of the directive has been helpful in encouraging their national governments to find increased resources for blood transfusion and its governance. Establishing the CA, recruiting and training inspectors and recruiting and training staff for the BE, plus improvements in the BEs infrastructure are all areas of increased expenditure that have been quoted. However, this clearly has not been easy in a number of states and it may well have put increased financial pressures on other parts of their healthcare systems. The author is not aware of any cost/benefit analysis having been carried out on the implementation of the directive across the EU and other EEA states, nor of whether more flexible, process-driven alternatives, have been considered instead of GMP.

2.4.7 VOLUNTARY AND NON-REMUNERATED DONORS

A number of professionals in blood transfusion have expressed regret that the directive does not mandate the exclusive use of blood and components from voluntary and non-remunerated donors. This principle is supported by such organisations as the Council of Europe, the World Health Organisation, the International Federation of Red Cross and Red Crescent Societies, and also EBA *(see chapter 4)*. As is mentioned above, the EU has co-sponsored the DOMAINE Project [12] to consult and advise on European good practice on blood collection. It is hoped that this project will strengthen the principle of voluntary and non-remunerated donation for reasons of both safety and ethics.

2.4.8 COMPETITION

By laying down minimum safety standards across the EU and EEA, the directive facilitates movement of blood and components within the EU, across Member State borders. This can clearly assist in an emergency; but it also opens up the possibility of competition between BEs.

EBA has made the point that proper regulation of this competition must be put in place before such competition is permitted *(see chapter 3)*. In particular, new entrants to a market must not be allowed to cherry-pick the lowest cost donors, hospitals and products, thereby leaving the most difficult and highest cost part of the BEs role to the existing BE. This would likely lead to existing BEs being forced out of business, without there being any stable supplier or suppliers to replace them.

2.4.9 ABILITY TO UPDATE

A number of BEs have mentioned that because the directive is very prescriptive it will need frequent updating and this can be difficult to achieve. When originally drafted, some BEs favoured a prescriptive approach as they considered this would tell them and their governments exactly what to do and might facilitate the necessary funding to fully implement the directive. Some BEs still favour a more prescriptive approach on which donor screening tests to use; for example, some would like the mandating of NAT.

There is support from a number of BEs for the good working relationship between the European Commission, EBA and the Council of Europe/ EDQM to be further enhanced so that practitioners in the field can work with the European Commission to ensure that timely updates take place. It is thought to be particularly important that these consultations include those who actually work in and manage BEs. If this does not happen, the directive will, over time, lag behind best practice.

2.5 LEGAL UNCLARITIES

Almost no EU Social/health competences exist; these remain a function of Member State competence. However, where they exist, they may contradict other EU competences, in which case either the European Parliament needs to clarify the matter, or the European Court of Justice (ECJ) must decide which takes precedence.

The EU competences most likely to contradict the Blood Directives have to do with the creation of an internal market, based on the four freedoms of movement (persons, goods, services and capital), and on fair competition.

In practice, three main sources of conflict exist: I) Unclarities in the blood directive itself *(see before in paragraph 2.3)*; II) Conflicts between the EU blood and plasma directives *(see paragraph 4.1)*; III) Conflicts between the EU blood directive and other EU legislation *(paragraph 4.2 and 4.3)*

2.5.1 CONFLICTS BETWEEN THE EU BLOOD AND PLASMA DIRECTIVES

This conflict mainly concerns unclarities with regards to scope.

The original Plasma directive 89/381/EEC [2] stated in Art. 1: that the directive

1. "... shall apply to medicinal products based on blood constituents which are prepared industrially by public or private establishments, hereinafter referred to as 'medicinal products derived from human blood or human plasma'; these medicinal products include, in particular, albumin, coagulating factors and immunoglobulins of human origin."
2. "... shall not apply to whole blood, to plasma or to blood cells of human origin."

This directive, in the meantime, has been integrated in a codifying directive 2001/83/EC [13] on pharmaceutical products for human use which states the following:

Art. 1: "... 10. *Medicinal products derived from human blood or human plasma*: Medicinal products based on blood constituents which are prepared industrially by public or private establishments, such medicinal products including, in particular, albumin, coagulating factors and immunoglobulins of human origin."

Art. 2: "1. This Directive shall apply to medicinal products for human use intended to be placed on the market in Member States and either prepared industrially or manufactured by a method involving an industrial process."

Art. 3: "This Directive shall not apply to: ... 6. Whole blood, plasma or blood cells of human origin, except for plasma which is prepared by a method involving an industrial process."

Note how Art. 1 and 3 are now at the very least ambiguous not to say contradictory, and especially how Art. 2 was added and Art. 3 amended from "shall not apply to Whole blood, plasma or blood cells of human origin" to "shall not apply to Whole blood, plasma

or blood cells of human origin, *except for plasma which is prepared by a method involving an industrial process*". Furthermore, the Blood Directive (2002/98/EC) states that:
Art. 2: "1. ... shall apply to the collection and testing of human blood and blood components, whatever their intended purpose, and to their processing, storage, and distribution when intended for transfusion."

Art.3: (b) 'blood component' shall mean a therapeutic constituent of blood (red cells, white cells, platelets, plasma) that can be prepared by various methods; and (c) 'blood product' shall mean any therapeutic product derived from human blood or plasma.

This leaves open a possible contradiction with regards to which directive regulates plasma, and ambiguity on what constitutes an industrial process. This can lead to remarkable situations.

In Belgium, for instance, BEs operate under the blood law which does not allow the use of pooling methods for the production and viro-inactivation of fresh frozen plasma (FFP). In contrast, thereto, a commercial company sells its own FFP product prepared using a pooling method, as a pharmaceutical product (not a blood product).

The company can do so because, under the EU directive on pharmaceutical products, any product that is authorised in a EU Member State is automatically also recognised in all other Member States. This means that basically the same product is permitted onto the Belgium market under two different types of legislation with different quality requirements, in effect discriminating the Belgian BEs by forcing more strict requirements on them.

2.5.2 FREEDOM OF MOVEMENT OF GOODS

As all goods should be allowed to cross the EU's internal frontiers freely, legal obstacles and laws or measures obstructing the free movement of goods, are in principle prohibited (art. 28-29 EC-treaty / art.34-35 TFEU). Obstacles can be fiscal (e.g. import-export duties; the abolition of these obstacles led to the creation of a customs union and a common customs tariff) or non-fiscal (e.g. trade regulation that may hinder intra-community trade).

However, legal obstacles can exceptionally be justified (based on the EC-treaty itself or on ECJ case law) if they are necessary in the general public interest, and if the measure is appropriate for, and in reasonable proportion to, the goal it wants to achieve:

- The EC-treaty defines a closed list of justification grounds including public morality, public policy, public security, protection of health and life of humans/animals/plants (e.g. the ban on import of English meat into France at the time of Mad Cow's disease), protection of national treasures possessing artistic, historic or archeological value, and protection of industrial and commercial property.
- ECJ case law includes as justification grounds areas such as consumer protection, public health, financial balance of social security, and environment protection. This is an open list: additional grounds can be added in future.

The lists thus include grounds that can justify creating barriers against the freedom of movement of goods such as blood products (protection of health and life of humans/animals/plants, public health, financial balance of social security, and possibly also public morality).

Also in health care, many truly economic "goods" exist: medicines, medical devices, etc.. But what about "body material" such as organs, human tissue, (labile and stabile) blood (products), etc...?

Medicines: The Softenon crisis [14] in 1965 triggered the EC- pharmaceutical legislation, and consists of many directives. The objective initially was to protect public health, but switched later to the creation of an internal market (art. 95 EC / 114 TFEU). Today, market authorisation is more or less a European authority with a centralised procedure by EMA (the European Medicines Agency), and a decentralised mutual recognition procedure. Price setting and reimbursement remain national competence, but (non) reimbursement issues need to be justified on the basis of objective criteria e.g. the financial balance of the social security system (price), or quality issues.

Medical devices: The relevant EC legislation dates back to 1990, and aims to promote the internal market (art. 95 EC / 114 TFEU). The CE-labelling of medical devices is a centralised authority. Price setting and reimbursement remain a national competence but must be justified: unclear reimbursement policy (e.g. requirements on top of CE-labelling) of wheelchairs was condemned because of "obstruction of the internal market".

Human body-derived materials: The donation and exchange of human tissues and organs is not without risk. The EU, therefore, has adopted directives to force national governments to adopt measures to guarantee safety, covering donation, processing, and utilisation of these substances. In addition, these materials must be fully traceable from donor to patient and back.

1. **Human tissues:** EC legislation exists since 2004 (Directives 2004/23/EC; 2006/17/EC; 2006/86/EC), and its objective initially was public health but with some indications towards internal market. Its legal ground is art. 152 EC-treaty (nowadays art. 168 TFEU) on "standards of quality and safety for the donation, procurement, testing, processing, preservation, storage and distribution of human tissues and cells". With regards to the donor side, the directive determines that VNRD contributes to safety, without making it compulsory.

2. **Human organs:** A new EU directive (2010/45/EU and later transposed into 2010/53/EU of 7 July 2010) was adopted in 2010. It concerns standards of quality and safety of human organs intended for transplantation, with the goal of facilitating the exchange of organs between Member States. With regard to the donor side, the directive determines that organ transplant programs must be based on VNRD (which paradoxically may pose problems for countries which in the past adopted the much-admired "opting-out" instead of the traditional "opting-in" system). This directive must be transposed into national law before August 27th, 2012 by the Member States.

3. **Human plasma:** Two large categories should be distinguished *(see also paragraph 3.2)*: **Plasma Derived Medicinal Products (also called stable plasma products)** - such as coagulation factors (for use by haemophiliacs), immunoglobulins and albumin - are made from human plasma that has either been expressly donated for this purpose by apheresis or has been donated as whole blood for both plasma products and blood components. These products have a long shelf life which is why they are called 'stable'. This also means that they can be quarantined before issue and be transported globally. In Europe this industry is subject to EU Competition Law (internal market).

Labile plasma products (mainly fresh frozen plasma) are obtained either from whole blood or from plasmapheresis, and are subject to the Blood Directive, although some ambiguity exists (as discussed in more detail under 4.1.).

With the important difference that product derived from paid donors is more customary and less contested for the production of stable plasma products, the donor selection and testing procedures are similar for both (and, where a whole blood donation is used for making both labile components and plasma products, the procedures should be the same).

4. **Human blood:** The Treaty of Amsterdam allowed the EC to develop what was to become the Blood Directive and its supporting Technical Directives. Their objective is "Public health" (safety of blood and self –sufficiency within the EU), not to create an internal market (and this in contrast to the pharmaceuticals and the medical devices directives).

   With regards to the donor side, the directive determines (art. 20) that "Member States shall … encourage voluntary and unpaid blood donations with a view to ensuring that blood and blood components are in so far as possible provided from such donations". However, it does not make voluntary and unpaid donations compulsory.

2.5.3 FREEDOM OF MOVEMENT OF SERVICES

The "freedom of movement of services" directive (the so-called Bolkestein directive, named after the EU commissioner who originally proposed it) ignited heated discussion on the applicability of this freedom to the national health care systems. Hence, it was heavily amended and changed to make sure that an abrupt implementation of this guideline would not disrupt (and in the process destroy) existing national health care systems which differ greatly in terms of organisation, financing, access, etc. This finally resulted, on March 9th 2011, in a European Directive (2011/24/EU) to be implemented by the member states by October 2013.

The legal ground for the directive is the organisation of the internal market, and not public health. The directive does not apply to the allocation of an access to organs for the purpose of transplantation. Blood and tissues are not explicitly mentioned.

As discussed before for goods, European law states that measures can be taken to obstruct the freedom of movement of healthcare services if they can be justified to be necessary in the general interest, and if the measure is appropriate for and in reasonable proportion to the goal it wants to achieve. Measures that have been regarded as both necessary and reasonable, and hence have been accepted before (Kohll Dekker and Smits Peerboom arrests of the ECJ) include the following:

1. Maintaining the financial equilibrium of social security.
2. The necessity to be able to plan the required care.
3. The criteria that are used to accept that patients are treated abroad must be objective, non discriminatory, and must be communicated beforehand.

(Note how these criteria can, literally, also be applied to the provision of blood products and transfusions).

The directive further stipulates in which cases a member state can insist on a "prior" permission to obtain medical care (most instances in which blood transfusions are likely to occur fall in this category), and that hospitals cannot ask higher prices for other EU patients than they do for patients of their own country.

Blood transfusion includes finding and motivating a safe donor; obtaining, manipulating and storing the product; haemovigilance from the donor to the patient and back; and advice about transfusion indication and usage. All of this requires close collaboration between the hospital physician and the BE (at the level of the individual patient). For those reasons, this author believes that blood should be treated as a medical "service" rather than a "good".

The EU Parliament should address the question as to the extent to which the EU's open market principles should be applied to all health care services. The general issue has been heavily debated in the European Parliament in recent years; however, the EU directives on human donor-derived "goods" such as blood were not specifically addressed.

Nobody paid much attention to the fact that human donor-derived tissues such as blood, tissues, and even organs would be classified and treated as other "goods" (such as tables, chairs, computers) instead of as "medical services". Had they done so, their use would have been covered by the discussion mentioned above. Therefore, whether the application of open market principles was appropriate for human donor-derived tissues was never explicitly discussed, and should be done now, as a matter of urgency.
In the meantime, as it is today regarded as a "good", it should receive the benefit of a similar amount of reflection by the EU Parliament (not just the ECJ) as have medical services with regards to the following:

- The acceptable obstructing criteria.
- The request of prior permission (to prevent the disruption of the blood supply in one country in favour of another).
- The price that can be charged (to prevent shifting blood to wherever the price is highest).

2.6 RELEVANT CASE LAW

Despite the fact that the Blood Directive is a public health directive, this does not unambiguously answer the question whether 'blood' is a good within the meaning of Article 28-29 of the EC Treaty (nowadays art. 34-35 TFEU). Indeed, when asked this question, even the European Commission couldn't give a definitive answer and wrote as follows:

"the definitive interpretation of Community Law can only be given by the Court of Justice" and that "Different legal interpretations are possible, but given the fact that there is no actual prohibition to pay for blood and given the fact that blood falls under the common customs tariff, blood could be considered a good under article 28 EC Treaty. However, it would not be useful to treat this question solely in an abstract way."

The key question is whether blood is a good "within the meaning of Article 28 of the EC Treaty?", and hence whether there is a free internal market for blood? This question is crucial.

If it is a good, Member States must accept blood in accordance with EU-minimum standards, even when having stricter rules of their own. The only exception is if Member States can justify every measure, stricter than the minimum standards of the Blood Directive (such as e.g. prohibition on paid donations, homosexual donations, donations from countries with another infection profile, ...). The ECJ will have to decide about this justification case by case.

On the other hand, if blood is not considered to be a "good", Member States are free to impose stricter rules.

Clear arguments against "blood as a good" exist, and include the scope and legal ground of the Blood Directive which is a public health directive, and the fact that both the EC Treaty (nowadays TFEU) and the Blood Directive (in particular with regards to the issue of unpaid donations) explicitly allow stricter measures. Furthermore, labile blood components are not manufactured or processed industrially or using an industrial method to the same extent as, for example, fractionated plasma products *(See paragraph 2.5)*.

There have been two specific occasions in the last 10 years where the provision of labile blood products has been subject to broader aspects of European Law, and has resulted in relevant Case Law.

2.6.1 THE 'BURTON CASE'

The so-called 'Burton Case' (named after the Judge who heard it) concluded in England in 2001, was brought against the National Blood Authority (NBA) on behalf of about 100 plaintiffs who were infected by HCV via blood transfusion in the period after a test became available but before the National Blood Service (NBS, as it then was) implemented it.

Before the case came to court, the Department of Health conceded that, for the purposes of this case, blood could be regarded as a product. Consequently, the case was considered under the European Consumer Protection Directive (CPD), and not under medical negligence legislation.

The purpose of the CPD is to protect the consumer from, or compensate them for, the consequences of a defective product, without the need to demonstrate that the producer has acted negligently: 'The producer shall be liable for damage caused by a defect in his product...'.

The effect of this was that BTSs providing blood components within the EU/EEA, in all cases where disease transmission could be demonstrably linked to blood transfusion, were now potentially exposed to the 'strict liability' regime of the CPD ('The injured person shall be required to prove the damage, the defect and the causal relationship between the defect and the damage....') rather than the more limited liability implied by negligence regimes ('to take reasonable care').

At the time, not all BTS leaders in Europe accepted that blood for transfusion was correctly regarded as a product in this context, and there have been no further cases involving EU BTSs heard under the CPD. However, the judgment has certainly led to two outcomes. It has encouraged BTSs to avoid making statements that blood transfusion presents 'zero risk' to recipients (in the UK, BTSs actively publicised statements that having a blood transfusion could not be without risk). It has ensured that their decision making processes around whether or not to introduce new safety interventions are both transparent and well-documented.

2.6.2 HUMANPLASMA AGAINST THE AUSTRIAN GOVERNMENT

In 2010, the European Court of Justice (ECJ) reached a preliminary ruling in the case brought by Humanplasma GmbH, a German for-profit blood service, against the Austrian Government.

1. **THE CASE:** Arose because Humanplasma considered that it had been unfairly excluded from a tendering process for supply of blood components to the Vienna Hospital Association (an association of hospitals in Vienna). It concerned a national law introduced by the Austrian Government in 2006 that was designed to prohibit the import into Austria of blood components that were derived from remunerated donors, in this case from Germany (but the restriction also applies to paid donations within Austria). The Austrian Government, supported by the European Commission, claimed that the protection of human health justified the measures that the national government had introduced.

2. **THE RULING:** The EJC noted that the protection of health is an important principle contained within the Treaty of Rome and it is the responsibility of the Member State Government to decide the priority they give to this and the means by which they want to achieve it. But whatever steps they take must be within the limits imposed by the Treaty of Rome as a whole.

   The preliminary ruling concluded that the requirement to exclude all payment, including compensation for expenses incurred by donors, 'went beyond what is necessary

to attain the objective pursued, that is, to ensure the quality and safety of the blood and of the blood components, and was, therefore, hindering intra-Community trade'.

The ECJ noted that, in order to justify impeding a fundamental principle of the internal market, such as the free movement of goods, a national government must take only proportionate measures. It noted that a government could meet its obligations under Directive 2002/98/EC 'to encourage voluntary and unpaid blood donations with a view to ensuring that blood and blood components are insofar as possible provided from such donations' without prohibiting the importation of blood components from donors 'that are not entirely unpaid'. It commented that banning the reimbursement of costs might actually act against achievement of the objective of encouraging such donors. It also noted that some other Member States reimburse costs to donors.

The ECJ thus ruled that the Austrian Government had taken disproportionate measures in fulfilling its responsibility to protect health. Therefore, its prohibition of importing blood components from blood donors that are not entirely unpaid was deemed illegal under EU law.

3. **ANALYSIS:** This case first of all illustrates the fact that there can be tensions between various aspects of EU legislation; and it is likely, particularly if borders continue to open up for healthcare in the EU, that – unless the EU Parliament clarifies certain issues - there will be more recourse to the courts for resolution and clarification. Once there, these issues are resolved in a purely legalistic way (see 2, 3, 4).

   The four main points of criticism most often heard with regards to this ruling are the following:

I. The lack of clear definition of paid versus unpaid donation

The discussion about what constitutes payment for a donation has a long, often confusing, history (for a more elaborate discussion: *see chapter 4*). In this particular case, the refusal by the Austrian government to accept blood for which an "expense allowance" had been paid was not accepted as appropriate to the goal pursued, i.e. the protection of public health. The court, however, did explicitly confirm that the refusal of paid blood donations (i.e. for which a "fixed allowance" or payment for the donation itself) can be appropriate to achieve its goal, i.e. high safety standards for blood and blood components. This is confusing since, ultimately, the court lets the issue be reduced to whatever definition a particular Member State accepts.

The Austrian Government took a position that was stricter than the CoE, and was overruled by ECJ. In Germany on the other hand, some commercial blood services pay donors who get time off at work to come and donate, without loss of pay, and hence incur no costs (not even their time) except their blood, yet they get paid 20 euros or more. Neither the definition of the CoE, nor the regulation in Austria and most other European countries, would accept calling this "cost reimbursement". However, the German government does, and is supported by the ECJ.

As the ECJ has ruled that the different interpretation of what constitutes "payment" versus "cost reimbursement" between the German and Austrian authorities cannot be contested by the Austrian Government, this makes every member state now dependent on the way other member states organize themselves with regards to donor recruitment.

To illustrate the point: If the Austrian competent authority were allowed to inspect in Germany, they would regard the above mentioned payments as a "fixed allowance", as it is independent of real costs incurred. Once labeled as such, the ECJ could then most likely (if consistent with this ruling) rule that it would be duly justified, appropriate and proportionate for the Austrian government to obstruct free movement of goods i.e. obstruct the import of such blood products.

The verdict of the ECJ thus circumvents/avoids the most important issue: the definition of what constitutes a fixed versus an expense allowance. In not defining this, the application of the legal principles becomes purely dependent on national inspection criteria. In other words, the EU directives have created a level playing field in terms of quality requirements between the different member states, but not yet in creating a level playing field in terms of quality inspection criteria. The ruling of the ECJ has opened the door for blood products to be introduced from paid donations even into those countries where by national law they are not allowed. Commercial companies will (and obviously already have) discover(ed) in which countries the lowest barrier to entry exist, and will use those countries as bases to expand into other EU member states.

II. Ruling blood to be a "good" rather than a medical "service"

The court ruling further implied that blood is indeed to be considered an "economic good" and thus that freedom of movement of goods (within the EU) does apply to blood products. One wonders whether it would not have been wiser to treat these products alongside and in conjunction with the EU directive on (medical) services and health care, for two important reasons.

First, insofar as blood transfusion is a medical service to the patient, one can argue that blood should be treated as a medical "service" rather than as a "good". Before the Blood Directive came into being, and underscoring the intrinsic link between blood and hospital services (that does not exist for traditional pharmaceutical products), in most countries blood was regulated and inspected by the department of the Ministry of Health that deals with hospitals, rather than by the agency responsible for pharmaceutical products.

In recent years, the European Parliament has heavily debated the extent to which the EU's open market principles should be applied to health care. However, no such debate was held when the EU directives on human donor-derived "goods" such as blood were passed. Nobody considered the possibility that human donor-derived tissues such as blood, tissues, and even organs would be classified and treated as any other "goods" (e.g. chairs, tables, or computers).

This is a pity because many of the considerations and conclusions that were held with regards to medical services are also relevant for the delivery of blood products and other human donor-derived tissues. Had they been lumped under the services directive (2011/24/EU), a ruling by the ECJ in this particular case may even have been unnecessary, as precedent rulings would have existed.

Let's take a fictional example: the variant Creutzfeld-Jacob Disease (vCJD) crisis. The English Blood Service recently considered buying red blood cells in another country to safeguard supply of red cells in England, in a context of potential threat of transmission of CJD agent (plasma was already bought in the US because of concerns about infection

transmission through blood products). What would have happened if this had upset blood supply in the country of origin? What rules would have been in place to which those affected might have appealed?

In the current situation, according to the Services Directive on Healthcare, and precedent ECJ ruling, limitations would be acceptable. Until the ECJ makes a specific ruling on these issues, the legal situation remains unclear and unsatisfactory.

III. Implications for other human tissues and organs

This ruling constitutes a precedent that likely will affect the situation of other human donor-derived materials. What does this, for instance, mean for tissues? If the competent authority of one Member State declares payment to a tissue donor to be an "expense allowance" and not a "fixed allowance", it thereby becomes legally acceptable to export tissues to Member States where such payment would be unacceptable. One step further: countries may attract donors from other countries where such payment is lower or non-existent, even if this disrupts the tissue supply in those countries? The list of potential extrapolations is long.

IV. The extrapolation of an internal market for "goods" to one for "human donors"

What should set the directives regulating human tissues apart from the directives regulating goods (including medicines and medical devices) is the fact that they do not only regulate the end product, but also have implicit "health" concerns regarding quality, safety, and traceability of the originating material (in this case: the human donor).

Instead of using the "health" consideration (which allows the EU directive to discuss issues related to the donor) to better define the rules for the "internal market", the judges here reversed the reasoning, and applied and extrapolated the "internal market" approach (meant to create a level playing field for the sales of goods) to the donor side.

This could result in an internal market for "donors", which is problematic for several reasons. In the first place there are ethical and legal issues (there is no legal basis for this). In addition, there is also a practical reason: for reasons that are to be found in donor motivation and the necessity to maintain a sense of community between donor and patient, on the (unpaid) donor side an internal market exists nowhere (not even in countries where markets for blood products are in theory completely open such as the US). The introduction of an internal market, with paid donors co-existing with unpaid donors, may ultimately destroy the unpaid donor base.

This extrapolation is furthermore not consistent with other aspects of the ruling:

1. It ultimately undermines any health reasons an individual Member State may use to justify imposing stricter criteria on donors.
2. If an "internal market" must exist for blood donors, the court should have upheld the highest rather than the lowest quality standards for donation criteria, as henceforth the lowest level will determine the standard throughout the EU.
3. Ultimately, this creates an uneven playing field for blood services operating in countries with stricter legislation (the opposite of the level playing field used to justify the ruling).

4. **CONCLUSIONS:** This ECJ judgement is helpful in setting out the issues that will determine the legal position with regard to whether EU competition law applies to blood components and the question as to the powers and responsibilities of Member State Governments in the application of this law.

   However, this ruling seems to have been driven more by the "internal market" perspective, whereas the directive is based on a "health" perspective. The judgement, therefore, does not, in itself, seem to determine where this issue will end. Consequently, more cases before the ECJ are to be expected.

   An important peculiarity of this case is the stringency of the Austrian law in seeking to prohibit importation of components from donors that are 'not entirely unpaid.' If the Austrian law had allowed the donors to be compensated for reasonable costs incurred, would the judgement have been the same? What are reasonable costs for which the donor might be compensated?

   Most remarkable in the judgment is that the judges not only implicitly consider blood to be a "good", but then go on to extrapolate the principles of the internal market for "goods" also to "donors", which is legally and ethically problematic, and may now be used as precedent with regards to, for instance, tissues and organs. In doing so, the ECJ is shifting the emphasis of the Blood Directive from being a "health" directive to being an "internal market" directive.

   The importance and complexity of this matter means that future cases and any subsequent appeals might run for a number of years before the issue is finally decided. At least the author considers that the best course would be for a political solution to be found, based on what is right for public health and what provides efficient blood services. The outcome of a long drawn out legal process, might, in any case, have to be tempered later by a political solution *(to illustrate what this means in daily reality see chapter 3.)*

2.7 OVERALL CONCLUSIONS AND RECOMMENDATIONS

The European Directive on Blood has been an important improvement in the way blood and blood components are obtained, produced and handled for most EU countries. However, the European Parliament should clarify some discrepancies and technical issues in the existing legislation, and more importantly should make some political choices so that it is not up to the judges to make those decisions.

At the political level, the European Parliament should decide whether, insofar as blood transfusion is a medical service to the patient, blood should have been treated as a medical "service" rather than a "good" *(for further illustration of this subject see chapter 4)*.

In the meantime, because of the ECJ ruling, blood (labile blood products) has to be regarded as a good, and, therefore, should be subject to the following considerations:

- It should receive a similar amount of reflection by the EU Parliament as healthcare services have with regards to the following:
  - the obstructing criteria that are acceptable;
  - the request of prior permission (to prevent the disruption of the blood supply in one country in favour of another);
  - and the price that can be charged (to prevent shifting blood to wherever the price is highest).
- In addition, the EU Parliament should clarify whether it indeed meant the donor side to be subjected to the principles of the internal market.
- The current situation in which paid and unpaid donations co-exist makes for an uneven playing field. VNRD should be made compulsory as this is the simplest way to resolve all legal maneuvering and to increase the minimum level of safety.

At the technical level, the European lawmaker should (more) unambiguously define the following issues:

- What constitutes payment (fixed allowance) and what constitutes cost or expense allowance / reimbursement?
- What is a stable versus labile blood product, i.e. what falls under the plasma or under the blood directive?
- What standardised inspection criteria and definitions are to be implemented in all member states? For this last point, the EuBIS and CATIE initiatives should significantly help.

After the recent assessment of blood directive implementation by SANCO, we hope that the process of revision of the EU blood directives, initiated in 2012, will give opportunity to clarify the issues regarding the status of blood component and blood donors. EBA will actively defend the position presented in this chapter, with the objective of maintaining security and safety of blood donor databases and blood supply, in ways both sustainable and compatible with EU ethical principles, for the primary benefit of patients.

REFERENCES

1. Directorate for the Quality of Medicines & HealthCare of the Council of Europe (EDQM). Guide to the Preparation, Use and Quality Assurance of Blood Components. Council of Europe ed., 2011. ISBN 978-92-871-7022-4. www.edqm.eu
2. Council Directive 89/381/EEC of 14 June 1989 extending the scope of Directives 65/65/EEC and 75/319/EEC on the approximation of provisions laid down by Law, Regulation or Administrative Action relating to proprietary medicinal products and laying down special provisions for medicinal products derived from human blood or human plasma. http://eur-lex.europa.eu/LexUriServ/LexUriServ.do?uri=OJ:L:1989:181:0044:0046:EN:PDF
3. Directive 2002/98/EC of the European Parliament and of the Council of 27 January 2003 setting standards of quality and safety for the collection, testing, processing, storage and distribution of human blood and blood components and amending Directive 2001/83/EC. http://eur-lex.europa.eu/LexUriServ/LexUriServ.do?uri=OJ:L:2003:033:0030:0040:EN:PDF
4. Commission Directive 2004/33/EC of 22 March 2004 implementing Directive 2002/98/EC of the European Parliament and of the Council as regards certain technical requirements for blood and blood components. http://eur-lex.europa.eu/LexUriServ/LexUriServ.do?uri=OJ:L:2004:091:0025:0039:EN:PDF
5. Commission Directive 2005/61/EC of 30 September 2005 implementing Directive 2002/98/EC of the European Parliament and of the Council as regards traceability requirements and notification of serious adverse reactions and events. http://eur-lex.europa.eu/LexUriServ/LexUriServ.do?uri=OJ:L:2005:256:0032:0040:EN:PDF
6. Commission Directive 2005/62/EC of 30 September 2005 implementing Directive 2002/98/EC of the European Parliament and of the Council as regards Community standards and specifications relating to a quality system for blood establishments. http://eur-lex.europa.eu/LexUriServ/LexUriServ.do?uri=OJ:L:2005:256:0041:0048:EN:PDF
7. EuBIS (European Blood Inspection System). Common Criteria for the Inspection of Blood Establishments (Manual). Seifried E, Seidl C ed. 2010. www.eubis-europe.eu
8. EuBIS (European Blood Inspection System). Audit/ Inspection Training Guide (Manual). Seifried E, Seidl C ed. 2010. www.eubis-europe.eu
9. CATIE (Competent Authority Training of Inspections in Europe). www.catie-europe.eu
10. EU-Q-Blood-SOP. Methodology for standard operational procedures. www.eu-q-blood-sop.de
11. McClelland DBL, Pirie E, Franklin IM for the EU Optimal Use of Blood Project Partners. Manual of Optimal Blood Use. Scottish National Blood Transfusion Service ed. 2010, p. 1 – 64. ISBN 978-0-9564680-0-0. www.optimalblooduse.eu
12. De Kort W, Veldhuizen I for the EU Donor Management in Europe Project Partners. Donor management manual. 2010. ISBN 978-90-815585-1-8. http://www.domaine-europe.eu
13. Directive 2001/83/EC of the European Parliament and of the Council of 6 November 2001 on the Community code relating to medicinal products for human use. Official Journal L-311, 28/11/2004, p. 67-128. http://www.emea.europa.eu/docs/en_GB/document_library/Regulatory_and_procedural_guideline/2009/10/WC500004481.pdf
14. http://en.wikipedia.org/wiki/Thalidomide

ACKNOWLEDGEMENTS

The author acknowledges the contribution of Martin Gorham and Angus W. Macmillan Douglas (DGP), Roeland Neyrinck and Paul Struys (legal counsel Belgian Red Cross-Flanders) in preparing parts of the manuscript. In writing parts of this chapter – mainly with regard to blood "as a good within the meaning of Article 28 of the EC Treaty" – the author relied on the outstanding legal analysis of the situation before the recent ruling of the European Court of Justice, by Prof. Danny Pieters, Prof. Paul Schoukens, and Mrs. Miek Peeters from the Institute for Social Law at the University of Leuven, Belgium, as summarised by Prof. Pieters in his presentation to the European Blood Alliance on the occasion of its 10th anniversary in Brussels, May 2009.

Philippe Vandekerckhove

03. REGULATION OF COMPETITION FOR THE PROVISION OF HUMAN BLOOD AND BLOOD COMPONENTS WITHIN THE EU

3.1 BACKGROUND TO THE ISSUE

Historically, throughout the EU, the blood components used in hospitals have been collected, tested, processed and delivered to the hospitals by not-for-profit organisations (either charities such as the Red Cross or public sector organisations such as Etablissement Français du Sang in France or the National Health Service in the UK). Whole blood is collected from volunteers who are not paid for the service that they provide (although, in some Member States, donors have traditionally been compensated for some costs incurred by them in giving blood). In most EU states, the blood service sells the processed *labile blood components* to the hospital at a price; often this price is regulated by the government.

In some states, there is competition to supply hospitals between not-for-profit blood services. In a few cases, blood components have been traded across EU Member State boundaries. Until recently, however, cross-border competition has been limited, and for-profit companies have not been primary players in the donor-patient supply chain for labile blood components (although blood services and hospitals do contract out specific activities to commercial companies, such as transport, information systems and even laboratory services).

This is in contrast to the position in the plasma derivatives industry (which produces *plasma derived medicinal products*), where for-profit companies feature significantly, many of them using plasma sourced in the USA; where a major proportion of products are traded across national borders, and where donors of products used in the EU (and sourced both within and outside Europe) are often paid.

In recent years, however, in both Austria and Germany, a small number of commercial companies have now also started providing labile blood components. In Austria, these companies have sourced their products from both non-remunerated and remunerated donors. One of the companies has not survived very long; another, which has as its main objective the collection of plasma for the plasma derived medicinal product industry, provides labile blood products from the same paid donor pool and sells these to selected hospitals.

In Germany, there is one major company that sources its blood components from remunerated donors. Some of these donors used to come from Poland and this led to two concerns. In Poland, it caused a shortage of donors along the border with Germany; while, in Germany, there was concern that, if any look-back exercise into the donor was required, it could not be carried out easily and promptly. In response, the Polish authorities allowed some compensation to be paid to donors in western Poland, although this has now ceased; while, in Germany, the above-mentioned company has stopped voluntarily targeting Polish donors.

There have also been attempts to import labile blood components into Austria. The Austrian government acted promptly to introduce rules so that blood components could only be imported into Austria if the Ministry of Health had given its prior permission and if the components were derived from voluntary and non-remunerated donors. However, this restriction was challenged at the European Court of Justice (ECJ) and the preliminary judgement delivered by the ECJ in December 2010 was that the Austrian Government could not prohibit imports of blood components from another Member State solely on the grounds that the donors of the blood from which the components were derived were 'not entirely unpaid' *(see paragraph 2.6.2)*.

3.2 THE DIFFERENCES BETWEEN LABILE BLOOD COMPONENTS AND STABLE PLASMA DERIVED MEDICINAL PRODUCTS (PMDP)

Labile blood components include red blood cells, platelets and fresh frozen plasma. Plasma derived medicinal products include fractionated products such as coagulation factors (for use by haemophiliacs), immunoglobulins and albumin. Both the labile components and PMDPs are derived from human blood, either through whole blood or apheresis (plasma, platelets, or red cell) donation.

Product derived from paid donors is less contested for PMDPs; otherwise, the donor selection and testing procedures are similar for both. Where a whole blood donation is used for making both labile components and PMDPs, they are the same. However, blood components and PMDPs have different characteristics, involve different risks in their provision, are often regulated by different legislation, and serve different functions in the treatment of patients.

1. **Plasma Derived Medicinal Products** are made from human plasma that has either been expressly donated for this purpose by apheresis or has been donated as whole blood for both plasma products and blood components. This plasma is then processed by a physico-chemical process (fractionation) to isolate the different proteins ('fractions') in the plasma, which are then used to make stable products. These products have a long shelf life (licences often last for two years), which is why they are called 'stable'. This also means that they can be quarantined (normally for six months) before issue. As they can be stored for long periods they can be transported globally, which helps to make their distribution relatively easy to plan and carry out, in contrast to labile blood products.

   Demand for plasma products is, with the notable exception of Immunoglobulins, declining in most economically developed countries: recombinant alternatives exist for many of the products. The risk of disease being transmitted via a stable plasma product is greatly reduced, as the fractionation process in itself kills most viruses. However, the fractionation process involves the pooling of thousands of individual donations; if any one does contain a pathogen, it can potentially affect many patients.

   PMDPs do not have to be matched to each patient precisely by blood group and antigen. In practice, they are treated as standard pharmaceutical products and are regulated as such. In Europe this industry is subject to EU Competition Law. Competition between companies for PMDPs is not the topic of this chapter.

2. **Labile blood components** are also derived from whole blood collection or apheresis. The whole blood is separated into its component parts by centrifugation. The donations are not pooled (with the possible exception of platelets), so that the components derived from an undetected infected donation are likely to infect only one patient. Moreover, blood components are labile and consequently cannot easily be treated to destroy pathogens, nor can they be subjected to extended quarantine (with the exception of FFP, which can be frozen for two years).

   Most BEs are not yet routinely using pathogen inactivation techniques for red cells (technology is being developed) and platelets (technology available but not yet widely implemented). These differences mean that the potential risk of transmitting infections is higher for blood components than for stable plasma products, although modern donor management procedures and testing regimes have proved very effective in managing that risk, justifying strict implementation of VNRBD and of the medical questionnaire.

   The short shelf life of blood components compared to plasma products, in particular, and pharmaceutical products, in general, (some 35 - 42 days for red blood cells – different countries apply different limits –and 4 to 7 days for platelets), means that, particularly in the case of platelets, it is less feasible to supply them over long distances. BEs are, therefore, required to develop sophisticated stock and distribution management capabilities. The immediate demand for these blood components is often very volatile; for example, a road accident or liver transplant can cause the use of tens of units of red cells for one patient in a night or certain serious cancer treatments can have a similar effect for platelet demand. A major incident can have an even greater effect on immediate demand.

   Blood components have to be compatible with the blood group of the patient (the main blood group systems tested for are ABO and Rhesus) and, in some cases, this has to go further than just matching the main blood groups (i.e. tests need to be done for additional blood group systems). Because the right blood component for an individual patient must be available in the right quantities when it is needed, the management of the whole supply chain from donor to blood service to hospital blood bank to patient has to be managed in an integrated yet flexible manner, 24 hours per day and 7 days per week. This can be particularly challenging at times of public holidays and bad winter weather.

   Under these circumstances, the supply chain becomes immediate and more local. It is possible for two competing organisations to supply such a market, but they both have to be able to meet all the requirements of the hospitals that they supply. If one has to cover for the other, in practice it means that this 'supplier of last resort' has to be able to meet any demand anywhere. This runs the risk of causing both work duplication and outdating of labile blood products.

   Infection risk: For labile blood components, governments in most countries, irrespective of their wider economic policies, have concentrated on trying to ensure sufficiency of supply and eradication of transfusion transmitted infections, such as HIV, Hepatitis and West Nile Virus. In most of the world these remain huge challenges that have not yet been fully overcome. In Europe, North America and some other jurisdictions these challenges have been mainly but not completely met, as a result of major and expensive campaigns by the governments, regulators and blood services concerned. These challenges have led governments to concentrate on ensuring that the donor base is secure and that the blood service is able to respond to the changing requirements of the hospitals that it serves.

The remainder of this chapter deals with issues surrounding competition of labile blood products, not of PMDPs.

3.3 THE REASON FOR THE EMERGENCE OF COMPETITION IN THE PROVISION OF BLOOD COMPONENTS IN EUROPE

Why has this issue arisen in Europe at this time? There seem to be six main reasons, that have to do with the *political preference* of the moment (I, II, and III), the *organisational potential* for profit (IV) and economies of scale (V), and the *legal context* that created a more level playing field (VI).

I. **Expanded services:** In Europe, the market economy has expanded into many areas of activity in which it did not previously operate. Specifically, competition between hospitals in some Member States has led these hospitals to look for choice in the provision of many of their supplies, including that of blood components.

II. **New costs:** The introduction of new measures over the last 15 years to reduce the possibility of a patient receiving a transfusion transmitted infection has made blood components safer but caused their price to hospitals to rise steeply. Blood components have become a significant cost for hospitals and health services. This has meant that their cost has come under close scrutiny across Europe as governments try to control their healthcare expenditure.

III. **Safety measures:** It is now well over a decade since there was a high profile problem with the safety of blood components within the EU at a level comparable with that of the transmission of HIV or hepatitis in the 80s and early 90s. The direct effect of vCJD has been limited to the UK. Therefore, blood safety may not at this moment be amongst the highest concerns of politicians, the media, hospital managements and health policy-makers. This is in stark contrast with the pressure to cut costs and increase productivity.

IV. **Profit potential:** The EU enlargement has made it possible to collect and process blood in a low cost economy and then sell the blood components in a high price economy. This provides, for the first time, the potential for some blood component suppliers to make significant profit.

V. **New territories:** Well-developed BEs have the desire and potential ability to expand their operations into new territories, thereby accessing the full potential economies of scale from their processing and testing activities and spreading their overheads and staff expertise over a greater activity whilst broadening their donor pool. This may be constrained by the mission statement of a BEs, geographical considerations, and by the legal requirements *(see paragraph 3.7)*.

VI. **New standards from directives:** The EU Blood Directive 2002/98/EC [1] (*see Chapter 2)* has set minimum standards for the collecting, testing, processing, storage and distribution of blood components within the EU States. This is making competition across the EU's internal borders more feasible, particularly in view of the reduced profile of the blood safety issue as noted in III) above.

3.4 THE PROBLEMS ARISING FROM THE EMERGENCE OF COMPETITION IN THE PROVISION OF BLOOD COMPONENTS IN EUROPE

Many people would accept that the introduction of choice and competition into many areas of life, where this did not exist a generation ago, has brought huge advantages in terms of more consumer orientated suppliers and more economically efficient operations. However, there are special problems in applying this to the supply of blood components. Some of the main problems are as follows:

I. **Paid versus unpaid donation:** In practice, where competition in the supply of blood components has been introduced, the new entrant tends to be for-profit and to pay donors for their services. Paying donors allows the new entrant to attract donors that are unwilling to donate without payment, or to take donors from the existing blood service quickly and to incentivise them so as to match supply with demand.

However, public health policy in most economically developed nations has been driven both by an ethical preference for unpaid donation and by the evidence that there is a real increase in the risk of paid donors suffering from a transfusion transmissible infection. This creates a potentially higher risk to patients who receive labile blood components than it does for those who receive a PMDP, for the reasons outlined in paragraph 3.2.

For these reasons, WHO, EU and Member State governments strongly promote the concept of the voluntary and unpaid donor for blood components. Article 20 of the EU Blood Directive 2002/98/EC [1] states that 'Member States shall take the necessary measures to encourage voluntary and unpaid blood donations with a view to ensuring that blood and blood components are insofar as possible provided from such donations.' This preference would very likely have become mandatory if it were not for the opposition of the commercial plasma fractionation industry and a complaint by the German State.

In order to maintain good public health, it would seem essential to allow only blood components from non-remunerated donors, as defined by the Council of Europe [2] for transfusion into humans within the EU. This is also the EBA position, fully developed in Chapter 4.

II. **Differences between countries:** The importation of blood components into one Member State from another may, in certain circumstances, increase the risk to patients, even when the blood is collected from voluntary and non-remunerated donors. This

results from the fact that the epidemiology in different Member States may be materially different. In addition, operational issues such as different donor selection criteria and different testing, processing and transport standards may increase the risk.

The German Red Cross Baden Württemberg – Hessen led the Equal and EuBIS projects (including over 20 participants from all over Europe, supported by EBA and part of the EU's public health programme) which aimed at improving standard operating procedures (SOPs), quality management systems [3] and inspection regimes across the EU states [4]. These measures will help alleviate these risks amongst participating blood services. But it will take time to achieve consistently high standards across the EU.

III. **Impact of unregulated competition for donors on the donor base:** The health services in any EU Member State are dependent on sufficient blood donors being available on a sustainable basis. Already in some Member States, collecting sufficient blood from high quality donors is a challenge.

All current evidence shows that blood donors cannot be switched on and off at short notice. Donorship often runs in families and loyalty is built up over many years. A new entrant into the blood supply activity that was looking for donors in a state that already has a developed blood service would almost certainly have to rely on recruiting donors away from the existing blood service. If this new entrant were a for-profit company, the risk would be that donors may not feel as committed to such a company as to a not-for-profit organisation and, should the for-profit company go out of business, these donors may be lost, either temporarily or permanently.

This happened in Austria several years ago when a commercial blood service went bankrupt. There have been two more recent cases in Germany, where a for-profit company that remunerated its donors withdrew abruptly from collecting blood and supplying hospitals in Prenzlau and in Brandenburg. As a consequence, the existing not-for-profit blood service was required to fill the gap at short notice.

Despite its best efforts the not-for-profit service found that, in both cases, it could only regain one out of six of the donors that the for-profit company had taken from it in the first place. This demonstrates that, once payment is started, it changes the expectation of what constitutes fair treatment in return for donating blood products and may make all donors unwilling to donate on a non-remunerated basis. Furthermore, once a stable relationship between a donor and a blood service is destroyed, it cannot be rebuilt easily.

IV. **Impact of unregulated competition for hospitals on the national healthcare systems:** The potential for cross border competition/Sales of blood is of course not limited to for-profit companies. From time to time, hospitals, especially when put under financial pressure, such as is the case currently in most European countries, look for cheaper alternatives for blood products, especially if these are logistically easy to organise (land border, short distances etc.). The sometimes large price differences between countries in the EU contribute to this.

One problem is, of course, that it is difficult to compare blood prices between EU countries, as they are embedded in their health care system, and costs are sometimes fully, sometimes only partially, covered and reimbursed by the blood price (in contrast to the US where the price transparently reflects costs). This may give hospitals a wrong idea about the real cost of blood products. The Belgian Red Cross-Flanders is contacted occasionally by hospitals from the southern part of the Netherlands, who would like to buy blood products because of the significantly lower prices than those charged in the Netherlands. It is clear that lack of competition, based solely on a gentleman's agreement between national providers, is not a stable basis for organizing the blood supply in Europe.

The fact that we are not able to produce a graph, as in the US *(see chapter 2)* reflecting the cost of a unit of red cells, further illustrates the fact that blood products, in this respect, resemble medical services more than pharmaceutical products, in that they are deeply embedded in the complex reimbursement systems of the different countries.

V. **Level playing field:** As with any economic activity, the new entrant, when motivated by profit, is likely to try to 'cherry pick' the most attractive suppliers, customers and regions. A new entrant blood service, therefore, would be likely to do the following:
   a. limit its blood supply to that of low cost donors that fit its logistics
   b. want to supply only those hospitals, probably in a highly populated area, that could be supplied at low cost and would pay prices that cover cost
   c. seek to avoid supplying specialist products, such as single donor platelets
   d. might want to avoid supplying 24/7 and peak demand, or supplying at certain times of the year.

Furthermore, it may not guarantee that its supply will meet demand.

If any of these were to be the case, the new entrant would only be providing part of the service already provided by the existing not-for-profit organisation. The latter would have to stay in business to provide a safety net (in economic terms, be a supplier 'of last resort'). Since the not-for-profit service would, however, have lost the most economic part of its market, it would be financially disadvantaged.

In the event that a competitor failed to supply a blood component required late one night, or failed to supply a specialist product for a particular patient, this could cause major problems. If the existing blood service had to cover a proportion of the demand normally met by its competitor, it could greatly complicate its stock management and mean a waste of resources (in the form of higher buffer stocks and hence higher expiration of products) and a waste of donor blood. This could cause financial damage to the existing blood service that might threaten its viability if it continued for more than a short period.

Therefore, a new entrant to a country or region that did not provide the complete service offered by the existing blood service would almost certainly cause a secure blood supply system to be replaced by a less secure one.

VI. **Business continuity risks with regard to supply:** This type of disruption could have serious consequences for the blood supply in general and potentially may be devastating for the supply of those blood components or platelets that need to be typed for special blood groups or tissue antigens.

Some people have argued that, if many competing blood services existed within a Member State, it would not matter if one went out of business because its market share would be small and could be easily taken over by the others. But, in practice, this is very unlikely to occur. In the US, where as free a market as anywhere else on the planet does exist

for blood services, the economies of scale are driving blood services to merge, not to become smaller. Therefore, if one blood service goes out of business, it is highly likely to cause a major disruption for donors, hospitals and, therefore, for the health service in the Member State concerned.

VII. **Business continuity risks with regard to legal issues and liability:** In recent years, blood services have introduced many new tests and processes, at the encouragement or insistence of governments, or as a result of legal rulings. A for-profit organisation might choose, or be forced into, liquidation rather than pay these cost increases. This would leave Member State governments to pick up the pieces in order to preserve a sufficient and safe blood supply.

In the same way, a for-profit company may not be able to pay the level of damages required by a court of law to compensate patients in cases of injury. Would this mean that the government would be left to pay the bill? Also, any such company (unless it were very large) may also find it difficult and expensive to achieve the level of insurance cover necessary to protect the public. Finally, what about traceability of donors if a company goes bankrupt? Who will be responsible for being able to trace back the donors involved to see whether they were carrying certain diseases (as was the case with the emergence of vCJD when donors had to be traced back after many years)?

VIII. **R&D:** Some existing not-for-profit blood services are closely integrated with hospitals and/or research institutes. For example, in Scotland, the not-for-profit blood service manages, on behalf of the National Health Service, a project aimed at improving the quality of the blood transfusion processes within hospitals. Many not-for-profit blood services such as Sanquin in The Netherlands run advanced research programmes. Price competition from for-profit companies, that may not have the same wider health responsibilities, would undermine the not-for-profits' ability to carry out all their current responsibilities. It would be possible for the EU or State to fund such activities separately. But again, the Government would have to act or there would likely be deterioration in health care and innovation.

IX. **Standards and implementation of new technologies:** Any introduction of significant competition into a blood supply system would mean that the existing provider would have to examine its fixed costs. If an existing service loses, say, 20% of its market, it may have to do any of the following:
   a. close a processing and testing centre
   b. (perhaps more logically) process and test blood under contract for its competitor, in order that both retain some of the economies of scale
   c. 'contract out' processing and testing entirely to a specialist, large-scale provider.

This examination of efficiencies within each link of the donor-patient supply chain would create pressure for the lowering of standards of facilities and of staff conditions to the minimum accepted level. Governments should think through the consequences of these changes before they agree the terms under which any competition would be allowed. If they do not, they could find standards in the Member State or in the EU, as a whole, falling behind the best global standards. The specific risk might be the failure to introduce improved technology and systems.

In summary: the introduction of competition that, in practice, will often involve for-profit companies and remunerated donors into the supply of blood components within the EU, raises some important issues for the safe and adequate supply of these components for patients. This, in turn, raises issues for the whole quality of patient care within the State concerned and across the EU as a whole, because the adequate and timely availability of safe blood components, cross-matched to individual patients, is fundamental to modern healthcare. Many consider that these issues need to be addressed by the EU and state policy-makers before such competition takes place. If the issues are not fully addressed, in advance of the introduction of competition, the political risk, as well as the risk to patients, is considerable.

It should be noted that many of the points raised here are very similar to the initial criticism of the Bolkestein directive (on freedom of movement of services) to the organisation of healthcare services. In that case the matter received the benefit of a large debate in the European Parliament, resulting in the exclusion of health services from the scope of the Services Directive, due to fears that provision of this crucial public service could be undermined.

Unfortunately, however, blood products (and presumably also organs and tissues) did not receive the benefit of such exchange of thought and these are still subject to the Bolkestein directive. In the event of dispute, the decision is left to judges who have to treat the matter in an abstract, purely legalistic way, testing it against broad legal principles *(see chapter 2)*.

3.5 PRACTICAL EXAMPLES OF HOW UNREGULATED COMPETITION CAN PUT AT RISK THE SUPPLIES OF BLOOD COMPONENTS WITHIN THE EU/EEA

I. In two Member States (Austria and Germany), there have been examples of 'for profit' companies remunerating donors for blood donations and then discontinuing this service at very short notice. In Austria, the example involved platelet collection. In both cases, the long established not-for-profit blood transfusion service (both Red Cross services) was expected to fill the gap at short notice. This meant that the Red Cross service had to re-recruit donors that it had given up when the competitor entered the market, and they also had to expand its testing and processing capacity, in order to ensure that all hospitals were provided with the full range of products that were required for patients. In both cases, this proved possible because of the dedication of the not-for-profit blood transfusion service and because the for-profit company had not had time to take over all the donors. But, had these companies withdrawn their services later, once they acquired larger market share, the situation would have been very serious. In the event, one failed financially and the other apparently decided that the hospitals concerned were not sufficiently profitable to supply.

   Even in the two German examples, it did not prove possible for the Red Cross to re-recruit many of its previous donors (only about one out of six in both cases), as the introduction of payments and obvious competition for donors had disrupted the previous close relationship between the blood service and its donors and many of these donors had been put off giving blood to anyone as a result *(see paragraph 4 (III) of this chapter)*.

   This outcome is very similar to the experience in the USA in the mid to late 1990s where unregulated competition was shown to irritate donors and cause disruption of blood supplies *(see paragraph 3.6)*.

   If the not-for-profit blood service had (re)acted in a more commercial manner, or if it had not existed (i.e. there had not been a supplier of 'last resort'), it is likely that hospitals would have run seriously short of blood components. This would have been a hugely backward step in the health provision of an economically rich part of the EU.

II. Companies remunerating donors for the collection of platelets and plasma may disrupt the orderly supply of all components, as it did in Austria. Such practices may make all donors unwilling to donate on a non-remunerated basis, and risk undermining the donor base of the existing blood service that relies on non-remunerated donors. Furthermore, it causes particular problems when these companies go out of business.

    The position is aggravated by the different standards that are applied for platelet collection across the EU. There is a case for minimum standards to be introduced at the EU level that would cover, for example, the number of times someone can donate, platelet numbers donated, etc.

    This position in Austria exemplifies the very different rules that exist for blood collection across Europe and the lack of a level playing field. The main for- profit company that remunerates donors for the collection of plasma and platelets has recently been acquired by LFB (the French plasma fractionator). LBF itself is a not-for-profit and state-owned organisation in France that is prohibited by statute from remunerating donors in its home country. Therefore, LFB appears to be engaged in paying donors in Austria, in a way that would be outlawed in its home Member State of France. In the absence of a clear political decision on the issue of paid versus unpaid donation at the EU level, such situations can co-exist within a purely legal logic.

III. The cases referred to above also exemplify the risks attached to allowing competition from organisations that offer to remunerate donors. In the economically poorer Member States and the poorer parts of the more economically developed states, it proves very hard for an existing blood service that does not remunerate its donors to retain these donors if there is a competing service that does offer to pay a significant amount of money for a donation.

    This problem will become more acute at a time of economic recession, such as we are experiencing in much of Europe, and as developing countries start to need more and more blood products, and are willing and able to pay for them. Over time, this would make the EU, or part of it, reliant on remunerated donors. This was demonstrated by the Polish authorities having to compensate donors for a short time until competition for their donations from a German company that remunerated the donors was stopped voluntarily. This is contrary to the intent of the EU Blood Directive 2002/98/EC [1] and of the WHO [5], and creates a risk to public health across Europe.

IV. In other Member States, the not-for-profit blood transfusion services have had experience, for a variety of reasons, of reducing the number of blood donors that they use and then having to try to re-engage these donors at a later date. It has proved very difficult to re-engage the donors.

    An example is the experience of the National Blood Service (NBS) in England, after it had turned away donors who had travelled to parts of the world where malaria was prevalent. Subsequently, having introduced a test for malaria, the NBS tried to re-recruit these donors but found this very difficult to achieve. This demonstrates that the blood supply is dependent on the established and respected blood service developing and maintaining long-term relationships with its donors. You cannot turn donors on and off at short notice or move them between blood services, without putting at risk the security of the blood supply as a whole. This is why EBA has been fully involved with the project

led by Sanquin and co-funded by the EU aimed at improving the relationships between donors and their local blood transfusion service. This project is called DOMAINE (Donor Management in Europe) and its final report has been published as a manual in 2010 [6].

v. Emerging infectious diseases are regularly bringing new potential threats to the transfused patient's safety. Climate change, increased travel and migration are increasing these threats as the recent examples of West Nile Virus, Chikungunya and SARS have demonstrated. Existing blood services work closely with their national departments of health and across the EU, both through EBA and by establishing and maintaining close relations with the European Commission, so that the EC, Member States and blood services can act quickly and in a concerted fashion in the face of a threat. The examples of SARS, West Nile Virus and Chikungunya have shown blood services acting quickly to introduce preventative measures such as donor selection/exclusion and/or donor testing.

   It is vital for the protection of patients and the European population as a whole that only those blood services that show this commitment to public health are permitted to operate in the EU. The risk was recently illustrated by the example in Germany. Donors from across the border in Poland were paid approximately €20 per donation. The practice was stopped, apparently because of epidemiological problems and because not all of the donors were traceable by the for-profit blood service involved should a look-back have been required. This is particularly serious because a threat to public health in one Member State can very quickly become a threat across the EU.

3.6 EXPERIENCE OF COMPETITION FOR BLOOD PRODUCTS WITHIN THE US

Experience in the US, where competition has been a feature of the supply of blood components for transfusion for many years, demonstrates some of the advantages and disadvantages of different models of competition.

All the labile blood components prepared for transfusion throughout the US are derived from non-remunerated donors (this excludes plasma donated only for fractionation, which comes from nearly 100% paid donors). This was not always the case.

Up to the early 1970s about 20 to 25 percent of blood components were prepared from donors who were paid to give blood. But a national blood policy, developed under the Nixon Presidency, to move to an all-volunteer and non-remunerated donor supply, coupled with regulatory requirements to label prominently whether the blood component came from a 'volunteer donor' or 'paid donor' has completely replaced this practice. Nearly all the blood components for transfusion are collected, tested and processed by not-for-profit organisations (the American Red Cross supplies about 45% of the blood components for transfusion and the community blood services supply about 50%; with supplies from hospitals and the armed forces making up the remainder). Competing blood services all operate under the same regulatory and inspection regimes.

Therefore, the major differences between competition in the US and the EU are as follows:

I. In the US, blood services are overwhelmingly not-for-profit and all use voluntary and non-remunerated donors. Competing centres are all subject to the same legislative, regulatory and inspection standards and, therefore, blood components for transfusion are viewed mainly as generic products of equal quality.
II. In contrast, in the EU, emerging competition comes almost entirely from for-profit companies (making decisions on who and what products to supply on a commercial basis), paying donors to receive their blood and operating under heterogeneous regulatory and inspection regimes. Therefore, competition can arise between blood services working to different regulatory standards, and, in contrast to the US, a level playing field does not exist.

Competition in the US has centred on winning supply contracts with hospitals and on recruiting donors. The main competitors are community blood centres (typically members of the America's Blood Centers organisation) and the American Red Cross. Competition is usually based on sustainable positions; for example, a blood service will not compete for a supply contract with a hospital that it cannot supply on an economic basis for the long-term.

In 2004, ABC and ARC have signed a national statement of understanding that sets an ethical framework for competition for donors. In any case, overt competition for the same donors tends to annoy the donors and may stop them from donating at all. This understanding was based on the experience of the mid to late 1990s and the realisation that competition without rules upset donors and caused disruption of supplies.

3.7 THE LEGAL POSITION

The legal position with regard to competition between blood services, the existence of for-profit providers and the remuneration/compensation of donors varies from Member State to Member State. For example, in Germany, none of the providers is owned by the state: competition is encouraged by the government; plasma (but not all blood) donors are compensated for their services, and there exists one for-profit provider that financially compensates its donors and is increasing its throughput strongly from year to year.

By way of contrast, in France, EFS is owned by the State, has a statutory monopoly for the provision of blood components, is a not-for profit organisation, and is not permitted to compensate or remunerate donors.

At the level of the EU, Blood Directive 2002/98/EC [1] lays down minimum standards for a blood establishment with regard to quality, licensing, inspection and the encouragement of voluntary and unpaid donors, although this is not mandatory - *(See Chapter 2)*.

Furthermore, there can be tensions between the EU Blood Directive and various other aspects of EU legislation. These tensions are most likely to be tested before the courts to clarify and resolve them. A critical issue with regard to competition in the supply of blood components is whether EU Competition Law applies to these components. If it does, this would suggest that national monopolies could not be enforced by law and that blood components could be traded across Member State borders, in accordance with the principle of free movement of goods that is enshrined in the Treaty of Rome.

In 2010, the European Court of Justice reached a preliminary ruling in the case brought by Humanplasma GmbH, a German for profit blood service, against the Austrian Government. The case *(considered in more detail in Chapter 2)* arose because Humanplasma considered that it had been unfairly excluded from a tendering process for supply of blood components to the Vienna Hospital Association as the Austrian Government passed legislation that banned any payment at all to blood donors after the tender had been issued.

The preliminary ruling concluded that, whilst Member States were entitled, in the interests of public health, to make requirements over and above the standards required in the Blood Directives, on this occasion the requirement to exclude all payment, including compensation for expenses incurred by donors, "went beyond what is necessary to attain the objective pursued, that is, to ensure the quality and safety of the blood and of the blood components", and was, therefore, hindering intra-Community trade.

The ECJ appears to have accepted that the blood components concerned were goods within the meaning of the Treaty of Rome and, therefore, that the fundamental principle of free movement across the EU applies. This point has been questioned in the past, as labile blood components are not manufactured or processed to the extent that, for example, are fractionated plasma products *(See paragraph 3.2)*.

This ECJ judgement is helpful in setting out the issues that will determine the legal position with regard to whether the EU Competition Law applies to blood components and what are the powers and responsibilities of Member State Governments in the application of this law. However, the judgement does not, in itself, seem to determine where this issue will end. An important peculiarity of this case is the stringency of the Austrian law in seeking to prohibit importation of components from donors that are 'not entirely unpaid.' If the Austrian law had allowed the donors to be compensated for reasonable costs incurred, would the judgement have been the same? What are reasonable costs for which the donor might be compensated?

The importance and complexity of this matter means that future cases and any subsequent appeals might run for a number of years before the issue is finally decided. At least the author considers that the best course would be for a political solution to be found, based on what is right for public health and what provides efficient blood services, rather than a long drawn out legal process, the outcome of which might later have to be tempered by a political solution.

Hence, there is need for debate in the European Parliament, such as was the case for the Bolkestein directive (on freedom of movement of services) with regard to the organisation of healthcare services. From a legal point of view, some of the examples described in this chapter are undoubtedly very interesting. From a patient and treating physician point of view, it is very different and potentially rather scary. In contrast to other goods covered by the EU directive on freedom of movements of goods, the customer does not always have a second chance. In reality, it is questionable whether the word "customer" is applicable at all in these circumstances.

A more detailed discussion of the legal issues can be found in Chapter 2.

3.8 THE WAY AHEAD

Many blood transfusion experts consider that any competition in the collection, testing and processing of blood, or in the provision of blood components to hospitals within the EU, is likely to create uncertainty in a part of the European health services that now works well for patients. Many believe that the final result of such competition would be to move Europe's blood supply from being overwhelmingly from non-remunerated donors to being, at least in part, from remunerated donors.

The opposing viewpoint is that the experiences in Germany and US show that competition could drive efficiencies through the blood services and reduce costs for the health services without putting safety at risk. However, as a matter of fact, this has not been clearly established so far. In any case, these advocates point to the importance of strong regulation, rather than the absence of competition, in preserving the appropriate standards. Some would say that a certain amount of movement of components across state borders is essential, if logistics are to be optimised and economies of scale achieved.

Most on either side of the argument seem to agree that competition, if it is to be introduced, must only be carried out in a way that provides sustainable advantages for patients and does not put at risk the safety of the blood and the efficacy of the transfusion process. This would appear best achieved by Member States and/or the EC introducing rules for competition before it takes place.

In order to achieve this, the following principles may be considered useful (these principles are laid out in EBA's Position Paper on Competition, which may be found on the EBA website):

I. Donors providing blood from which labile blood components are derived, for use in an EU State, must not be remunerated for the service that they provide, i.e. they must be voluntary and non-remunerated, as defined by the Council of Europe [2]. Note that the Council of Europe guidance would allow time off work that is reasonably needed for the donation and travel, plus small tokens, refreshments and reimbursements of direct travel costs.

   This rule should be applied even if the blood were to be collected outside the EU. This principle is strongly supported by the European Commission, WHO [5], and the recent ruling of the ECJ [7], in order to avoid the mistakes of the past and to maintain blood safety. However, as became clear in the recent ruling, the lack of a clearer definition as to what constitutes "payment" versus "cost reimbursement" allows companies and countries to respect the letter of the law without respecting the spirit of the law.

II. Any new labile blood component supplier to an EU State (i.e. a supplier of red cells, platelets or fresh frozen plasma) must comply with all the terms of the Blood Directive. This should be enforced by the state, even when that state has not yet transposed the directive into state law. If a state fails to do this, it risks allowing its blood supply service to be severely damaged and patients to be put at risk even before the terms of the directive become operative in the state concerned.

III. Any blood establishment collecting, testing or processing blood for use in an EU State (even if the establishment is situated outside the EU) should be subject to regular inspections by the regulator in the receiving State. If this does not happen, the safety standards enshrined in the Blood Directive would be undermined.

IV. Any new blood component supplier to an EU State should be required to take its share of high cost customers and products and meet the full obligations of a normal not-for-profit blood service (e.g. meeting peak demand; providing the full range of blood components, including specialist products; providing an advice service on product use, cost of research and development etc.).

If the new entrant cannot fulfil these obligations, it must fully remunerate the existing non-for-profit service to act as a 'supplier of last resort' and carry out these essential services on its behalf. If the state government does not ensure that this happens, the capacity of the not-for-profit service would become eroded through financial pressure, as it loses its most economic donors and hospitals. Essential products and hospitals may, under these conditions not be supplied. This would cause deterioration of health care and long-term problems at both the EU and state government levels.

The infrastructure required to provide both a comprehensive and modern blood transfusion service must remain in place in a form that is both sustainable and capable of being updated continually in the light of new technological and medical developments and emerging diseases.

V. Any blood service operating within the EU should provide an enforceable guarantee (with redress from its parent company or a bank in the event of default), to ensure that it could meet any legal claims found against it or to fund the cost of disruption caused if it were to withdraw abruptly from the market (e.g. to fund the cost of finding new donors, etc.). If such a guarantee were not to be entered into, the government could be left with substantial costs if the company were to enter into liquidation or to otherwise cease trading in the state concerned.

VI. **Most importantly, the authorities at EU and State levels should examine the advantages and disadvantages of various types of competition before they occur and introduce appropriate regulation, since once a national blood service and its donor base have been eroded or destroyed it would take years to re-establish them.**

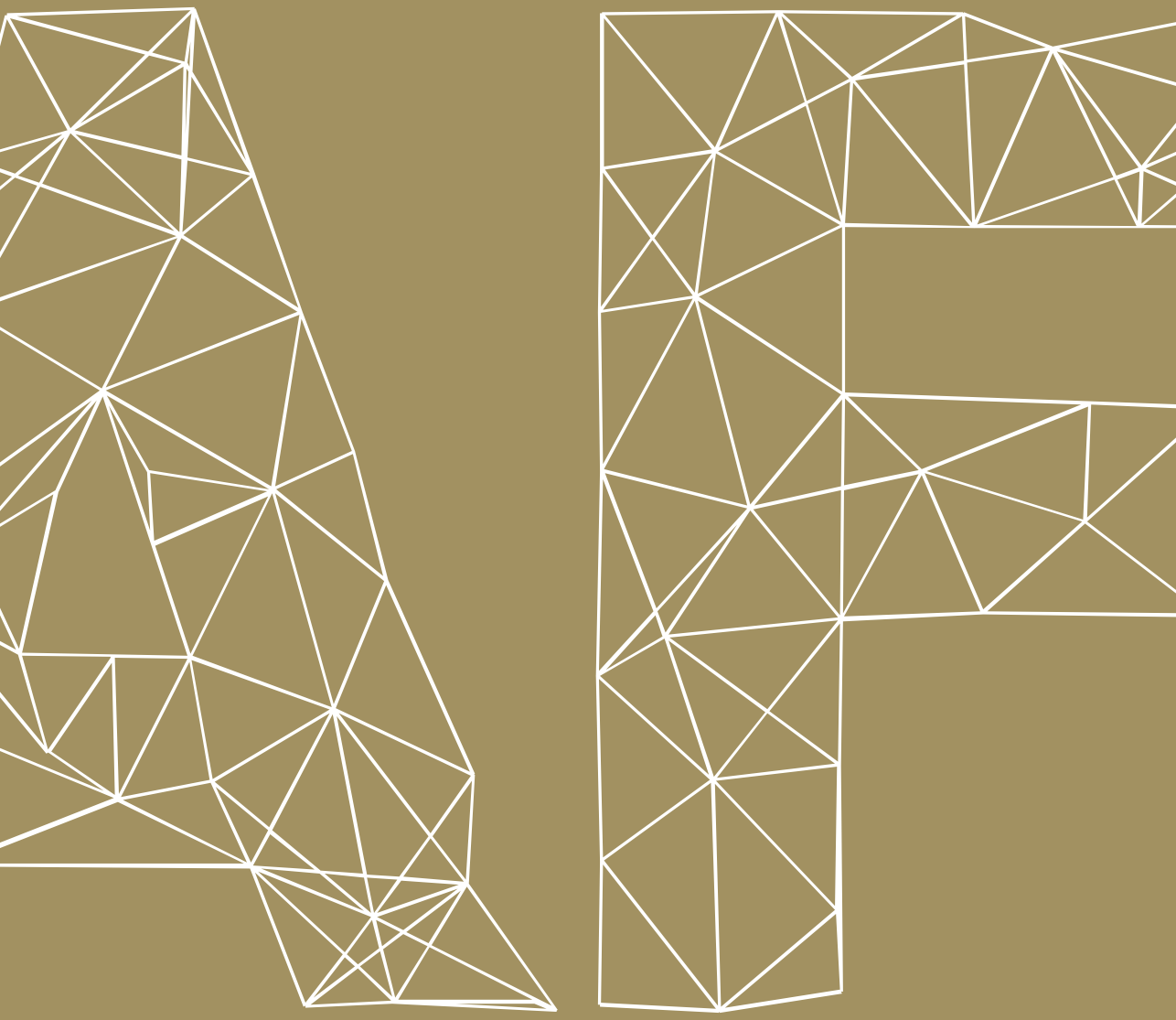
In addition, may be added one further principle involving the all-important relationship between the donors and their blood service. **There should be no unregulated competition for donors.** Experience in both Germany and the USA (referred to above) shows that this irritates donors and stops many of them from donating; for others, it irreversibly changes their expectation/motivation to be paid. The loss of an adequate number of reliable and safe donors is one of the greatest threats that can exist to safe blood transfusion and modern healthcare.

REFERENCES

1. Directive 2002/98/EC of the European Parliament and of the Council of 27 January 2003 setting standards of quality and safety for the collection, testing, processing, storage and distribution of human blood and blood components and amending Directive 2001/83/EC. http://eur-lex.europa.eu/LexUriServ/LexUriServ.do?uri=OJ:L:2003:033:0030:0040:EN:PDF
2. Council of Europe Committee of Ministers. Recommendation No. R (90) 9 of the Committee of Ministers to Member States on plasma products and European self-sufficiency (Adopted by the Committee of Ministers on 29 March 1990, at the 436th meeting of the Ministers' Deputies). http://www.msps.es/profesionales/saludPublica/medicinaTransfusional/recomendaciones/docs/Rec90_9.pdf
3. EU-Q-Blood-SOP Project. Development of a pan-European standard operating procedure (SOP) methodology reflecting European best practice within the area addressing the quality and safety of blood. http://www.eu-q-blood-sop.de
4. EuBIS. European Blood Inspection System. Quality management and inspection of blood establishments. European project addreesin the safety of blood transfusion. http://www.eubis-europe.eu
5. WHO Expert Group. Expert Consensus Statement on achieving self-sufficiency in safe blood and blood products, based on voluntary non-remunerated blood donation (VNRBD). Vox Sang. 2012; 103: 337-42. http://dx.doi.org/10.1111/j.1423-0410.2012.01630.x
6. De Kort W, Veldhuizen I for the EU Donor Management in Europe Project Partners. Donor management manual. Architecture and infrastructure. 2010, p. 31 – 54. ISBN 978-90-815585-1-8. http://www.domaine-europe.eu
7. JUDGMENT OF THE COURT (First Chamber) of 9 December 2010: (Articles 28 EC and 30 EC – National rules prohibiting the importation of blood products provided from donations which were not entirely unpaid). In Case C-421/09. *Reports of cases are not yet published.* http://curia.europa.eu/juris/liste.jsf?language=en&jur=C,T,F&num=C-421/09&td=ALL

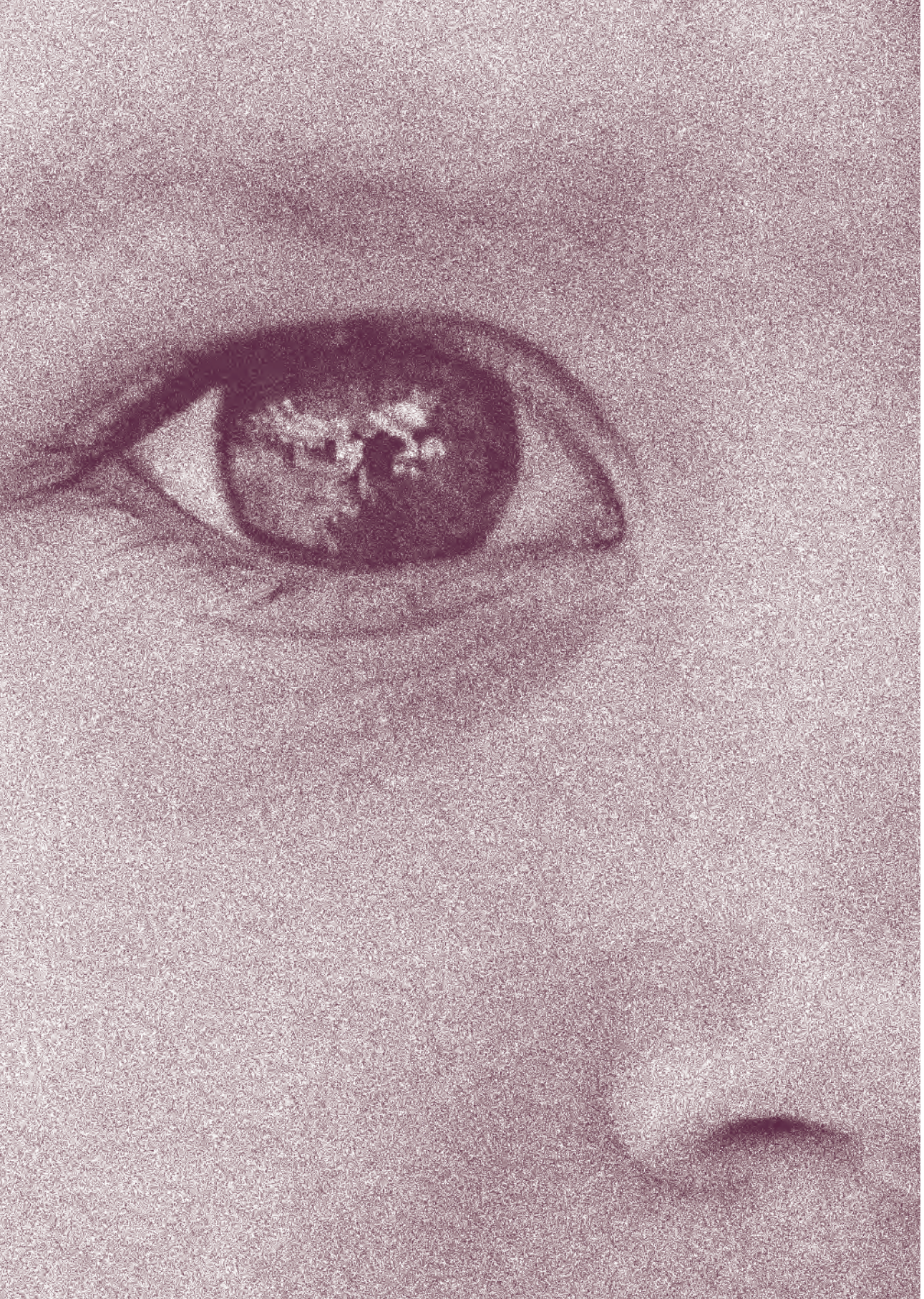
ACKNOWLEDGEMENTS

The author acknowledges the contribution of Martin Gorham and Angus W. Macmillan Douglas (DGP) in preparing parts of the manuscript



BY VNRD

Legislation and challenges



Blood, tissues and cells from human origin: the European Blood Alliance Perspective

SAFETY BY VNRD

Legislation and challenges

Gilles Folléa
Wim de Kort
Guenther Wittauer
Olivia Ligia Burta
Philippe Vandekerckhove

04. WHY VOLUNTARY NON REMUNERATED BLOOD DONATIONS ARE NOW MORE IMPORTANT THAN EVER?

PRINCIPLES AND PERSPECTIVES OF THE EUROPEAN BLOOD ALLIANCE

4.1 SUMMARY

Safe blood and blood products are universally acknowledged to be a critical aspect of health care and public health that saves millions of lives and improves the health and quality of life of many patients. Voluntary non remunerated blood donors (VNRD) have been recognised as the cornerstone of a safe and sustainable supply of blood and blood products sufficient to meet the transfusion requirements of the patient population. Scientific evidence and ethical principles supporting VNRD have been well established and promoted by the Council of Europe, the European Union, most of the EU countries and the World Health Organization.

Despite the wide endorsement of these principles, in the last past few years it has been observed that in some EU countries the practice is increasing that 'for-profit' companies use blood donations collected from paid donors. The violation of these ethical principles has led the European Blood Alliance to review and present updated evidence to explain why volunteer persons who donate blood and blood components for treating patients needing blood transfusion should not be paid for their donation. Recommendations are proposed at the end of this review.

UPDATED EVIDENCE

The following four issues outline the reasons why voluntary non-remunerated donations should be preferred to paid donations.

Blood safety for patients: Based on published scientific data, recently confirmed, paid blood and plasma donors have repeatedly been shown to have a higher risk of blood-borne infectious diseases than voluntary non remunerated donors. Paid donations result in a higher risk that potentially infectious labile blood components (red blood cells, platelets, fresh frozen plasma) escape detection by known routine screening tests. To protect against future emerging infections, preference for voluntary non-remunerated donations is justified as a precautionary measure for blood safety.

Continuity of blood supply: Recent examples clearly illustrate the risk of competition for donors between non-profit blood establishments collecting voluntary non-remunerated donations and organisations collecting paid donations. These examples have demonstrated the effect of abandoning blood collection as a result of commercial considerations, its subsequent longer term destabilizing impact on the donor base, and also for donor recruitment and retention. A stable and secure blood supply is also potentially affected by competition between the blood component sector (mainly non-profit blood establishments) and the plasma sector (mainly pharmaceutical companies), attracting donors using a monetary incentive.

Donor safety: A major risk for donors receiving a monetary incentive is allowing a too high frequency of donation potentially impacting a donor's health. This could result in alteration of normal blood elements, such as a significant decrease in immunoglobulin G content in high-frequency, high-volume plasmapheresis donors.

Ethical / legal reasons for donors: As stated in the Charter of Fundamental Rights of the European Union, "Human dignity is inviolable. It must be respected and protected". This is closely related to the "prohibition on making the human body and its parts, as such, a source of financial gain".

According to principles of non-maleficence and beneficence, the donor should not be subject to unnecessary or unreasonable harm, yet payment and profit encourage high frequency donations with potential harmful consequences for the donors.

Relating to the principle of autonomy: payment of blood donation makes it more attractive to those from lower socio-economic groups. Since they have a greater need to use this option to gain income, payment could be viewed as coercion against donors, compromising their autonomous decision making. The principles of justice require that the burden of donation not fall disproportionately on a particular group or class, especially when the benefit accrues to a different group or class. This applies to lower socio-economic groups, which are more prevalent among paid donors.

From the updated evidence presented above, EBA concludes that the EU blood supply largely based on Voluntary Non-Remunerated Donations is under increasing pressure from paid donation systems and that encouragement of voluntary non-remunerated blood donations should be taken one step further.

RECOMMENDATIONS

To help promote voluntary non-remunerated donations of blood and blood components, and to monitor its implementation and impact on patients' and donors' safety, EBA has formulated the following recommendations.

- Adopt the clarification statement of the current definition of voluntary non-remunerated donations (of blood and blood components) as proposed in paragraph 4.3 of this chapter.

- Elaborate and adopt complementary tools to help objectively assess, monitor and mandate reporting on the voluntary non-remunerated donation implementation and its consequences for the patients' and donors' safety. These tools should be used particularly to improve the current questionnaire of the regular EC report on this subject. EBA will propose such new tools.

- Make the labelling of blood components mandatory (red blood cells, platelets, and fresh frozen plasma) to include the origin of donation, either voluntary and non-remunerated or paid. This will offer physicians and patients a choice, both in terms of safety profile and in terms of ethical procurement of donation.

- Make available public aggregated anonymised epidemiological reports, including paid plasma donations and voluntary non-remunerated plasma donations, to allow for a full comparison of voluntary non-remunerated and paid donors with regard to patient safety. At present, each of the commercial plasma fractionators provides the European Medicine Agency with this information, as proprietary material, in their plasma master file.

- Make available public relevant donor vigilance data, both from voluntary non-remunerated and paid donors, to allow for transparency towards the public and particularly for donors, and help improve donor safety.

- Consider collection of blood, plasma or other Substance of Human Origin (not the preparation or manufacture of end products) as a Service of General Economic Interest. Consequently, as these "starting materials" are in fact Substances of Human Origin and not commodities, internal market rules and competition should not apply.

For the benefit of donors and patients, support from the European Commission and the Members of the European Parliament is sought to help implement the above recommendations.

4.2 BACKGROUND

History of blood donation: Transfusion of blood and blood products, which includes blood components and plasma derivatives, has been in use for decades and established as a proven cure for patients with deficiencies in red blood cells, platelets, plasma or plasma proteins. Safe blood and blood products are universally acknowledged as a critical aspect of health care and public health that saves millions of lives and improves the health and quality of life for many patients.

Following the emergence of AIDS/HIV, scientific, medical and public attention to the safety of transfusion products escalated in the nineteen eighties. Many guidelines and standards are available to define the indications of blood components and plasma derivatives, and the measures adding to the safety of blood products [1–3].

Key principles: The key principles for obtaining safe blood and blood products from voluntary non remunerated donations and the ethics thereof have been recommended and promoted by the Council of Europe (CoE) and have been defined in Article 2 of CoE Recommendation No. R (95) 14 [4]. In addition, the European Convention on Human Rights and Biomedicine of 1997 ("Oviedo Convention") prohibits any financial gain from the human body and its parts [5].

Oviedo Convention: This provision, which is a consequence of the principle of human dignity, means that blood, organs and tissues should not be bought or sold, or give rise to financial gain for the person from whom they have been removed or for a third party. The "Oviedo Convention", entered into force in 1999, and has been ratified so far by 29 Member States of the Council of Europe (of which 16 are EU countries). An additional protocol to this convention, concerning transplantation of organs and tissues of human origin, has been issued in 2002. Surprisingly, no such additional protocol concerning blood has been established so far.

Safety: In the Directive 2002/98/EC [6], the European Union has also taken a similar position in stating: "Voluntary and unpaid blood donations are a factor which can contribute to high safety standards for blood and blood components and therefore to the protection of human health. The efforts of the Council of Europe in this area should be supported and all necessary measures should be taken to encourage voluntary and unpaid donations through appropriate measures and initiatives… " The "prohibition on making the human body and its parts as such a source of financial gain", has further clearly been integrated in the Nice Charter of Fundamental Rights of the European Union [7]. Many other countries and jurisdictions have taken similar positions.

The World Health Organization (WHO), in its Melbourne declaration [8], reiterated this position to the World Health Assembly resolution WHA 28.72 on utilisation and Supply of Human Blood and Blood Products [9], and urged Member States to promote the development of national blood services based on voluntary non remunerated blood donation. This declaration recognised that "evidence supports that regular voluntary non remunerated blood donors are the cornerstone of a safe and sustainable national supply of blood and blood products sufficient to meet the transfusion requirements of the patient population."

For-profit developments: Despite the wide endorsement of these principles, there is evidence of increasing practices by 'for-profit' companies utilising blood donations collected from paid donors in some EU countries. This constitutes a significant violation of these ethical principles and also represents a potential threat to the health of patients and donors. The following recent examples further illustrate these risks.

Austria: A blood supply shortage resulting from unregulated competition between a non-profit blood establishment (BE) collecting Voluntary Non-Remunerated Donations and a for-profit company occurred in Austria in 2006 when a commercial Blood Service went bankrupt.

Germany: There have been two more recent similar cases in Germany, in 2007, where a for-profit company that paid donors withdrew abruptly from collecting blood and supplying hospitals in Prenzlau and in Brandenburg. As a consequence, the existing non-profit BEs were required to fill the gap at short notice. Despite their best efforts, the non-profit services found that they could only regain one out of six of the donors that the profit company had taken from it in the first place. This demonstrates that such competition for the donors between both kinds of blood services could threaten the blood supply and the stability of the donor base, and thus affect the sustainability of supply for patients' health.

Infection risk: Repeatedly during the past decades, a significantly higher rate of transmissible infectious agents in paid blood or plasma donors compared to Voluntary Non-Remunerated Donors has been observed by scientific studies. This risk was again recently illustrated by one example in Germany, where the use of paid blood donors (resident in Polish border areas) by a commercial company was stopped by the Competent Authority as a result of epidemiological data indicating an elevated frequency of infectious disease markers from this donor population: the rate of detection of hepatitis B was far higher in this population than in the Voluntary Non-Remunerated Donors collected by the nonprofit BE.

Role of Competent Authorities: A practice in one Member State could pose a serious threat to public health in other Member States if such commercial blood companies, primarily driven by profit, could continue to operate until specific epidemiological issues are identified by the Competent Authorities. It is well acknowledged that collection of blood from paid donors selects different populations, sometimes geographically distinct, but often from lower socio-economic populations, and associated with more prominent illegal drug use and higher rates of blood and sexually transmissible infections.

The fact that such data, available at regulatory offices, is not transparent is very questionable. In the USA, in 1989, the Governmental Accounting Office reported anonymously on the issue, and it is questionable why EU regulatory agencies do not report likewise, for instance on an annual, anonymised basis.

Furthermore, it has become common practice in Germany that private blood banks and blood banks from state communities and universities offer a fixed allowance of up to €25 to the donor to compensate for time and travel costs. These centres pay a fixed amount of money per donation to persons who had no travel costs or considerably less travel costs than the fixed fee offered, even on mobile blood donation sessions in rural areas or in companies, where the BE sends a mobile donor clinic. These centres are typically located in areas where the fixed fee becomes an important amount of money, especially when given for repeated apheresis donations. In the USA these donations would be properly labelled by the FDA as paid donations.

European Blood Alliance (EBA): The European Blood Alliance, EBA, is an association of non-profit Blood Establishments collecting voluntary non-remunerated donors, with 23 members throughout the European Union and EFTA States. Its mission is threefold:

- To contribute to the availability, quality, safety and cost-effectiveness of the blood and tissue supply for the citizens of Europe by developing and maintaining an effective and efficient collaboration amongst European blood and tissue services.
- To increase public and professional awareness of voluntary non-remunerated donation of blood and blood components [10], as the basis for preparation of blood components as an indispensable therapeutic means of saving patients.
- To assist European blood establishments to continuously improve their performance based on scientific and ethical principles for the benefit of patients.

In light of this context of continuing debate about donor remuneration and related threats to the blood supply and safety, the EBA formed a task force to review the question and to develop a policy statement for its consideration and adoption. Here, we present updated evidence to explain why volunteer persons who donate blood and blood components for treating patients needing blood transfusion should not be paid for their donation. Recommendations will be proposed at the end of this review.

4.3 NEED FOR A CLARIFICATION IN THE DEFINITION FOR VOLUNTARY NON-REMUNERATED DONATION

The most widely used definition of Voluntary Non-Remunerated Donation is the one provided by the CoE in its Recommendation No. R (95) 14 [4]. The CoE and WHO only use this wording, while the EC official documents alternately use this terminology and also "voluntary and unpaid donation".

The European Parliament and Council, the WHO, the International Federation of Red Crescents [11], the International Society for Blood Transfusion [12] have all approved this definition, the wording of which is as following.

"*Donation is considered voluntary and non-remunerated if the person who gives blood, plasma or cellular components of his/her own free will and receives no payment for it, either in the form of cash or in kind which could be considered a substitute for money. This would include time off work other than that reasonably needed for the donation and travel. Small tokens, refreshments and reimbursements of direct travel costs are compatible with voluntary, non-remunerated donation*".

European Court of Justice ruling: Regarding reimbursement of travel costs, although the CoE definition in principle is clear enough, meaning that money should be given to donors only to reimburse their *direct* travel expenses (as established by presentation of related receipts), a recent judgment of the European Court of Justice [13] dealt with this item.

The Court ruled on the legality of a national regulation (Austrian) with regards to the free movement of goods, prohibiting the import of blood products from blood donations that are not fulfilling the definition of VNRD. The major issue concerned the payment of a fixed allowance to donors. The final judgment by the European Court of Justice is that any legislation, which prohibits a fixed allowance, is permissible if it serves to improve the quality and safety of blood and blood components and, subsequently, the protection of human health. In addition, there shall be no other less stringent measures through which the objective may be achieved.

In other words, the criteria for prohibiting a fixed allowance would be met if such a fixed allowance led to blood donors benefiting from a financial advantage or being encouraged to donate blood by the fixed allowance. This would also apply if a fixed allowance exceeded the actual travel costs, as proven by the deposition of a ticket or receipt of the actual amount paid for the travel.

The quality and safety of blood and blood components must be ensured and improved (see paragraph 4.4.1), Therefore, to avoid voluntary non-remunerated blood donors receiving a financial reward for their blood donation through a fixed allowance, or potential donors being encouraged to donate blood by a fixed allowance, in the light of this judgment, we propose the following clarification of the CoE definition of VNRD (below, in bold).

"*Donation is considered voluntary and non-remunerated if the person who gives blood, plasma or cellular components of his/her own free will and receives no payment for it, either in the form of cash or in kind which could be considered a substitute for money. This* ***should*** *include time off work other than that reasonably needed for the donation and travel. Small tokens, refreshments and reimbursements of direct travel costs are compatible with voluntary, non-remunerated donation****. Fixed allowances are not compatible with voluntary non-remunerated donation.***"

Direct travels costs only: With this clarification, reimbursements of direct travel expenses to voluntary non-remunerated blood donors would only be acceptable as reimbursement of direct travel costs as proven by the deposition of a ticket or receipt of the actual amount paid for the travel, thus excluding fixed allowances. The adoption of this clarified definition would also provide an opportunity to remind organisations that donors benefiting from "*time off work other than that reasonably needed for the donation and travel*" should not be considered as voluntary and non-remunerated.

Member States that have removed "days off" for voluntary non remunerated donors, such as France in 1994 and Romania in 2009, have shown that this is compatible with a sufficient blood supply, as the majority of donors expressed strong willingness to continue donating despite the removal of such an historical advantage.

If deemed necessary, further clarification of this definition could also include non-monetary recognition items for donation milestones, for acknowledging and encouraging regular donors. This could be informed by the FDA definition of volunteer donors with the following answers to questions on incentives to donors [14].

Is the incentive transferable to someone else than the donor? Is the incentive refundable or redeemable for cash? Does a market exist for the incentive?

However, with the clarified CoE definition we do not think there is a need to add anything else. As indicated in the Dublin consensus statement [15], "incentives offered will differ and reflect the social, economic, ethical and cultural environment in which the blood and plasma sectors operate. However, all incentives should be of a kind that pose no risk of harm, [and] do not overwhelm the capacity of the donor to make an informed decision about whether or not to donate."

4.4 REASONS WHY VOLUNTARY NON-REMUNERATED DONATIONS SHOULD BE PREFERRED TO PAID DONATIONS

4.4.1 BLOOD SAFETY FOR PATIENTS

Evidence of risk: Based on published scientific data, paid blood and plasma donors have repeatedly been shown to have a higher risk of blood-borne infectious diseases than voluntary non remunerated donors. Eastlund, in reviewing published studies from many countries over several decades [16], observed that hepatitis B virus (HBV) carriers were found more frequently in donations from paid than from volunteer donors. The frequency of hepatitis C virus (HCV) antibody positive was reported to be 11 to 50 times greater in paid than in volunteer blood donors and the frequency of HIV antibody positive has been 3 to 70 times greater in paid plasma donors than in volunteer blood donors.

Unchanged evidence over time: In this review, the increased risk of infectious disease was not balanced by a demonstrated need to pay donors to ensure availability of blood products. More recently, from an analysis of the relative risk estimates for infectious disease markers among paid and unpaid donors from 28 published data sets, evidence was not found to indicate that the difference in risk for infectious disease markers between paid donors and unpaid donors had diminished over time [17]. This has been recently confirmed again with data from Lithuania [18] and Germany.

Undesirable effects of incentives: Monetary incentives, as fixed allowances, can encourage undesirable donor behaviour through concealment of existing risk factors in the pre-donation interview. This can pose a threat to the quality of collected blood and ultimately to patient safety. In the South of the USA, donors from Mexico, some of whom are illegal drug users, travel across the US border to donate at centres offering even modest payments, whereas they do not donate in Mexico itself, because payment for donations there is forbidden [19]. It is noteworthy that similar practices are presently developing along the eastern borders of Germany and Austria.

Window periods: Higher risk profiles in a donor population create a higher risk that paid donors donate blood during the "window-period" of the disease's incubation. This "window period" is the period during which an infectious blood donation may escape blood screening tests for the presently known transmissible viruses. Unfortunately, blood screening tests without a "window period" do not exist, and probably never will. Molecular based technologies, such as Nucleic Acid Testing (NAT), have helped reduce this window period but do not eliminate it. Paid donations, therefore, result in a higher risk that potentially infectious labile blood components (red blood cells, platelets, fresh frozen plasma) escape detection by known routine screening tests.

Viral inactivation: For blood components, at present, viral inactivation methods are only applicable to fresh frozen plasma and platelet concentrates, and no method is available for red blood cells, despite decades of research. Whether or not the application of existing viral inactivation methods to fresh frozen plasma and platelet concentrates should be extended in all countries is still a matter of debate [20,21].

Plasma derived medicinal products: Regarding the production of plasma derived medicinal products, manufactured from human pooled plasma, the effectiveness of current inactivation steps may render the difference in safety between paid and voluntary non-remunerated donors less relevant. However, for all production processes it is clear that the safety profile of the end-products depends on the safety of the starting material [22]. And recent scientific data has shown that some viruses resist viral inactivation, as some haemophiliacs have been contaminated by a blood borne virus (human parvovirus 4), through clotting factor concentrates, despite the inactivation steps [23].

Emerging infections: In any case, all blood safety measures which are presently applied are based on present knowledge. Important lessons have been learned over the last decades. In particular whenever a new blood-transmissible infectious disease has emerged, or new blood screening tests have been introduced, paid donors have higher rates of infection. In terms of safety, therefore, it is prudent to rely on voluntary non-remunerated donations, based on the experience of the last decades, during which formerly unknown, but latterly important blood-borne agents emerged. To protect against future emerging infections, preference for voluntary non-remunerated donations is justified as a precautionary measure for blood safety.

United States practice: The early recognition of the increased risk of blood transfusion obtained from paid donors in the United States led to a federal government regulation in 1978 that all blood components be labelled as derived from either volunteer- or from paid-donor blood [24]. This resulted in a rapid reduction in the use of paid donations for blood components by physicians and hospital policies in the USA. It is surprising that such a measure has not been implemented so far in the EU, not only as a key safety measure, but also to allow the end-user to make an informed ethical choice.

Information sharing: In order to properly assess the safety of donations, complete transparency and sharing by all parties of relevant (but anonymised) data to authorities and the scientific world is needed. The Directive 2002/98/EC requires Blood Establishments to include the incidence and prevalence of transfusion transmissible infectious markers in donors of blood and blood components in their annual report to their Competent Authority [6].

Annual reporting of prevalence and incidence data of HIV, HBV and HCV per 100,000 donors is regularly presented publicly by the CoE [25]. Given the findings of different risk profiles among paid and voluntary non-remunerated donors, withholding such relevant information from the public is not acceptable. For plasma fractionators this information is annually reported in the plasma master file. Although it could be argued that such data may be proprietary information, there is no argument against publication of the data on paid and voluntary non-remunerated donors in an aggregated anonymised annual report. Also, presently an unequal playing field exists, as public blood systems are making their data public.

A system is required to allow the publication of all epidemiological data, as is done regularly by blood establishments for blood and blood components. This will allow a full comparison of transmissible disease markers in all voluntary non-remunerated compared with paid donors. The main outcomes of such an analysis should be integrated in the regular EC report on voluntary unpaid donation. This important information was not included in the last report [26].

4.4.2 CONTINUITY OF BLOOD SUPPLY

Risks of competition: Recent examples in Austria and Germany clearly illustrate the risk of competition for donors between non-profit blood establishments collecting voluntary non-remunerated donations and organisations collecting paid donations. These examples have demonstrated the effect of abandoning blood collection as a result of commercial considerations and its subsequent longer term destabilizing impact on the donor base, and thus for donor recruitment and retention. If repeated and unregulated, this could threaten the blood supply and, therefore, patient safety.

Market dictates: This phenomenon was also seen some years ago when the supply of IV Immunoglobulins shifted to higher price and higher use areas. This is a logical result from allowing market mechanisms to meet supply. If the market is less profitable in a particular region, supply will tend to follow price into regions of greater profitability resulting in shortages or absence of supply. This underlines the need to view blood donation in the EU in the long term perspective as a strategic supply, based on public trust and benevolence, and to avoid detrimental competition for donors based on conventional market principles.

Donor stability: The importance of the regular adaptation of donor bases for the patients' needs for blood components has been well established in the donor management in Europe (DOMAINE), EBA promoted and EU co-funded project [27]. It is essential to avoid donor losses and motivation shift for long term donations and allow for more sustainable donor bases. It will also affect donations for other Substances Of Human Origin, such as tissues and cells, as the public quite logically regard all such donations as interrelated and underpinned by the same public policy principles.

Blood components and plasma: A stable and secure blood supply is also potentially affected by competition between the blood component sector (mainly non-profit blood establishments) and the plasma sector (mainly pharmaceutical companies). There is a risk that supply will be impacted, particularly with underprivileged donors attracted by a monetary incentive, and preferring to donate plasma for monetary reward rather than donating blood or blood components for preparing labile blood products (red cells, platelets, fresh frozen plasma).

Presently most of the plasma collected in the EU is derived from donors donating blood or components such as plasma on a voluntary non-remunerated basis. Furthermore, the International Plasma Fractionation Association and EBA have clearly established that, with a total of 3.6 million litres of plasma collected from voluntary non-remunerated donors in the former EU 13 countries, excluding UK and Ireland, where mainly US plasma is used as a vCJD risk reduction measure, the level of sufficiency achieved for the IV Immune globulin (driving factor) is in the range of 80–86% [28]. This indicates that the EU goal of self-sufficiency from voluntary non-remunerated donors throughout the Community' is achievable. This position should be strengthened and supported by the EU.

The current contribution of paid plasma-derived products to EU supply appears primarily as a reflection of the free and open competitive market which exists in the EU, and which allows importation of licensed products (or export of products derived from plasma donated in the EU). It does not primarily result from a shortage of plasma or product from the non-profit sector based on voluntary non-remunerated donors.

Social cohesion: The blood component supply issues could be positively impacted by regional and/or national social cohesion, using the principles of voluntary non-remunerated donation, resulting in a better link between donors and patients, as reciprocity to one's peer group. Public perception in Europe is largely in favour of voluntary non-remunerated donation, being considered a contribution to society. Participation in voluntary non-remunerated donation programmes, therefore, stimulates social cohesion.

Practical ways to encourage such a social cohesion are illustrated in blood establishment websites of several member states, displaying regularly updated status of red blood cell inventories at the regional or national level. Some are called 'blood barometers' and presented as 'weather forecasts'. This link, only feasible with voluntary non-remunerated donation programmes, is a good way to establish the important link between blood collection and patients' needs for blood components. It is also fully compatible with a structured vision of blood supply management, starting from the patients' needs, as recently proposed by a CoE working group on blood supply management [29].

Consistent with the above comments, it is also important to recall that a recent WHO resolution [30] urged members 'to establish, implement and support nationally-coordinated, efficiently-managed and sustainable blood and plasma programmes… with the aim of achieving self-sufficiency of supply for patients.' The Dublin consensus statement [15] pointed out that the coexistence of two independent collection systems, one for blood and one for plasma, in the same region or country, could create a risk of shortage in the supply of blood components. It also stressed the importance of cooperation between the blood and plasma sectors to ensure that the best community outcomes are achieved, including sufficiency of supply for all patients.

4.4.3 DONOR SAFETY

Directive 2002/98/EC [6] states that blood and blood components used for therapeutic purposes or for use in medical devices should be "obtained from individuals whose health status is such that no detrimental effects will ensue as a result of the donation and that any risk of transmission of infectious diseases is minimised", and that "this Directive shall apply to the collection and testing of human blood and blood components, whatever their intended purpose".

A major risk for donors receiving a monetary incentive is in allowing a too high frequency of donation with potential impact on donor health. In a scientific study, plasma pools from US high-frequency, high-volume plasmapheresis donors showed significantly lower protein markers, as, for example, total immunoglobulin G (IgG) contents (-24%), when compared to voluntary non remunerated EU or US whole-blood or plasmapheresis donors [31].

This low content of IgG was the most likely indirect cause of deaths in patients having received IgG concentrates after a modification of the manufacturing process aiming at increasing the IgG yield from such donors. Currently, although donor safety is increasingly

studied to find factors helping to prevent donation complications and to retain healthy donors, more scientific data and assessment of donor safety for high frequency donors is needed. In this respect, donor vigilance data should be made publicly available both from voluntary non-remunerated and paid donors. This could be included in the future in the regular EC report on Voluntary and Unpaid Donation of Blood and Blood Components.

4.4.4 ETHICAL / LEGAL REASONS FOR DONORS

The ethical motives to continue promoting voluntary non remunerated donations have been recently reviewed and updated, both for blood donations [32] and haematopoietic stem cells [33]. Updated evidence concerning the ethical principles of dignity, non-maleficence, beneficence, autonomy and justice, applied to blood donation is summarised below.

I. DIGNITY

As stated in the Charter of Fundamental Rights of the European Union [7], "Human dignity is inviolable. It must be respected and protected". From a Kantian perspective, the offer and acceptance of payment for blood could be considered as constituting an instrumentalisation of a person, in that the paid donor becomes a mere means to the ends of others. In this view, payment for blood donation would violate the principle of human dignity. In putting a 'price' on a personal 'good' – blood – human dignity would be threatened through devaluation of the person involved [34].

Blood donation should thus be considered as a "special" kind of activity, as is donating a live kidney, different in relevant respects from other potentially paid activities, and in need of "protection" from any financial transaction. This is closely related to the "prohibition on making the human body and its parts as such a source of financial gain", clearly stated in the Charter of Fundamental Rights of the European Union [7].

Also paid donation systems gradually lead to the devaluation of (parts of) the human body to the status of a commodity, and, thereby, also devalues the present EU supply system largely based on Voluntary Non-Remunerated Donors. Therefore, the donation of blood as other Substances Of Human Origin should remain a public responsibility and a public affair.

Service of General Economic Interest (SGEI) Status: A way to comply with this ethical principle and current EU legislation could be to give blood and plasma collection, and donor management, the status of Service of General Economic Interest (SGEI), putting de facto blood donations outside of the internal market rules. SGEIs, acknowledged in the Article 16 of the Treaty establishing the European Community [35], are different from ordinary services in that public authorities consider that they need to be provided even where the market is not sufficiently profitable for the supply of such services.

The concept of SGEIs is based on the concern to ensure that a quality service is provided at an affordable price everywhere for everyone. SGEIs contribute to achieving the objectives of solidarity and equality of treatment underlying the European model of society. The role assigned to SGEIs and the special rights which may attach to them stem from general interest considerations such as security of supply, environmental protection, economic and social solidarity, regional planning and the promotion of consumer interests. The guiding principles are continuity, equality of access, universality and transparency of the services.

II. NON-MALEFICENCE AND BENEFICENCE

The donor should not be subject to unnecessary or unreasonable harm. As indicated above (paragraph 4.4.3), the fact that payment and profit encourage high frequency donations with potential harmful consequences for the donors has been established objectively. Donor safety is all the more important as the act of donation is a medical procedure for which the donor will not derive any direct benefit. This is a major difference from patients undergoing medical procedures, as they are expecting therapeutic benefit from them. However, even collecting a simple 500 mL of whole blood is a medical intervention, and blood establishments are the only entities which are responsible and accountable for the medical care of donors.

Donor safety: It is remarkable that the EU regulations have only minimally addressed the safety issues of the donors. Furthermore, any harm that might result from the donation will not be offset by any health or medical benefit to the donor undergoing the procedure. Therefore, concern for safety of donors must be uncompromising. All in all, the donor may experience a sense of satisfaction derived from an altruistic act, but the implied trust and contract between donor and blood service demands maximal medical care and ethical standards towards him/her, and importantly towards the use of the products.

Donor safety is now the subject of active research. The above considerations should encourage the development of more active donor vigilance with the results made publicly available. Comparing data between voluntary non-remunerated and paid donors would be an important part of such studies.

III. COMPROMISED AUTONOMY: COERCION/PRESSURE

Lower socio-economic groups: As it may be more attractive to those from lower socio-economic groups who have a greater need to use this option to gain income, payment for blood could be viewed as coercion against donors, compromising their autonomous decision making. Such pressures probably exist in EU countries in which students are frequently invited to donate plasma for a fixed allowance. Precise questions to further explore such situations should be added to the questionnaire of the regular EC report on Voluntary and Unpaid Donation of Blood and Blood Components [24].

IV. JUSTICE

The principles of justice and fairness require that the burden of donation does not fall disproportionately on a particular group or class, especially when the benefit accrues to a different group or class. The fact that those from lower socio-economic groups are more prevalent among paid donors has been labelled an injustice [36]. When payment is used as an inducement to provide blood or blood components, it is argued that a wealthier population will exploit poorer populations. The 'burden of donation' thus is being shifted to underprivileged populations. This is clearly the case when companies transport paid donors from less wealthy Eastern European regions to richer western countries such as Germany or Austria to organise blood collections to manufacture blood products. The Competent Authority of Germany only stopped this in the case of Polish donors when they observed that this donor population had higher risks of transmissible disease (hepatitis B).

V. CONCLUSIONS AND RECOMMENDATIONS

From the updated evidence presented above, EBA concludes that the EU blood supply largely based on Voluntary Non-Remunerated Donations is under increasing pressure

from paid donation systems. Encouragement of voluntary non-remunerated blood donations should be taken one step further, for the following reasons:

- It is shown to be safer in helping to lower the risks of transmissible diseases for recipients of blood components for known infectious agents. Voluntary Non-Remunerated Donations are expected on a precautionary basis to be safer for emerging diseases if these are sexually transmitted or common among drug users.
- For plasma derived medicinal products the safety of the donor population is relevant in risk analyses.
- It is totally compatible with meeting the demand in the future and with the security of blood supply.
- It is consistent with the Charter of Fundamental Rights of the European Union and the Oviedo Convention, and their ethical principles.
- It is fully supported by the donor organisations, helping in recruiting and retaining the donors required for collecting the annual 22,000,000 voluntary non-remunerated donations needed for patients in the EU, hence stabilising the required donor base [23].
- It strengthens regional and/or national social cohesion, in developing and maintaining a better link between donors and patients, as reciprocity to one's peer group.
- It is widely supported by public perception in the European Community, with a majority willing to act altruistically in donating blood out of benevolence, with indirect positive links to the voluntary non-remunerated donations of other Substances Of Human Origin.

To help further promote voluntary non-remunerated donations of blood and blood components and monitor its implementation and impact on patients' and donors' safety, EBA has formulated the following recommendations. They are fully consistent with the Consensus Statement recently published by a WHO Expert Group on a closely related subject [37], and aim at an implementation adapted to Europe.

- Adopt a clarification of the current definition of voluntary non-remunerated donations of blood and blood components (see paragraph 4.3).
- Elaborate and adopt complementary tools to help objectively assess, monitor and ensure mandatory reporting on the voluntary non-remunerated donation implementation and its consequences for the patients' and donors' safety. These tools should be used particularly to improve the current questionnaire of the regular EC report on this subject. EBA will propose such new tools before the end of 2012.
- Make labelling blood components mandatory (red blood cells, platelets, and fresh frozen plasma) with the origin of donation, either voluntary and non-remunerated or paid, to offer physicians and patients a choice, both in terms of safety profile and in terms of ethical procurement of donation.
- Make available public aggregated anonymised epidemiological reports, including paid plasma donations and voluntary non-remunerated plasma donations, to allow for a full comparison of voluntary non-remunerated and paid donors with regard to patient safety. At present, each of the commercial plasma fractionators provides the European Medicine Agency with this information, as proprietary material, in their plasma master file.
- Make available public relevant donor vigilance data, both from voluntary non-remunerated and paid donors, to allow for transparency towards the public and particularly for donors, and to help improve donor safety.
- Consider collection of blood, plasma or other Substance of Human Origin (not the preparation or manufacture of end products) as a Service of General Economic Interest. Consequently, as these "starting materials" are in fact Substances of Human Origin and not commodities, internal market rules and competition should not apply.

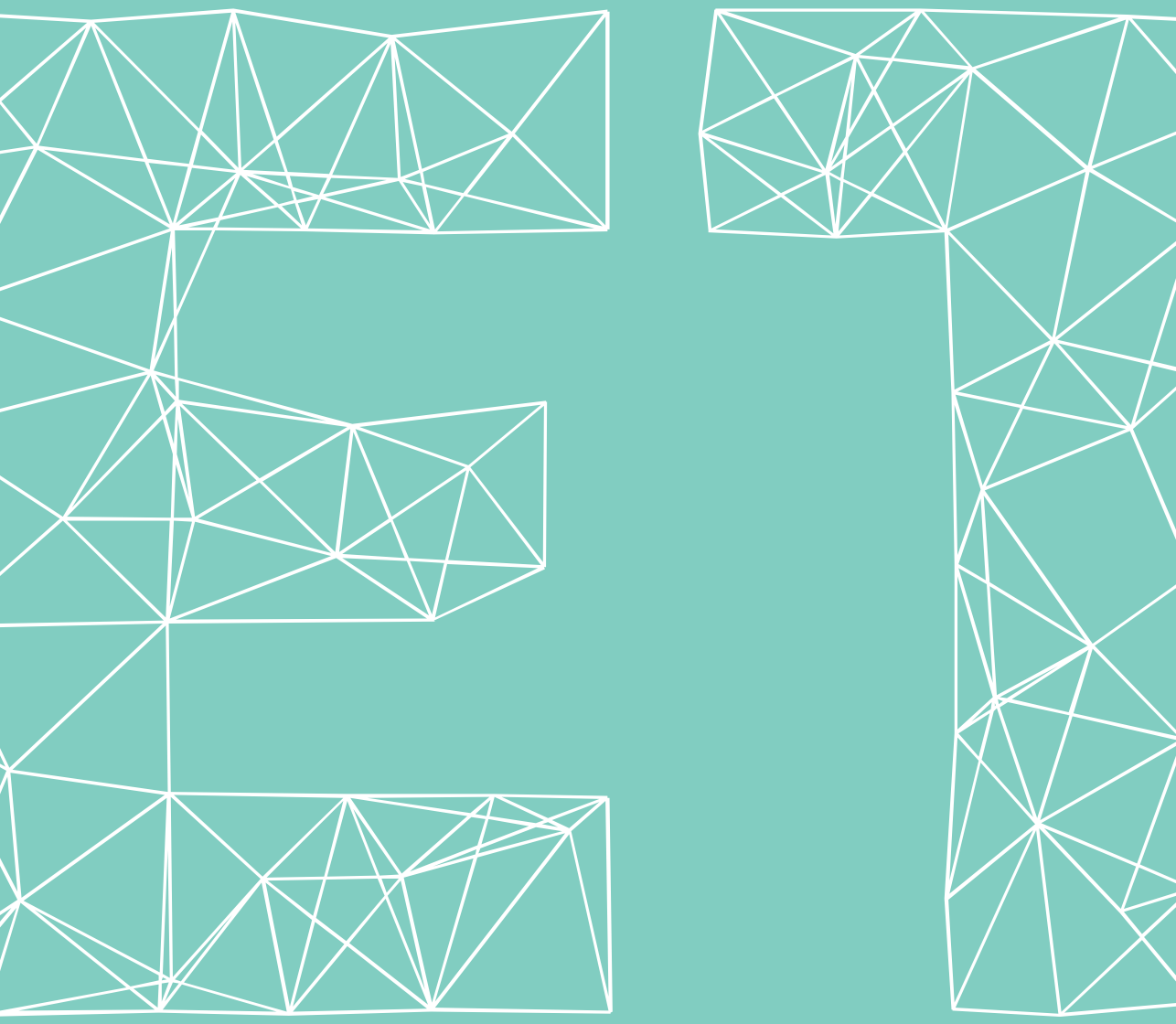
REFERENCES

1. UK Blood Transfusion Services. Guidelines for the Blood Transfusion Services in the United Kingdom, 7th edition (2011). http://www.transfusionguidelines.org.uk/index.aspx?Publication=RB
2. Germany. Bundesärztekammer (German Medical Association). Cross-sectional guidelines for therapy with blood components and plasma derivates, 4th edition (2009). www.iakh.de/tl_files/iakh/public/richtlinien/Querschnittsleitlinie_4._Auflage_-_englisch_05.01.2011%20copy.pdf
3. National Users' Board Sanquin Blood Supply (The Netherlands). Blood Transfusion Guidelines, 2nd edition (2011). http://www.sanquin.nl/repository/documenten/en/prod-en-dienst/287294/blood-transfusion-guideline.pdf
4. Council of Europe Committee of Ministers. Recommendation No R(95)14 of the Committee of Ministers to member states on the preparation, use and quality assurance of blood components. Adopted by the Committee of Ministers on 12 October 1995, at the 545th meeting of the Ministers' Deputies. http://www.msssi.gob.es/profesionales/saludPublica/medicinaTransfusional/recomendaciones/docs/Rec95_14.pdf
5. European Convention on Human Rights and Biomedicine (1997, "Oviedo Convention") http://conventions.coe.int/Treaty/en/Treaties/Html/164.htm
6. Directive 2002/98/EC of the European Parliament and of the Council of 27 January 2003 setting standards of quality and safety for the collection, testing, processing, storage and distribution of human blood and blood components and amending Directive 2001/83/EC. http://eur-lex.europa.eu/LexUriServ/LexUriServ.do?uri=CELEX:32002L0098:EN:HTML
7. Charter of Fundamental Rights of the European Union (2000/C 364/01). Official Journal of the European Communities. http://www.europarl.europa.eu/charter/pdf/text_en.pdf
8. World Health Organization. The Melbourne Declaration on 100% Voluntary Non-Remunerated Donation of Blood and Blood Components. http://www.who.int/worldblooddonorday/MelbourneDeclarationWBDD09.pdf
9. World Health Assembly resolution WHA 28.72 on utilization and Supply of Human Blood and Blood Products. http://www.who.int/bloodsafety/BTS_ResolutionsAdopted.pdf
10. European Blood Alliance. Position paper on Voluntary Non Remunerated Donation (2009). http://ebaweb.files.wordpress.com/2012/08/eba-position-paper-on-non-remunerated-donors-20091002.pdf
11. International Federation of Red Crescents. Global action towards 100 per cent voluntary, non-remunerated blood donation http://www.ifrc.org/en/what-we-do/health/blood-services/global-action-towards-100-per-cent-voluntary-non-remunerated-blood-donation/
12. ISBT: A code of ethics for blood donation and transfusion. http://www.isbtweb.org/fileadmin/user_upload/ISBT_Code_of_Ethics/Code_of_ethics_new_logo_-_feb_2011.pdf
13. JUDGMENT OF THE COURT (First Chamber) of 9 December 2010: (Articles 28 EC and 30 EC – National rules prohibiting the importation of blood products provided from donations which were not entirely unpaid). In Case C-421/09. http://curia.europa.eu/juris/liste.jsf?language=en&jur=C,T,F&num=C-421/09&td=ALL
14. FDA. CPG Sec. 230.150 Blood Donor Classification Statement, Paid or Volunteer Donor http://www.fda.gov/ICECI/ComplianceManuals/CompliancePolicyGuidanceManual/UCM122798
15. Mahony BO, Turner A. The Dublin Consensus Statement on vital issues relating to the collection of blood and plasma and the manufacture of plasma products. Vox Sang. 2010; 98: 447-50. http://dx.doi.org/10.1111/j.1423-0410.2010.01310.x
16. Eastlund T. Monetary blood donation incentives and the risk of transfusion-transmitted infection. Transfusion, 1998; 38:874-82. http://dx.doi.org/10.1046/j.1537-2995.1998.38998409009.x
17. Van der Poel CL, Seifried E, Schaasberg WP. Paying for blood donations: still a risk? Vox Sang. 2002; 83: 285–293. http://dx.doi.org/10.1046/j.1423-0410.2002.00239.x
18. Kalibatas V. Payment for whole blood donations in Lithuania: the risk for infectious disease markers. Vox Sang. 2008, 94: 209–215. http://dx.doi.org/10.1111/j.1423-0410.2007.01015.x
19. Volkow P, Brouwer KC, Loza O, Ramos R, Lozada R, Garfein RS, Magis-Rodriguez C, Firestone-Cruz M, Strathdee SA. Cross-border paid plasma donation among injection drug users in two Mexico-U.S. border cities. Int J Drug Policy. 2009, 5: 409-12. http://dx.doi.org/10.1016/j.drugpo.2008.12.006
20. Klein HG, Anderson D, Bernardi MJ, Cable R, Carey W, Hoch JS, Robitaille N, Sivilotti MLA, Smaill F. Pathogen inactivation: making decisions about new technologies – preliminary report of a consensus conference. Vox Sanguinis, 2007. http://dx.doi.org/10.1111/j.1537-2995.2007.01512.x
21. European Directorate for the Quality of Medicines & HealthCare. Symposium on Implementation of Pathogen Reduction Technologies for Blood Components. Executive summary, 2011. http://www.edqm.eu/medias/fichiers/Executive_Summary_Pathogen_Reduction.pdf
22. Janssen MP, Over J, van der Poel CL, Cuijpers HT, van Hout BA. A probabilistic model for analyzing viral risks of plasma-derived medicinal products. Transfusion. 2008, 48:153-62. http://dx.doi.org/10.1111/j.1537-2995.2007.01493.x
23. Sharp CP, Lail A, Donfield S, Gomperts ED, SimmondsP. Virologic and clinical features of primary infection with human parvovirus 4 in subjects with hemophilia: frequent transmission by virally inactivated clotting factor concentrates. Transfusion, 2011. http://dx.doi.org/10.1111/j.1537-2995.2011.03420.x/pdf
24. Federal Register 1978; 43:2142. http://www.fda.gov/OHRMS/DOCKETS/98fr/001679gd.pdf
25. Poel van der CL, Janssen MP, Borkent-Raven B. Report on the collection, testing and the use of blood and blood components in Europe in 2008. Committee (Partial Agreement) on Blood Transfusion (CD-P-TS) of the Council of Europe; 2010. http://www.edqm.eu/medias/fichiers/NEW_2008_Report_on_the_.pdf.
26. European Commission. 2nd Report on Voluntary and Unpaid Donation of Blood and Blood Components, 2011. http://ec.europa.eu/health/blood_tissues_organs/docs/blood_reportdonation_en.pdf
27. Donor Management Manual. W de Kort ed, 2010. http://www.domaine-europe.eu
28. Rossi F, Perry R, de Wit J, Evers T, Folléa G. How expanding voluntary non-remunerated blood donations would benefit patients, donors and healthcare systems? Vox Sanguinis, 2011. http://dx.doi.org/10.1111/j.1423-0410.2011.01495.x
29. Folléa G, Behr-Gross ME, de Kort W, Mpuntsha L. Red Blood Cell Supply Management: tools for assessment and improvement. Communication, 2012. Meeting of the International Society of Blood Transfusion, Working Party on Blood Supply Management. http://www.isbtweb.org/mexico/programme/tuesday-july-10/0830-1530/
30. World Health Organisation. Resolution WHA 63.12 on Availability, safety and quality of blood products. 2010; http://apps.who.int/gb/ebwha/pdf_files/WHA63/A63_R12-en.pdf
31. Laub R, Baurin S, Timmerman D, Branckaert T, Strengers P. Specific protein content of pools of plasma for fractionation from different sources: impact of frequency of donations. Vox Sang 2010; 99:220–231. http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3001115/pdf/vox0099-0220.pdf
32. Buyx AM. Blood Donation, Payment, and Non-Cash Incentives: Classical Questions Drawing Renewed Interest. Transfus Med Hemother 2009; 36: 329–339. http://dx.doi.org/10.1159/000235608
33. Boo M, van Walraven SM, Chapman J, Lindberg B, Schmidt AH, Shaw BE, Switzer GE, Yang E, Egeland T and on behalf of the World Marrow Donor Association. Remuneration of hematopoietic stem cell donors: principles and perspective of the World Marrow Donor Association. Blood 2011, 117: 21-25. http://bloodjournal.hematologylibrary.org/content/117/1/21.long
34. Archard D: Selling yourself: Titmuss's argument against a market in blood. J Ethics 2002;6:87–103. URL: http://www.jstor.org/stable/25115716
35. Services of General Interest in Europe. http://europa.eu/legislation_summaries/other/l26087_en.htm

36. Beal RW, van Aken WG: Gift or good? A contemporary examination of the voluntary and commercial aspects of blood donation. Vox Sang 1992; 63:1–5. http://dx.doi.org/10.1111/j.1423-0410.1992.tb01210.x
37. WHO Expert Group. Expert Consensus Statement on achieving self-sufficiency in safe blood and blood products, based on voluntary non-remunerated blood donation (VNRBD). Vox Sanguinis, 2012. http://dx.doi.org/10.1111/j.1423-0410.2012.01630.x

ANNEX

This document has been supported by the following Board Members of the European Blood Alliance: Wolfgang Mayr, Markus Jarnig (Austria); Christine Maes (Belgium); Jørgen Georgsen, Morten Bagge Hansen (Denmark); Riin Kullaste, Helve König (Estonia); Tom Krusius, Martti Syrjälä (Finland); Yves Charpak, Pierre Tiberghien (France); Erhard Seifried, Peter Heimer (Germany); Andy Kelly, Ian Franklin (Ireland); Giuliano Grazzini, Claudio Velati (Italy); Paul Courrier (Luxembourg); Alexander Aquilina, Stefan Laspina (Malta); Jeroen de Wit, Eric Jansen (the Netherlands); Mario Muon, Gracinda Souza (Portugal); Andrei Rosin (Romania); Irena Razborsek, Irena Bricl (Slovenia); Rosario Arrieta, Miguel Vesga, Eduardo Muñiz-Diaz (Spain); Beatrice Diedrich, Gunilla Martinez-Riqué (Sweden); Rudolf Schwabe, Behrouz Mansouri Taleghani (Switzerland); Geoff Poole, Lynda Hamlyn, Lorna Williamson (United Kingdom). It has also been supported by Cees van der Poel (European Committee (Partial Agreement) on Blood Transfusion (CD-P-TS) of the Council of Europe), Heidrun Maier de Kruijff (CEEP, Austria) and the International Plasma Fractionation Association (IPFA).



BY MANAGEMENT

Blood and Blood components of Human origin

Blood, tissues and cells from human origin: the European Blood Alliance Perspective

SAFETY BY MANAGEMENT

Blood and Blood components of Human origin

Wim de Kort

05. BLOOD DONOR PROFILES IN EUROPE

WHAT'S UP IN THE NEXT YEARS?

5.1 INTRODUCTION

In Europe, donor management faces several challenges, some of them with considerable political weight. At least three factors, different in nature, are responsible.

a. Demographic changes
b. Remuneration and commercial activities
c. Competition in the blood product supply chain

This chapter discusses these factors, including some data on remuneration of donors. It builds on the efforts made in the Donor MAnagement IN Europe, or DOMAINE project. This project was co-funded by the European Community. Altogether 18 countries, the patient driven Thalassaemia International Federation and the South-Eastern Europe Health Network worked together to produce a survey report on donor management in Europe. While writing this chapter, a manual on Good Donor Management has been published (www.domaine-europe.eu). Parts of the survey report and of the manual have been incorporated here.

5.2 DEMOGRAPHIC CHANGES

Migration throughout Europe and ageing effects in its population have had enormous consequences on blood product supply and demand *(see Table 1)*. One statistic that reflects the proportion of migration is the percentage of foreigners in European countries, which in the 27 EU-member states on average is 6.2% and varies from 0.1% in Romania, to 42.6% in Luxembourg [1]. Migrant populations show different disease patterns, each with different medical demands, while the available data suggests that migrants tend not to become blood donors in their new country. For example, in the Netherlands, the percentage of blood donors who are so-called 'originally non-Dutch citizens' is less than a tenth of the percentage of the general population who are 'originally non-Dutch citizens' (Atsma et al., unpublished data).

An important type of migrant diseases that have an impact on the demand for blood products are haemoglobin disorders, such as thalassaemia and sickle cell disease. Globally, it is estimated that more than 500,000 children with haemoglobin disorders are born every year [2]. Of these children, 40% are born with thalassaemia and 60% with sickle cell anaemia. It is estimated that about 20,000 living transfusion-dependent patients reside in Europe, and an additional 1,500-2,000 babies with these disorders are born each year [3]. As a result, the blood supply needs to increase each year, to cover the needs of these patients.

The ageing of the European population, reflected in an increasing Old-Age-Dependent-Ratio (OADR, *see Table 1*), has a double negative effect on the blood supply. First, the demand for blood products is likely to increase with age. Second, an increasing OADR entails a relative decrease on the part of the population that is eligible to donate, implying an imminent decrease in available donors. Unchanged age-adjusted blood demand, therefore, requires a vigorous change in donor recruitment and retention, because the percentage of donors in the eligible population has to rise steeply to keep fulfilling the blood demand.

5.3 COMMERCIAL ACTIVITIES

5.3.1 REMUNERATION OR COMPENSATION

DOMAINE SURVEY FINDINGS

The DOMAINE project performed a survey on current blood donor management practices throughout Europe in 2007. Using a questionnaire, European blood establishments were asked to provide information on their donor management practices. Relevant for this chapter are the results on remuneration and compensation.

In six of the 35 countries involved in the DOMAINE survey, donors might be given an expense allowance in cash, based on the incurred expenditure and the particular type of donation. Not all six countries are EU member states. Expense allowance mainly relates to plasma or platelet apheresis donations, and in only one country all donors are offered an amount of money. The sum, given to donors, ranges from €12 to €25 per donation.

The principle of voluntary and unpaid donations does not exclude compensation for donors, if it is limited to reimbursing the expenses and inconveniences related to the donation. These expense allowances can be given in different ways. In some blood establishments such compensation is limited to travelling costs reimbursement, or a food voucher. The DOMAINE survey showed that donors are allowed free time off work in fourteen countries. In most of these countries, this time is capped to the time needed for the entire donation process or to a limited amount of time (e.g. two or four hours). However, some blood establishments continue to allow donors to get a full day off work and this obviously is closer to real remuneration. Most countries have discontinued such a practice.

Figure 1 shows the percentages of European blood establishments that did or did not remunerate their donors for their donation. *Figure 2* illustrates the kind of compensation (other than remuneration) that donors received for time or expenses.

5.3.2 COMMERCIAL BLOOD ESTABLISHMENTS

Commercial establishments now operate in 20% of the European countries, mainly in collecting and processing plasma. In the plasma derived pharmaceutical business, paid donors do occur throughout the world, including the Americas and Europe. Although in most cases, the commercial establishments only collect plasma for fractionation, in some countries they also collect whole blood. This introduces competition for both donor recruitment and blood product selling. Together with the phenomenon of paid donors, this may impact on donor retention, donor safety and patient safety.

Notably, among all the actors in the blood transfusion chain, recipients, volunteers and donors are the ones who do not make money. Recipients of blood products (patients, or 'clients') can, in fact, be expected to pay for blood products, either themselves or through their insurance, or in whatever way, depending on a country's health care financing system. Their gain for this payment is extra life expectancy and quality of life. Since, by definition, volunteers decline payment, this situation leaves the blood donor as the only person breaking the common rules of economics in the entire transfusion chain. This works out well, as long as no shortages arise [4]. All the others in the blood transfusion chain, such as blood establishment staff, suppliers to blood establishments and health care workers, do make money, not uncommonly, even for a living.

There is probably nothing wrong with that, as long as market principles are considered a socially acceptable elaboration in accordance with distributive justice [5]. Subsequently, these 'paid actors' in the transfusion chain must guarantee individual rights and well being.

5.4 COMPETITION AND DONOR MANAGEMENT

5.4.1 GENERAL ASPECTS

In general, the supply of blood products for direct use in patients through blood establishments is not a market oriented activity. Most European countries have blood establishments that are organised on a regional or on a national level. In those countries, regionally or national self-supporting systems exist, and competition between blood establishments does not yet occur, or only so on an occasional basis.

However, the debate on introducing competition in the field of blood supply for direct use in patients is growing throughout Europe. For example, compare the point of view of the European Blood Alliance, EBA, see the reference for that [6]. Pricing of blood components and access to donors are the major arguments for starting this debate. For example, prices for blood components differ to a great extent between European countries. Insurers and hospital managers ask questions on how these differences are to be explained or could be diminished. In addition, pharmaceutical industries want to have equal access to (plasma) donors, which is not yet allowed in many countries.

Given the mere fact that there is a demand for products or services, competition is likely to occur. This is true for commercial enterprises and non-profit-making enterprises. Until now it has been felt that commercialisation of body parts, such as organs, tissues and blood needs to be approached with great caution, given the strong moral implications. Therefore, non-remuneration of donors - the suppliers of these products - still is the written basic principle throughout Europe. However, in the plasma derived pharmaceutical business, paid donors do occur throughout the world, including the Americas and Europe. Competition for donors is rife between blood establishments, in relation to collecting blood (components) for direct use in patients, on the one hand, and organisations collecting plasma as a raw material for the pharmaceutical industries on the other.

Of course, it is not necessarily the case that a new player will aim to provide the whole range of services or products. An organisation could decide to collect and produce profitable components, leaving out products that are too expensive to produce, e.g. HLA-typed platelet concentrates or red blood cell concentrates from donors having rare blood groups. This might constitute an unacceptable form of 'cherry picking'. [7].

Competition in a not-for-profit environment is not uncommon. An important example is the competition that exists between charity organisations. The charity-market is huge, but there are limits to the amount of money people are willing to donate for charity purposes. Depending on many factors, people decide to donate money to one or some aid organisations. Consequently, aid organisations try to attract as many benefactors as possible. True competition exists there.

Competing for blood donors is not a common feature yet. Although similarities between the profile of blood donors and of charity fund contributors exist, differences are known as well [8]. In addition, large, self explanatory differences exist regarding the act of donating either parts of your own bodily or 'just' money. Giving money does not entail intrusion of one's body; it can be done at home, and there are no fears to be overcome.

5.4.2 CONSEQUENCES

Where competition on blood donors occurs, donor management is likely to change. Some aspects for donor management need special attention. Two of these aspects are the following:

I. REQUESTED/POTENTIAL DONOR BASE

To a certain extent, hospital and industry demand together determine the donor base needed to fulfil the total demand for blood products. However, only the product range and market share of the blood establishment determine the qualitative and quantitative requirements of the donor base needed. For example, if a blood establishment decides to produce only apheresis plasma and only non-sub typed ABO-red cell and platelet concentrates for the lowest possible price, then the donor base will be essentially different from the donor base needed to produce the full range of blood products and blood components. In addition, one may expect that pricing of blood products between the two blood establishments is likely to be different. Blood establishments producing only certain commodities probably will be able to set lower prices compared to blood establishments that produce the full range of blood products.

II. QUALITY/SAFETY BALANCE

Minimum quality and safety standards are laid down in European Directives and must be met by each blood establishment. However, a rise in quality assurance inevitably has its price. The precautionary principle, by definition, confronts blood establishments with possibly large costs. Therefore, in straightened economic circumstances, the precautionary principle [9] will, likely, be the first to be attacked with a subsequent potential rise in patient risk.

A special feature arises regarding donor safety, when donors decide to go shopping among blood establishments. The only sure way to prevent any adverse reactions, e.g. due to frequent donations in different blood establishments, will be data exchange on donors between different blood establishments, when operating in border regions.

5.5 CONCLUDING REMARKS

The introduction of competition in donor management will bring about great changes, enhanced by commercialisation of the transfusion chain. These changes will be felt by hospitals/doctors, and donors. Both groups will experience advantages, as well as disadvantages. Hospitals (doctors) are likely to get commodity blood products at lower prices; however, the cost will be much higher prices for specialties. Donors might experience an increased level of service. However, a change in attitude or motivation cannot be excluded. Blood establishments must anticipate more or less fluctuations in both their client base (shopping hospitals) and donor base (shopping donors). Expected changes in demographic relations further stress the need for rationalising donor management.

REFERENCES AND NOTES

1. http://epp.eurostat.ec.europa.eu/portal/page/portal/population/data/main_tables
2. World Bank 2006, report of a joint WHO-March of Dimes meeting, 2006. www.who.int/entity/genomics/publications/reports/en/
3. Management of haemoglobin disorders, report of joint WHO-TIF meeting, November 2007. www.who.int/entity/genomics/publications/reports/en/
4 Del Pozo PR. Paying donors and the ethics of blood supply. J Med Ethics 1994; 20:31-35. http://dx.doi.org/10.1136/jme.20.1.31
5 Distributive Justice. Principles of distributive justice are normative principles designed to guide the allocation of the benefits and burdens of economic activity.
The first relatively simple principle of distributive justice examined *[for further explanation, see the website page,]* is strict egalitarianism, which advocates the allocation of equal material goods to all members of society. John Rawls' alternative distributive principle, which he calls the Difference Principle, is then examined. The Difference Principle allows allocation that does not conform to strict equality so long as the inequality has the effect that the least advantaged in society are materially better off than they would be under strict equality. However, some have thought that Rawls' Difference Principle is not sensitive to the responsibility people have for their economic choices. Resource-based distributive principles, and principles based on what people deserve because of their work, endeavour to incorporate this idea of economic responsibility. Stanford Encyclopedia of Philosophy. http://plato.stanford.edu/entries/justice-distributive/ (cited 2010-02-12)
6 http://www.europeanbloodalliance.eu.
7 Macpherson CR, Domen RE, Perlin T. Ethical Issues in Transfusion Medicine. Bethesda, Maryland, AABB Press, 2001. http://www.lavoisier.fr/livre/notice.asp?id=2SOWAAALRXKOWN
8 Bekkers, R. & Veldhuizen, I. (2008). 'Geographical Differences in Blood Donation and Philanthropy in the Netherlands: What Role for Social Capital?' Journal of Economic & Social Geography, 99 (4): 483-496. http://dx.doi.org/10.1111/j.1467-9663.2008.00483.x
9 The definition of the precautionary principle most widely used relates to environmental issues and stems from the Rio Declaration of the UN, 1992: 'In order to protect the environment, the precautionary approach shall be widely applied by States according to their capabilities. Where there are threats of serious or irreversible damage, lack of full scientific certainty shall not be used as a reason for postponing cost-effective measures to prevent environmental degradation.' There is no law or European Directive on the precautionary principle. However, the EU Commission stated that the principle might be invoked where 'preliminary objective scientific evaluation, indicates that there are reasonable grounds for concern that the potentially dangerous effects on the environment, human, animal or plant health may be inconsistent with the high level of protection chosen for the Community'. EU, C.O.T.E.C. (2000) Communication from the Commission on the Precautionary Principle. European Commission, Brussels, 02.02.2000 COM (2000) 1. http://europa.eu/rapid/pressReleasesAction.do?reference=IP/00/96&format=HTML&aged=0&language=EN&guiLanguage=en

Table 1: Demographic data

	Inhabitants	% Foreigners [a]	Old Age Dependency ratio [b]		
	2008	2008	2008	2020	2030
European Union (27 countries)	497.649.125	6,2%	25%	31%	38%
Belgium	10,666,866	9,1%	26%	31%	38%
Bulgaria	7,640,238	0,3%	25%	31%	36%
Czech Republic	10,381,130	3,3%	21%	31%	36%
Denmark	5,475,791	5,5%	24%	32%	38%
Germany	82,217,837	8,8%	30%	35%	46%
Estonia	1,340,935	17,1%	25%	29%	34%
Ireland	4,401,335	12,6%	16%	20%	25%
Greece	11,213,785	8,1%	28%	33%	38%
Spain	45,283,259	11,6%	24%	27%	34%
France	63,982,881	5,7%	25%	33%	39%
Italy	59,619,290	5,8%	30%	35%	42%
Cyprus	789,269	15,9%	18%	22%	27%
Latvia	2,270,894	18,3%	25%	28%	35%
Lithuania	3,366,357	1,3%	23%	25%	35%
Luxembourg	483,799	42,6%	21%	24%	31%
Hungary	10,045,401	1,8%	24%	30%	34%
Malta	410,290	3,8%	20%	31%	39%
Netherlands	16,405,399	4,2%	22%	31%	40%
Austria	8,318,592	10,0%	25%	29%	38%
Poland	38,115,641	0,2%	19%	27%	36%
Portugal	10,617,575	4,2%	23%	31%	37%
Romania	21,528,627	0,1%	21%	26%	30%
Slovenia	2,010,269	3,4%	23%	31%	41%
Slovakia	5,400,998	0,8%	17%	24%	32%
Finland	5,300,484	2,5%	25%	37%	43%
Sweden	9,182,927	5,7%	27%	34%	37%
United Kingdom	61,179,256	6,6%	24%	29%	33%
Norway	4,737,171	5,6%	22%	28%	34%
Switzerland	7,593,494	21,1%	24%	30%	38%

[a] Percentage of foreigners, including citizens of other EU Member States and non-EU citizens, usually resident in the reporting country. 'Citizenship' denotes the particular legal bond between individuals and their State, acquired by birth or naturalisation, whether by declaration, choice, marriage or other means according to national legislation. 'Citizenship' is, therefore, not synonymous with 'ethnicity'.

[b] This indicator is the ratio between the total number of elderly persons of an age when they are generally economically inactive (aged 65 and over) and the number of persons of working age (from 15 to 64).

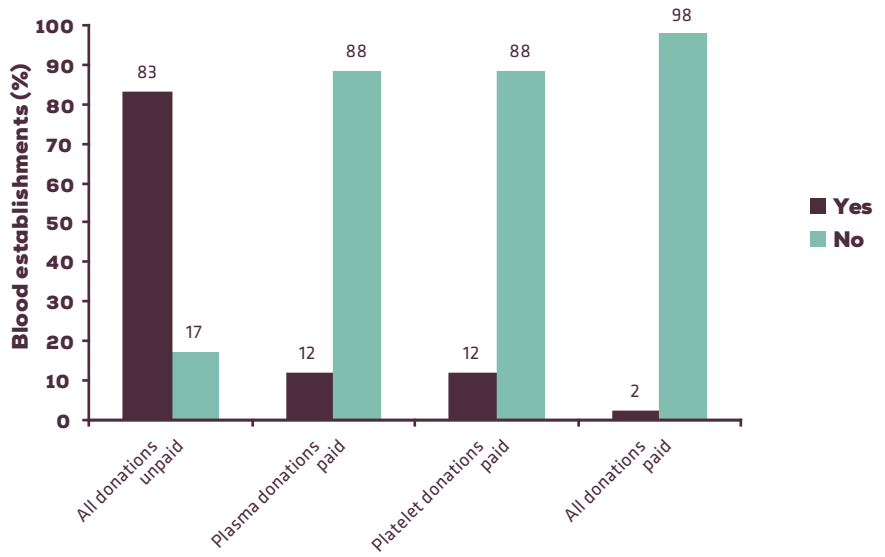


Figure 1: Remuneration of donations to the donor.

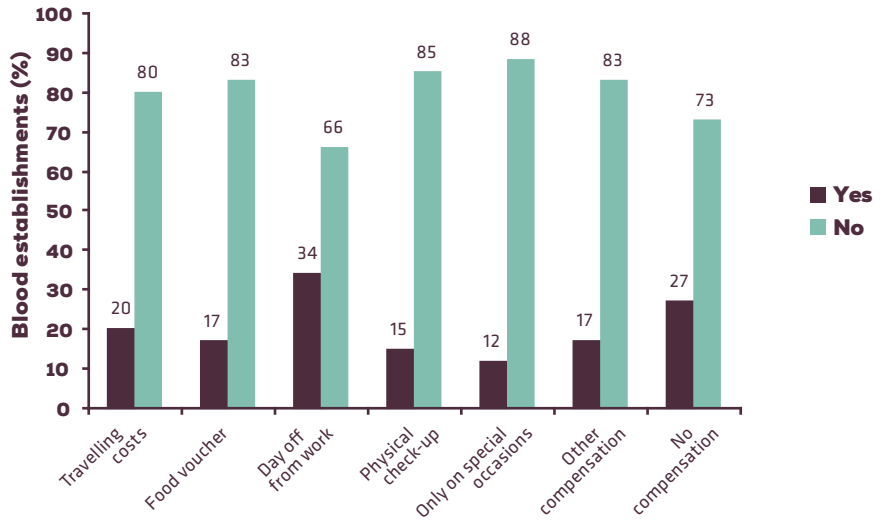


Figure 2: Compensations for time or expenses to the donor.

Wim de Kort
Elze Wagenmans
Karen van der Toren

06. MINORITIES AND ETHICS IN THE EURO-PEAN BLOOD TRANSFUSION

6.1 INTRODUCTION

The Donor MAnagement IN Europe, or DOMAINE project, has been in operation over the past three years. DOMAINE was co-funded by the European Community. Altogether 18 countries, the patient driven Thalassaemia International Federation and the South-Eastern Europe Health Network worked together in listing and analysing current practice in donor management throughout Europe.

The three preset goals of DOMAINE were as follows:

- To analyse current practices for donor management at both participating blood establishments and blood establishments in other European countries.
- To put together a Donor Management Manual based on these survey results, including topics such as donor recruitment, donor invitation and retention strategies, donor deferral procedures, donor management in relation to patients requiring multiple transfusions, and supporting issues such as managerial aspects, human resources management, training, ICT and ethical issues [1].
- To develop a Training Programme based on the Donor Management Manual, to provide practical tools on how each blood establishment can best use the manual to achieve optimal practice in its local context.

The analysis of current practice was based on a questionnaire survey among 37 European countries. The survey report, which was completed in 2009, formed the basis for the manual. The manual was written in a joint project team effort and presented at the 2010 XXIst ISBT congress in Berlin, Germany. The ensuing training programme was developed in cooperation with an advice agency specialising in training and education. The first course of the training programme has been delivered at the occasion of the XXIst ISBT Regional Congress in Lisbon, Portugal.

Still, some important challenges are unresolved. In particular, the non-involvement of minorities in the blood supply is troublesome. Parallel to this issue, ethical issues have been raised many times. This chapter tries to address these two aspects.

6.2 MINORITY INVOLVEMENT AND CULTURAL DIFFERENCES

6.2.1 DEMOGRAPHICS

Both migrations throughout Europe and ageing effects in its population have enormous consequences on blood product supply and demand [2]. One statistic that reflects the proportion of migration is the percentage of foreigners in European countries, which in the 27 EU-member states on average is 6.2% and varies from 0.1% in Romania to 42.6% in Luxembourg [3]. Migrant populations show different disease patterns with different transfusion demands, while available data suggests that, at the same time, migrants tend not to donate blood in their new country.

For example, in the Netherlands, the percentage of the blood donors who are so-called 'originally non-Dutch citizens' is less than a tenth of the percentage of the general population who are 'originally non-Dutch citizens' (unpublished data). In the USA some data on minority participation in the donor base is available [4]. An important aspect of migration is its impact on the demand for blood products for specific diseases such as are haemoglobin disorders *(see also Chapter 5 Blood donor profiles)*.

6.2.2 FACTORS EXPLAINING LOW MINORITY PARTICIPATION

Several factors could explain the low minority participation in the donor base. Factors most often mentioned in the literature are religion, distrust, culture, lack of social/ethnic identification, fear and lack of information.

Religion is often mentioned as a potential barrier for blood donation. However, in general this is not the case [5], although in some cultures more ancient sentiments could play a role [5,6]. Regarding organ donation, literature shows that distrust of the medical system and worries about discriminative treatment also plays a role in deciding whether or not to donate [7]. Also important is the sentiment that many minorities would prefer their blood donation to be used for their own (ethnic) group [8-10]. Here, 'Own-Group-Identification' and 'In-Group-Altruism' do seem to be important notions [11]. Other cultural differences are likely to play a role as well [12]. The effect of fear and (lack of) information are similar to their effect on donor participation in general, but may have a different effect in minorities [13].

Thus, minority groups tend not to participate in the blood supply in their new country. However, they do require blood products, often even with special characteristics that are not present in the indigenous blood donor population. In these situations, supply and demand are out of balance, which might lead to inequalities in health care quality. This is where ethical considerations come into play. What are the underlying principles of blood donation? Can blood products be considered as a commodity? Who can donate blood and should blood donation be voluntary?

6.3 ETHICAL AND ETHICO-LEGAL ISSUES IN BLOOD DONATION

This part is an adapted version of Chapter 13 of the DOMAINE Donor Management Manual [1].

For good reasons, participating in the blood product chain, from donation to transfusion, entails a series of ethical [14] issues. Blood is of human origin and this precious resource has a limited shelf life. Donor management carries a two-sided moral responsibility towards both donors and blood product recipients. This often entails negotiating between different interests and ethical decision making.
Policy and donor management decisions are founded on four ethical principles.

- Respect for individuals and their autonomy
- Protecting individuals' rights and well being
- Avoiding exploitation, part of the more general principle of distributive justice [15]
- The Hippocratic principle of *primum non nocere* or 'first, do no harm'

In donor management, some special ethical issues arise and can be divided into two groups.
Commercial considerations: There is a lengthy and heated debate on the permissibility of trading one's own blood. Given that blood products derive from non-remunerated donations, how can one avoid exploitation and ensure distributive justice if such products then enter a commercial chain?

Mistreatment of donors and prospective donors: Blood is a sensitive matter, and perceived or true mistreatment of donors can have a strong impact on public and political discussions.
This paper touches upon some of the ethical issues. For additional information and discussion, further references are mentioned hereafter; *(see also chapter 4)*.

6.3.1 REMUNERATION OR NOT?

All over the world, donating blood, tissues or even organs represents for many, their giving the priceless, special 'gift of life'. Preferably, this is done out of true altruism and is simply meant to help others in need of blood products, without which they soon would die or lose quality of life.

Dangers of exploitation: Selling one's bodily parts, such as blood, traditionally is 'not done'. Even though hardly any risk is involved in the act of blood donation, exploitation may easily emerge when bodily parts become subject to the market system. Importantly, the blood products donated become 'joint property', meaning that everybody is entitled to receive them, if appropriate, for improving health. From that point of view, this unique human act precludes any trade or commercialisation [16-19].

6.3.2 BLOOD AS COMMODITY?

In contrast, some people argue that blood is a commodity or good like many other health care products, albeit that it has special and partially unique properties. Every individual produces blood in the same way: only 'production conditions' vary and so do some of the product specifications, such as blood type. Commercialisation from that point of view is a logical result.

6.3.3 SELLING BLOOD?

Some argue that 'People sell their talent, experience, skills, services, creations, et cetera, and their value is determined by the laws of the market. So, why should persons not be able to sell their blood? There is hardly any risk involved in donating blood, is there?'
Notably, among all the actors in the blood transfusion chain, recipients, volunteers and donors are the only ones who do not make money.

1. RECIPIENTS

Recipients of blood products (patients, or 'clients') can, in fact, be expected to pay for blood products, either themselves or through their insurance, or in whatever way, depending on a country's health care financing system. The patient's gain for this payment is extra life expectancy and quality of life.

2. VOLUNTEERS

By definition, volunteers deny payment. We all accept their choice, and take appropriate advantage of it.

3. DONORS

This leaves the blood donor as the only person breaking the common rules of economics in the entire transfusion chain. This works out well, as long as no shortages arise [20].
All the others in the blood transfusion chain do make money, not uncommonly, even for a living. They include the following groups of persons.

- Management and employees of a blood establishment
- Suppliers of equipment, disposables, housing and all other materials necessary to run a blood establishment
- Health care workers, such as prescribing doctors, those involved in administering blood products and supporting activities such as laboratory testing and distribution

There is probably nothing wrong with that, as long as market principles are considered a socially acceptable elaboration in accordance with distributive justice. Subsequently, these 'paid actors' in the transfusion chain must guarantee individual rights and well being. Paid staff must show respect for a different set of opinions. They should, for example, not refuse transfusing blood products to people merely on the grounds that they are not (or have not been) blood donors themselves.

6.3.4 BLOOD AS TRADABLE GOOD?

All of this may imply that blood is some kind of tradable commodity or good. However, from a legal point of view, the question arises as to whether blood or blood products can actually be considered a good.

In the European Union goods have been defined as: 'products which can be valued in money and which are capable, as such, of forming the subject of commercial transactions' [21]. In their reasoning, the European Commission did not exclude the possibility that blood may be considered a 'good' for the following reasons.

- Although, international treaties prohibit financial gain of blood, these treaties are not binding.
- In the European Community, blood is subject to normal customs tariff.

The question as to whether or not blood is a 'good' has not yet been decided and could become a matter before the European Court of Justice. The door to commercialisation has not been closed.

6.3.5 RECIPIENT SAFETY

Another important reason remains for not wanting blood to be commercialised: the safety of the recipient. It is a proven fact that donors paid in cash show a much higher risk of having a transfusion transmittable infectious disease [22]. But also other types of payment, including vouchers or free tickets and time off work, could imply an increased risk [23]. A plausible reason behind that increased risk is that the prospective donor involved might be inclined to "forget" recent risky behaviour or health impairment that could interfere with their being eligible for blood donations.

6.4 VOLUNTARY DONATION

6.4.1 POSSIBLE COERCION?

As is laid down, for example, in the ISBT Code of Ethics, 'blood donation including haematopoietic tissues for transplantation shall, in all circumstances, be voluntary and non-remunerated; no coercion should be brought to bear upon the donor' [24]. Although many people and organisations, including the WHO, agree with the above principles, in many places some kind of coercion is present, as is the case when so-called replacement donations occur.

6.4.2 DONOR MOTIVATION

When donors are asked why they donate, five primary motives emerge.

- Altruism: out of unselfish concern for others, or, for the benefit of someone else, not impossibly at one's own expense
- Solidarity: for the unity resulting from common interests, feelings, or sympathies
- Social Capital: some people donate blood, others donate money or goods and so, everybody takes their share of duties
- Reciprocity: exchanging blood donations with others for mutual benefit. "I donate blood now, because I want to get it when I need it"
- Incentives ('quid pro quo'): better self-esteem, items of small or limited value, payment, compensation, health check, or anything else that represents value to the donor

6.4.3 RIGHT TO DONATE

From the outset, the question regularly arises: are all people eligible to donate blood? This is definitely not the case. Of course, all free persons have the right to present themselves for blood donation. But this does not mean that they have the right to donate blood. What is the justification for refusing some people, or even groups of people from donation?

Safety: The safety of both donor and recipient is the main reason for deferring prospective donors, thus ensuring the second principle: protection of the individual. A person is only entitled to donate blood, when he or she fulfils the eligibility criteria. Eligibility criteria must not be in conflict with other, fundamental rights. Eligibility criteria must not entail discrimination – i.e. unjustified distinction, meaning that eligibility criteria must be built on solid ground. The burden of proof for criteria to be acceptable rests with the person or organisation formulating them.

6.5 PRECAUTIONARY PRINCIPLE

On several occasions the precautionary principle [25] is applied. In health care and transfusion contexts this principle is applied by letting the safety of the recipient prevail. This becomes tricky when sensitive issues arise, such as the exclusion of men having had sex with other men (MSM) [26]. Clearly, discrimination must be avoided.

6.5.1 CRITERIA FOR EXCLUSION

Justified distinctions may still be made for deferring certain groups of prospective donors, when clear health risks for the recipient exist [27]. The primary reason for excluding candidate male donors on the ground of MSM is not that being homosexual made them non-eligible, but that their sexual behaviour carries a greater risk of transmitting HIV-infected blood. The deferral criteria are not a judgement on behaviour or (sexual) preference or (ethnic) descent, but a judgement on the (general, anticipated) risk related to behaviour. Having travelled in the jungle does not make someone a bad person, but does entail that person carrying a greater risk of transmitting malaria.

6.5.2 AGE CONCERNS

Inclusion of certain groups may also cause concern and debate, as the example of minors show. Most countries do not allow persons under 18 to donate. But the threat of blood shortages forces many countries to lower, or consider lowering the age standard down to 17 or 16. Here, not the safety of the recipient, but the safety of the donor is at issue. Younger donors show a higher risk of adverse reactions to donating blood [28,29].

6.5.3 OTHER POTENTIAL LIMITATIONS

There seems to be a general consensus that being handicapped or disabled should not prevent people from donating blood. On the contrary, it is generally felt that all should be done to increase accessibility of collection centres, so as to facilitate donating blood by people who may experience some kind of limitation. Many limitations can be neutralised by personal help, environmental accommodations, or special equipment.

6.6 DOMAINE SURVEY FINDINGS[1]

6.6.1 REMUNERATION OF DONORS

The principle of voluntary and unpaid donations does not exclude compensation for donors, if it is limited to reimbursing the expenses and inconveniences related to the donation. These expense allowances can be given in different ways. In some blood establishments such compensation is limited to travelling costs reimbursement, or a food voucher. *(see also Chapter 5 Blood donor profiles)*.

6.6.2 FREE TIME OFF WORK

The DOMAINE survey shows that donors are allowed free time off work in 14 countries. In most of these countries, this time is capped to the time needed for the entire donation process or to a limited amount of time (e.g. two or four hours). However, some blood establishments continue to allow donors to get a full day off work and this obviously is closer to real remuneration. Most countries have discontinued such practices. It is important to underline that this discontinuation never resulted in a shortage of donors.

6.6.3 OTHER INCENTIVES

Other establishments may offer a free physical check-up, or a free vaccination for influenza in winter. To some extent, these two means may be considered as useful for the blood establishment to maintain a safe donor population.

6.7 CULTURAL DIFFERENCES AND ETHICS: A GREAT CHALLENGE AHEAD

Voluntary, non-remunerated blood donation forms the ethical cornerstone for donor management worldwide and is reflected in written literature and ethical deliberations. However, discussions are ongoing and the DOMAINE survey indicated that the margin between compensation and remuneration in practice is not always clear.

In addition, past, present and future migration throughout Europe has enormous effects on blood product supply and demand, due to its influences on both potential European blood donors and patient populations.

Ideally, the donor population should reflect the general population. However, a common language on how to define and describe relevant (donor) population characteristics is lacking. It appears that migrants tend not to donate blood in their new country. As a consequence – on top of the effect of the general European demographic developments regarding age distribution – potential blood resources are not available for use, which further threatens the blood supply.

Migration developments bring along imminent inequalities in health care quality between different population groups in EU member states. Migrant populations show different disease patterns and different infectious disease load. They also have specific needs for blood products. Therefore, population shifts entail certain consequences for the necessary availability of adequate blood products and the subsequent quality of health care offered. Especially in cases where specific tissue and blood group matching between patient and donor are life saving (as in stem cell therapies), shortages already occur, especially in minority populations. Communicative difficulties and complex logistics enhance these shortages in an indirect, but substantial way.

The need for focussing on participation of (ethnic) minorities in the blood supply chain emerges. Proper attention towards cultural differences is crucial. Even an unchanged blood demand requires a vigorous change in donor recruitment and retention; otherwise the percentage of donors in the eligible non-minority population has to rise steeply to keep fulfilling the blood demand. Here specific ethical issues may arise. For example, the reciprocity issue: 'you may get blood products transfused, if you are or have been willing to donate yourself' immediately leads to strong debates. In analogous ways, nearly all ethical issues may have an impact on the cultural differences and vice versa. The challenge ahead of us is, using a transcultural language, to discuss this imminent problem of shortages related to differential participation within the population, while keeping in mind the more universal adopted ethical principles.

REFERENCES

1. Donor Management Manual 2010. DOMAINE project. De Kort W, Veldhuizen I (Eds.). DOMAINE, Nijmegen, the Netherlands, 2010. ISBN 978-90-815585-1-8, www.domaine-europe.eu.
2. De Kort W, Donor management in Europe, DOMAINE – the European perspective. ISBT Science Series 2010; 5: 201-205. http://dx.doi.org/10.1111/j.1751-2824.2010.01373.x
3. http://epp.eurostat.ec.europa.eu/portal/page/portal/population/data/main_tables
4. Murphy EL, Shaz B, Hillyer CD, Carey P, Custer BS, Hirschler N, Fang J, Schreiber GB. Minority and foreign-born representation among US blood Donors: demographics and donation frequency for 2006. Transfusion 2009; 49: 2221-2228. http://dx.doi.org/10.1111/j.1537-2995.2009.02271.x
5. Grassineau D, Papa K, Ducourneau A, Duboz P, Boetsch G, Chiaroni J. Improving minority blood donation: anthropologic approach in a migrant community. Transfusion 2007;47;402-409. http://dx.doi.org/10.1111/j.1537-2995.2007.01130.x
6. Tison GH, Liu C, Ren F, Nelson K, Shan H. Influences of general and traditional Chinese beliefs on the decision to donate blood among employer-organized and volunteer donors in Beijing, China. Transfusion, 2007; 47: 1871-1879. http://dx.doi.org/10.1111/j.1537-2995.2007.01410.x
7. Siminoff LA, Burant CJ, Ibrahim SA. Racial disparities in preferences and perceptions regarding organ donation. J Gen Intern Med, 2006; 21: 995-1000. http://dx.doi.org/10.1111/j.1525-1497.2006.00516.x
8. Mathew SM, King MR, Glynn SA, Dietz SK, Caswell SL, Schreiber GB. Opinions about donating blood among those who never gave and those who stopped: a focus group assessment. Transfusion, 2007;47:729-735. http://dx.doi.org/10.1111/j.1537-2995.2007.01177.x
9. Shaz BH, Zimring JC, Demmons DG, & Hillyer CD. Blood donation and blood transfusion: special considerations for African Americans. Transfus.Med.Rev, 2008; 22: 202-214. http://dx.doi.org/10.1016/j.tmrv.2008.02.006
10. Shaz BH, Demmons DG, Hillyer KL, Jones RE, Hillyer CD. Racial differences in motivators and barriers to blood donation among blood donors. Arch Pathol Lab Med 2009; 133:1444-1447. http://www.archivesofpathology.org/doi/full/10.1043/1543-2165-133.9.1444
11. Tajfel H, Turner JC. The Social Identity Theory of Intergroup Behavior. In S.Worchel & L. W. Austin (Eds.). Psychology of Intergroup Relations 1986; 7-24. Chicago: Nelson-Hall. http://ssi.sagepub.com/content/13/2/65.full.pdf
12. De Kort W, Wagenmans E, Van Dongen A, Slotboom Y, HofstedeG, Veldhuizen I. Blood product collection and supply: a matter of money? Vox Sanguinis 2010; 98:e201–e208. http://dx.doi.org/10.1111/j.1423-0410.2009.01297.x
13. Schreiber GB, Schlumpf KS, Glynn SA, Wright DJ, Tu Y, King MR, et al. Convenience, the bane of our existence, and other barriers to donating. Transfusion, 2006; 46; 545-553. http://dx.doi.org/10.1111/j.1537-2995.2006.00757.x
14. Ethics (Oxford English Dictionary): the moral principles governing or influencing conduct. http://oxforddictionaries.com/definition/english/ethics?q=ethics
15. Distributive Justice. Principles of distributive justice are normative principles designed to guide the allocation of the benefits and burdens of economic activity. The first relatively simple principle of distributive justice examined [for further explanation, see the webpage, Eds] is strict egalitarianism, which advocates the allocation of equal material goods to all members of society. John Rawls' alternative distributive principle, which he calls the Difference Principle, is then examined. The Difference Principle allows allocation that does not conform to strict equality so long as the inequality has the effect that the least advantaged in society are materially better off than they would be under strict equality. However, some have thought that Rawls' Difference Principle is not sensitive to the responsibility people have for their economic choices. Resource-based distributive principles, and principles based on what people deserve because of their work, endeavor to incorporate this idea of economic responsibility. Advocates of Welfare-based principles do not believe that the primary distributive concern

should be material goods and services. They argue that material goods and services have no intrinsic value and are valuable only in so far as they increase welfare. Hence, they argue, the distributive principles should be designed and assessed according to how they affect welfare. Advocates of Libertarian principles, on the other hand, generally criticize any patterned distributive ideal, whether it is welfare or material goods that are the subjects of the pattern. They generally argue that such distributive principles conflict with more important moral demands such as those of liberty or respecting self-ownership. Finally, feminist critiques of existing distributive principles note that they tend to ignore the particular circumstances of women, especially the fact that women often have primary responsibility for child-rearing. Some feminists therefore are developing and/or modifying distributive principles to make them sensitive to the circumstances of women and to the fact that, on average, women spend less of their lifetimes in the market economy than men. Stanford Encyclopedia of Phylosophy. http:// plato.stanford.edu/entries/justice-distributive/

16. Titmuss RM (1971). The gift relationship: from human blood to social policy. London: Allen & Unwin. http://books.google.nl/books/about/The_gift_relationship.html?id=IZw4AAAAMAAJ&redir_esc=y
17. Hagen PJ (1982). Blood: gift or merchandise. New York, Alan R. Liss Inc. http://books.google.nl/books?id=D9oirqPhCpwC&pg=PA221&lpg=PA221&dq=Hagen+PJ+(1982).+Blood:+gift+or+merchandise&source=bl&ots=nj7jGnd6ky&sig=2-Tskgce5p43CJzyQmLXKFimZlE&hl=nl&sa=X&ei=ESVcUIa2OIftsgbOo4D4DQ&ved=0CDAQ6AEwAA#v=onepage&q=Hagen%20PJ%20(1982).%20Blood%3A%20gift%20or%20merchandise&f=false
18. Macpherson CR, Domen RE & Perlin T (2001). Ethical Issues in Transfusion Medicine. Bethesda, Maryland, AABB Press. http://content.karger.com/ProdukteDB/produkte.asp?Aktion=showproducts&searchWhat=books&ProduktNr=224299
19. Robinson EA (1999). Altruism: is it alive and well? Proceedings of the international seminar, Royal College of Pathologists, November 13th, 1998. Transfusion Medicine, 9, 351-382. http://dx.doi.org/10.1046/j.1365-3148.1999.00219.x
20. Del Pozo PR (1994). Paying donors and the ethics of blood supply. Journal of Medical Ethics, 20, 31-35. http://dx.doi.org/10.1136/jme.20.1.31
21. Case law European Court of Justice, Commission vs. Italy, 1968. http://eur-lex.europa.eu/smartapi/cgi/sga_doc?smartapi!celexplus!prod!CELEXnumdoc&lg=en&numdoc=61968J0007
22. Eastlund T (1998). Monetary donation incentives and the risk of transfusion-transmitted infection. Transfusion 38, 874-882. http://www.ncbi.nlm.nih.gov/pubmed/9738629
23. Oswalt RM & Napoliello M (1974). Motivations of blood donors and non-donors. Journal of Applied Psychology 59, 122-124. http://doi.apa.org/journals/apl/59/1/122.pdf
24. International Society of Blood Transfusion. A code of ethics for blood donation and transfusion. Retrieved 19 March 2010 from http://www.isbtweb.org/about-isbt/code-of-ethics/
25. The definition of the precautionary principle most widely used relates to environmental issues and stems from the Rio Declaration of the UN, 1992 (http://www.un.org/documents/ga/conf151/aconf15126-1annex1.htm): 'In order to protect the environment, the precautionary approach shall be widely applied by States according to their capabilities. Where there are threats of serious or irreversible damage, lack of full scientific certainty shall not be used as a reason for postponing cost-effective measures to prevent environmental degradation.' There is no law or European Directive on the precautionary principle. However, the EU Commission stated that the principle might be invoked where 'preliminary objective scientific evaluation, indicates that there are reasonable grounds for concern that the potentially dangerous effects on the environment, human, animal or plant health may be inconsistent with the high level of protection chosen for the Community'. Commission of the European Communities (2000) Communication from the Commission on the Precautionary Principle. Brussels: Commission of the European Communities. http://ec.europa.eu/environment/docum/20001_en.htm
26. Franklin IM (2007). Is there a right to donate blood? Patient rights; donor responsibilities. Transfusion Medicine, 17, 161-168. http://dx.doi.org/10.1111/j.1365-3148.2007.00754.x
27. "Commissie Gelijke Behandeling, CGB", (Netherlands Equal Treatment Commission, NETC, 2007). CBG opinion about whether the Red Cross Blood Bank Central Netherlands, based in Utrecht, had discriminated against MrXX within the meaning of the Equal Treatment Act. In: CGB (Equal Treatment Commission), Utrecht, the Netherlands, 1–22. http://www.mensenrechten.nl/publicaties/oordelen/2007-85
28. Eder AH, Hillyer CD, By BA, Notari EP & Benjamin RJ (2008). Adverse reactions to allogeneic whole blood donation by 16- and 17-year-olds. JAMA, 299, 2279-2286. http://dx.doi.org/10.1001/jama.299.19.2279
29. Jones RL (2009). Young donors: opportunity, responsibility, vulnerability—report on YDAR task force. Transfusion 2009, 49 2019-2020. http://dx.doi.org/10.1111/j.1537-2995.2009.02268.x

Jolanta Antoniewicz-Papis
Reinhard Henschler
Erhard Seifried

07. TRENDS IN BLOOD COMPONENT PREPARATION IN EUROPE

7.1 INTRODUCTION

This chapter aims to analyze the current state of blood component production in Europe, to propose future possibilities, and to identify future opportunities for BEs.

In order to improve bacterial safety of blood components, as well as to facilitate semi-automated or fully automated processing of whole blood into components at the donation site, important technological advances have become available for processes, such as pre-donation side-sampling. Moreover, improvements in controlling the conditions for transport of donated blood to the production sites have reached technical maturity, and better validated computerized systems are available to safeguard and control the processing of donated blood during the production chain. All these, and further measures constitute constant adaptation and improvements.

In addition, blood component separation technologies are continuously advancing, and now include, in part, fully automated processes, e.g. for platelet production from whole blood. The separation machineries, which in Europe solely rely on a buffy coat–mediated component production from whole blood donations, are undergoing further technical improvements, including the introduction of safer valve breaks and frangibles. The globalization process has so far led to the opening of new production sites for blood bags throughout Europe, with implications for finding ways to further improve, or at least maintain, the required quality standards.

In the past five years, several European blood centres have introduced pathogen-inactivation for platelet concentrates, in part also for plasma components. The current situation and the foreseeable trends in the use of further development of the technology and its implications for both blood quality as well as cost-effectiveness in our health care systems shall be discussed in this chapter. Further scientific work has paid attention to a better characterization of the red cell storage lesion. The results of this research and the implications for further blood use shall also be summarized in this chapter.

7.2 QUESTIONNAIRE-BASED DESCRIPTION ON THE CURRENT STATUS OF BLOOD COMPONENT PREPARATION IN EUROPE

A ten part questionnaire was sent out to representatives of blood establishments in European Countries: one centre answered centrally for each individual country. Questions included trends and situations in the use of whole blood versus apheresis; pre-donation sample diversion; automated component separation; auto-sterilization and temperature control; use of IT-based systems and automated separation; leuko-depletion and pathogen-inactivation. Centres were allowed to provide estimates or semi-quantitative descriptions of trends if official numbers were not available. Overall, 13 countries responded.

7.2.1 SOURCE OF PRODUCTS GENERATED

Figure 1 shows the proportion of blood components produced by apheresis in different countries. Six out of thirteen countries have started to produce red cell concentrates from apheresis donors, and their proportion currently reaches up to one percent of all produced red cell concentrates *(Figure 1A)*. A trend in increasing the use of apheresis for red cell concentrate (RCC) production was only reported by 1/13 countries.

A very mixed picture is seen in the case of platelet concentrates (PCs), which are currently derived at 20% or less from apheresis in 6/13 countries, between 30 and 60% in 5/13 countries, and predominantly from apheresis in only one country *(Figure 1B)*. Similarly, for fresh frozen plasma (FFP) 3/13 countries use apheresis as a predominant source, whereas the majority (10/13) use almost exclusively whole blood-derived FFP *(Figure 1C)*.

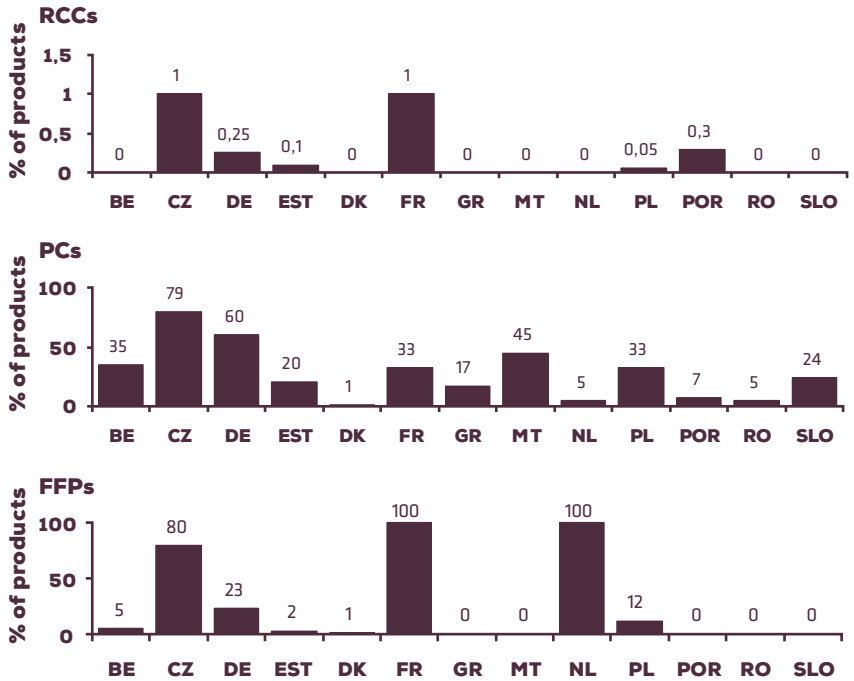


Figure 1: Percentage of the three main blood components produced by apheresis in different European countries. Whole blood is the source for the remaining parts up to 100%. (A) RCCs, (B), PCs, (C), FFPs.

7.2.2 CRITICAL PARAMETERS DURING THE DONATION PROCESS AND THE TIME BEFORE COMPONENT SEPARATION.

Current European legislation has ensured that the generally accepted minimum requirements for haemoglobin content of blood donors have been implemented. However, other procedures, such as donor arm disinfection and the use of inlet-line diversion of the first millilitres of donated blood into a separate sampling pouch that is later used for testing, are implemented to a lesser degree. It has been shown that the use of this latter procedure, in combination with improved donor arm disinfection, can reduce the contamination in blood components by 40-80 % (Mc Donald et al. 2006; Eder et al. 2009). The current trends are summarized in *table 1*.

At the donation process and during the subsequent steps until the blood component reaches the production department, a wide variation in the implementation of improvement measures has been recorded *(Table 1)*. This comprises pre-donation sampling, as well as "auto-sterilization" for which donated blood is generally maintained between 1 and 10 h, mainly 2h *(Table 1)*. "Auto-sterilization" refers to the bactericidal action of the donor leucocytes when blood is stored for a few hours at room temperature. This could only eliminate low numbers of bacteria which could have come from the donation process. In contrast, the more recently developed techniques of on-site component separation during whole blood donation process are still at the beginning stage.

Table 1: Status of the establishment of measures at the early production steps of blood components in different EU countries.

	BE	CZ	DE	DK	EST	FR	GR	MT	NL	PL	POR	RO	SLO
predonation sampling in place	100%	95%	100%	100%	yes	yes	yes	yes	yes	yes	yes	yes	yes
component separation at WB donation	no	no	<1%	no	no	no	no	no	yes*	yes	yes	no	no
leave time for autosterilization	100%	80%	100%	100%	100%	100%	no	yes	100%	50-70%	100%	100%	no
- period	3h	>1h	>3h	1h	2h	10h	NP	2h	2h	< 2h	8h	> 2h	NP
temperature control during transport	yes	no	yes	yes	yes	yes	no	yes	yes	yes	yes	yes	no

NP, not provided ** only plasma, platelets*

TEMPERATURE CONTROL DURING DONATION, TRANSPORT AND STORAGE PRIOR TO SEPARATION.

Temperature control measures during donation and during transport to the blood establishment are also currently a matter of concern. It seems that this matter has received a high level of attention Europe-wide *(Table 1)*.

The scientific basis for the phagocytosis process of auto-sterilization in freshly donated blood has been made clear long ago (reviewed by Dzik, 1994). Red cell concentrates, for example, have been shown to accumulate microvesicles; to undergo ultrastructural changes in membrane composition and signalling components (Kriebardis et al., 2008); and to undergo changes resulting in altered in vitro rheological properties of red cells (Berezina et al., 2002).

Recently, regarding the quality of red cell concentrates, Gulliksson et al. (2009a,b) have reported that red cell concentrates from overnight-stored whole blood contain significantly lower levels of extracellular potassium, 2,3-diphosphorglycerate as well as higher ATP as compared to eight hours stored blood, and have reported differences between bags from different manufacturers.

Cold storage seemed to negatively affect blood quality by increasing haemolysis rates, and it is not used in any centres that prepare platelet concentrates from whole blood. Additionally, FFP quality may be affected; e.g. accumulation of enzymes probably released from neutrophils which are captured in leukocyte depletion filters. An example of such enzyme activity is that elastase is found in increasing quantities after overnight storage as compared to 6h stored whole blood (Heiden et al., 2004). Generally, the quality of plasma from overnight stored components has been shown to be acceptable (Wilsher et al. 2008; Serrano et al, 2010). Possibly, there are more leukocyte fragments in leukoreduced PCs if the whole blood was stored overnight prior to filtration (Diekstra-Tiekstra et al, 2004).

7.2.3 SEPARATION AND COMPONENT PREPARATION

Further technical improvements have been introduced into component separation in recent years. Among these, semi-automated component separators have been further developed and now allow for more efficient and more rapid separation of whole blood into components. Moreover, blood establishment staff can now better follow the separation of each individual product, recognize mistakes, and remove from the production chain units with potential errors/mistakes in the production process. Manufacturers have also recently

provided automatic valve-breaking devices and improved break-valve/frangible designs. It remains to be determined what influence these measures have on the overall quality, specifically of RCCs, haemolysis rates and frequency of units with doubtful haemolysis values. Fully-automated systems for platelet production from several buffy coats have been implemented by some blood establishments. An overview is given in *Table 2*.

Table 2: Proportions of manual, semi-automated and fully automated component separation from whole blood-derived donations in different European countries.

	BE	CZ	DE	DK	EST	FR	GR	MT	NL	PL	POR	RO	SLO
manual	0%	10%	0%	0%	0%	0%	100%	0%	0%	0%	0%	0%	0%
semiautomated (Optipress, Compomat or similar)	100%	90%	100%	98%	90%	100%	0%	100%	100%	100%	40%	100%	100%
fully automated	0%	0%	0%	2%	10%	100%*	0%	0%	0%	partly*	60%	0%	70%*

* platelet concentrates only

7.2.4 LEUKO-DEPLETION

We have recently reviewed the value of leuko-depletion on the evidence-based clinical outcome (Müller et al, 2009). Only a few reports have so far been published which allow evidence based conclusions on whether universal leuko-depletion has a beneficial effect (Williamson et al, 2007), and these have identified a reduction of transfusion-associated graft versus host-disease, and a lower incidence of post-transfusion purpura. Nevertheless, the introduction of leukocyte inline filtration has proceeded for more than 10 years in Europe to a high level. The current production practice in Europe is visualized in *table 3*, and reveals current implementation of general leukocyte depletion in several of the EU states who became new members in 2004.

Table 3: Usage of leukodepletion in different European countries, and current trends.

	BE	CZ	DE	DK	EST	FR	GR	MT	NL	PL	POR	RO	SLO
proportion of leukodepleted products	100%	30%	100%*	100%	10-20%*	100%	50%	100%	100%	15%	100%	0%	90%
- trend	=	↑	=	=	↑	=	=	=	=	↑	=	=	↑

* only cellular products, not plasma = stable ↑ increasing

7.2.5 PATHOGEN INACTIVATION TECHNOLOGIES

Our survey revealed that up to date, 7/13 countries have introduced pathogen-inactivated PCs and/or FFPs into routine use. Data are presented in *figure 2*.

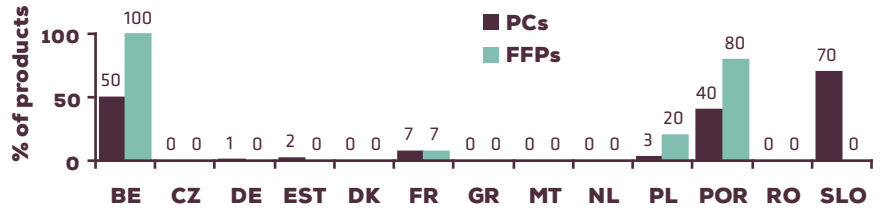


Figure 2: Use of pathogen inactivation technologies in different European countries according to the questionnaire survey.

7.2.6 USE OF SOFTWARE TECHNIQUES

The use of software techniques has been briefly addressed in the current survey. As shown in *table 4*, the standard of PC-based software use is well-developed throughout Europe. Manual documentation systems are an absolute rarity, although current guidelines do not strictly prohibit this procedure. Although technically feasible, we did not encounter blood services using RFID-based identification, either passive or active, in routine production.

Table 4: Usage of computer-based systems for the workup of blood components and their tracing after they have left the blood service. Abbreviations: i, institute-developed; c, commercially available.

	BE	CZ	DE	DK	EST	FR	GR	MT	NL	PL	POR	RO	SLO
PC system for workup	100%	yes	100%*	100%	yes	100%	NA	yes	100%	yes	yes	no	100%
- source	i, c	c	i, c	i, c	i	c		c	c	c, i	i		i
PC system for tracing components which have left the blood service	100%	yes	partly	yes	no	100%	no	yes	100%	yes	yes	no	no
- source	i, c	c	i, c	i, c		c		c	c	c, i	i		↑

7.3 SUMMARY AND CONCLUSIONS, GENERAL TRENDS, DEVELOPMENTS AND OUTLOOK INTO THE FUTURE IN THE FIELD OF BLOOD COMPONENT PRODUCTION IN EUROPE

Until recently, based on manual work, blood component production has been a highly conservative part of transfusion medicine. Activities have included the following: the careful placing of hundreds or thousands of 3– or 4 blood bag systems into centrifuge buckets; inserting connection tubes into valves and welding holders in semi-automated separators; turning bag systems upside down to flush leukocyte depletion filters; filling plasma freezers with FFP bags piece by piece. For many of these steps, further automation will require relatively high amounts of technological development. Likely, the relatively low economic impact of the manual work on total production costs has been a main contributor to the observed slow technological developments in this field. Moreover, there are also major arguments in favour of manual handling of blood component bag systems, in particular, since this enables continuous screening for possible leaks – a procedure that demands full technical supervision.

Major breakthroughs have been made that impact on the quality of produced blood. Some came merely from sound thinking and very basic observations, and required no technological developments. Others required technological developments and have revolutionized blood component production. Examples of such developments are the following: whole blood separation on-site or specially designed devices with procedures for centrifugation of whole blood into red cells; buffy coat and plasma where each component is separately taken out from the centrifuge bucket.

Interestingly, the latter have not had any breakthrough, whereas with the former, over the last decade, simple technical improvements such as pre-donation (on site) sampling or "auto-sterilization" (as well as leukodepletion) have rapidly become general standard in Europe. Semi-automated component separation may be seen as an intermediate between the above mentioned extremes. Increasingly this has received attention and, by now, has been relatively widely introduced.

Our survey also dealt with another crucial technical advance in blood component production: the pathogen inactivation technology. Here, technical development is principally revolutionary since, for the first time, "almost sterilized" blood has become available for clinical use. However, to date, no red cell inactivation method has entered routine clinical use, because the functional deficit in the inactivated components has not, as yet, been fully evaluated and its clinical relevance is yet unclear.

It is further possible that the legal requirements for infectious marker testing imposed in most European countries have precluded a more intensive development of pathogen inactivation technology for routine component production. Lastly, the price for the additional steps exceeds the cost of routine production of a blood component many-fold, which possibly presents some impediments to its more rapid introduction.

The development of IT systems used to control blood component production is still in its infancy, and few definitions and classification methods are in place. Therefore, it is difficult to compare standards, or to analyse trends and make predictions. We expect, however, that in the future blood component quality may benefit from the implementation of methods for establishing, supervising, and maintaining standardized IT systems and their performance.

In conclusion, the recorded improvements in the use of blood component production techniques reflect a visible trend towards high quality and Europe-wide harmonized production standards for blood components. The clinical significance of the new technologies in use for the safety of the transfused patients receiving such blood components is not, however, easy to determine. Therefore, it is expected that, for the foreseeable future, adherence to European Union directives and Council of Europe recommendations will remain the main safeguard for blood processing leading to the provision of safe and good quality blood to patients.

REFERENCES

- Berezina TL, Zaets SB, Morgan C, et al. Influence of storage on red blood cell rheological properties. J Surg Res 2002; 102: 6-12. http://dx.doi.org/10.1006/jsre.2001.6306
- Dijkstra-Tiekstra MJ, van der Schoot CE, Pietersz RN, Huijgens PC, van der Meer PF, Reesink HW. Development of white blood cell fragments, during the preparation and storage of platelet concentrates, as measured by using real-time polymerase chain reaction. Vox Sang. 2004; 87: 250-6. http://dx.doi.org/10.1111/j.1423-0410.2004.00576.x
- Dzik S. Prestorage leukocyte reduction of cellular blood components. Transfus Sci. 1994; 15: 131-9. http://dx.doi.org/10.1016/0955-3886(94)90087-6
- Eder AF, Kennedy JM, Dy BA, Notari EP, Skeate R, Bachowski G, Mair DC, Webb JS, Wagner SJ, Dodd RY, Benjamin RJ; the American Red Cross Regional Blood Centers. Limiting and detecting bacterial contamination of apheresis platelets: inlet-line diversion and increased culture volume improve component safety. Transfusion 2009; 49: 1554-63. http://dx.doi.org/10.1111/j.1537-2995.2009.02192.x
- Gulliksson H, Vesterinen M, Payrat JM, Mayaudon V. Extended storage of whole blood before the preparation of blood components: in vitro effects on red blood cells in Erythro-Sol environment. Vox Sang. 2009; 96: 199-205. http://dx.doi.org/10.1111/j.1423-0410.2008.01152.x
- Gulliksson H, van der Meer PF. Storage of whole blood overnight in different blood bags preceding preparation of blood components: in vitro effects on red blood cells. Blood Transfus. 2009;7:210-5. http://dx.doi.org/10.2450/2009.0074-08
- Heiden M, Salge U, Henschler R, Pfeiffer HU, Volkers P, Hesse J, Sireis W, Seitz R. Plasma quality after whole-blood filtration depends on storage temperature and filter type. Transfus. Med. 2004;14: 297-304. http://dx.doi.org/10.1111/j.0958-7578.2004.00517.x
- Kriebardis AG, Antonelou MH, Stamoulis KE, Economou-Petersen E, Margaritis LH, Papassideri IS. RBC-derived vesicles during storage: ultrastructure, protein composition, oxidation, and signaling components. Transfusion 2008; 48: 1943-53. http://dx.doi.org/10.1111/j.1537-2995.2008.01794.x
- Krailadsiri P, Seghatchian J, Macgregor I, Drummond O, Perrin R, Spring F, Prescott R, Williamson L, Prowse C, Anstee D, Turner M. The effects of leukodepletion on the generation and removal of microvesicles and prion protein in blood components. Transfusion 2006; 46: 407-417. http://dx.doi.org/10.1111/j.1537-2995.2006.00737.x
- McDonald CP. Bacterial risk reduction by improved donor arm disinfection, diversion and bacterial screening. Review. Transfus Med, 2006; 16: 381-96. http://dx.doi.org/10.1111/j.1365-3148.2006.00697.x
- Van der Meer PF, Pietersz RNI, Reesink HW. Storage of platelets in additive solution for up to 12 days with maintenance of good in-vitro quality. Transfusion 2004; 44:1204- 1211. http://dx.doi.org/10.1111/j.1537-2995.2004.04010.x
- Williamson LM, Stainsby D, Jones H, Love E, Chapman CE, Navarette C, Lucas G, Beatty C, Casbard A, Cohen H. The impact of universal leukodepletion of the blood supply on hemovigilance reports of posttransfusion purpura and transfusion-associated graft-versus-host disease. Transfusion 2007; 47: 1455-1467. http://dx.doi.org/10.1111/j.1537-2995.2007.01281.x
- Wilsher C, Garwood M, Sutherland J, Turner C, Cardigan R. The effect of storing whole blood at 22 degrees C for up to 24 hours with and without rapid cooling on the quality of red cell concentrates and fresh-frozen plasma. Transfusion 2008; 48: 2338-47. http://dx.doi.org/10.1111/j.1537-2995.2008.01842.x
- Serrano K, Scammell K, Weiss S, Culibrk B, Levin E, Gyöngyössy-Issa M, Devine DV. Plasma and cryoprecipitate manufactured from whole blood held overnight at room temperature meet quality standards. Transfusion. 2010; 50: 344-53. http://dx.doi.org/10.1111/j.1537-2995.2009.02441.x

FURTHER READING

- Benjamin RJ, Mintz PD. Bacterial detection and extended platelet storage: the next step forward. Transfusion 2005; 45: 1832-5. http://dx.doi.org/10.1111/j.1537-2995.2005.00683.x
- Benjamin R, Dodd Y. Red-Cell Storage and Complications of Cardiac Surgery. N Engl J Med 2008; 358: 2840-2. http://dx.doi.org/10.1056/NEJMc080874
- Benjamin RJ, Kline L, Dy BA, Kennedy J, Pisciotto P, Sapatnekar S, Mercado R, Eder AF. Bacterial contamination of whole-blood-derived platelets: the introduction of sample diversion and prestorage pooling with culture testing in the American Red Cross. Transfusion 2008; 48: 2348-55. http://dx.doi.org/10.1111/j.1537-2995.2008.01853.x
- Cardigan R, Sutherland J, Garwood M, Bashir S, Turner C, Smith K, Hancock V, Wiltshire M, Pergande C, Williamson LM. *In vitro* function of buffy coat-derived platelet concentrates stored for 9 days in CompoSol, PASII or 100% plasma in three different storage bags. Vox Sang 2008; 94: 103–112. http://dx.doi.org/10.1111/j.1423-0410.2007.01008.x
- d'Almeida MS, Jagger J, Duggan M, White M, Ellis C, Chin-Yee IH. A comparison of biochemical and functional alterations of rat and human erythrocytes stored in CPDA-1 for 29 days: implications for animal models of transfusion. Transfus Med 2000; 10: 291-303. http://dx.doi.org/10.1046/j.1365-3148.2000.00267.x
- Dijkstra-Tiekstra MJ, Kuipers W, Setroikromo AC, de Wildt-Eggen J. Platelet capacity of various platelet pooling systems for buffy coat-derived platelet concentrates. Transfusion 2008; 48: 2114-21. http://dx.doi.org/10.1111/j.1537-2995.2008.01849.x
- Douay L, Andreu G. Ex vivo production of human red blood cells from hematopoietic stem cells: what is the future in transfusion? Transfus Med Rev 2007; 21: 91–100. http://dx.doi.org/10.1016/j.tmrv.2006.11.004
- Dumont LJ, Kleinman S, Murphy JR, Lippincott R, Schuyler R, Houghton J, Metzel P. Screening of single-donor apheresis platelets for bacterial contamination: the PASSPORT study results_ Transfusion 2010; 50; 589-599. http://dx.doi.org/10.1111/j.1537-2995.2009.02460.x
- Fuller AK, Uglik KM, Savage WJ, Ness PM, King KE. Bacterial culture reduces but does not eliminate the risk of septic transfusion reactions to single-donor platelets. Transfusion 2009; 49: 2588-93. http://dx.doi.org/10.1111/j.1537-2995.2009.02348.x
- Gandhi MJ, Drachman JG, Reems JA, et al: A novel strategy for generating platelet-like fragments from megakaryocytic cell lines and human progenitor cells. Blood Cells Mol Dis 2005; 35: 70-73. http://dx.doi.org/10.1016/j.bcmd.2005.04.002
- Giarratana MC, Kobari L, Lapillonne H, Chalmers D, Kiger L, Cynober T, Marden MC, Wajcman H, Douay L: Ex vivo generation of fully mature human red blood cells from hematopoietic stem cells. Nat Biotechnol 2005; 23: 69–74. http://dx.doi.org/10.1038/nbt1047
- Karam O, Tucci M, Toledano BJ, Robitaille N, Cousineau J, Thibault L, Lacroix J, Le Deist F. Length of storage and in vitro immunomodulation induced by prestorage leukoreduced red blood cells. Transfusion 2009; 49: 2326-34. http://dx.doi.org/10.1111/j.1537-2995.2009.02319.x
- Kirkpatrick UJ, Adams RA, Lardi A, McCollum CN. Rheological properties and function of blood cells in stored bank blood and salvaged blood. Br J Haematol 1998;101: 364-8. http://dx.doi.org/10.1046/j.1365-2141.1998.00689.x
- Koch CG, Li L, Sessler DI, Figueroa P, Hoeltge GA, Mihaljevic T, Blackstone EH. Duration of red-cell storage and complications after cardiac surgery. N Engl J Med 2008; 358: 1229-39. http://dx.doi.org/10.1056/NEJMoa070403
- Matsunaga T, Tanaka I, Kobune M, Kawano Y, Tanaka M, Kuribayashi K, Iyama S, Sato T, Sato Y, Takimoto R, Takayama T, Kato J, Ninomiya T, Hamada H, Niitsu Y. Ex vivo large-scale generation of human platelets from cord blood CD34+ cells. Stem Cells 2006; 24: 2877-87. http://dx.doi.org/10.1634/stemcells.2006-0309

- McFaul SJ, Corley JB, Mester CW, Nath J. Packed blood cells stored in AS-5 become proinflammatory during storage. Transfusion 2009; 49: 1451-60. http://dx.doi.org/10.1111/j.1537-2995.2009.02158.x
- Neildez-Nguyen TM, Wajcman H, Marden MC, Bensidhoum M, Moncollin V, Giarratana MC, Kobari L, Thierry D, Douay L. Human erythroid cells produced ex vivo at large scale differentiate into red blood cells in vivo. Nat Biotechnol 2002; 20: 467–472. http://dx.doi.org/10.1038/nbt0502-467
- Ohto H, Ezuki S, Kanno T, Nollet KE. Extending platelet storage: safety and quality considerations. ISBT Science Series 2009; 4: 266–270. http://dx.doi.org/10.1111/j.1751-2824.2009.01247.x
- Ringwald J, Zimmermann R, and Reinhold Eckstein. The New Generation of Platelet Additive Solution for Storage at 22˚C: Development and Current Experience. Transfus Med Rev 2006; 20: 158-164. http://dx.doi.org/10.1016/j.tmrv.2005.11.003
- Schrezenmeier H, Walther-Wenke G, Müller TH, Weinauer F, Younis A, Holland-Letz T, Geis G, Asmus J, Bauerfeind U, Burkhart J, Deitenbeck R, Förstemann E, Gebauer W, Höchsmann B, Karakassopoulos A, Liebscher UM, Sänger W, Schmidt M, Schunter F, Sireis W, Seifried E. Bacterial contamination of platelet concentrates: results of a prospective multicenter study comparing pooled whole blood-derived platelets and apheresis platelets. Transfusion 2007; 47: 644-52. http://dx.doi.org/10.1111/j.1537-2995.2007.01166.x
- Schwertz H, Köster S, Kahr WH, Michetti N, Kraemer BF, Weitz DA, Blaylock RC, Kraiss LW, Greinacher A, Zimmerman GA, Weyrich AS. Anucleate platelets generate progeny. Blood, 2010; 115(18): 3801-9. http://dx.doi.org/10.1182/blood-2009-08-239558
- Steil L, Thiele T, Hammer E, Bux J, Kalus M, Völker U, Greinacher A. Proteomic characterization of freeze-dried human plasma: providing treatment of bleeding disorders without the need for a cold chain. Transfusion 2008; 48: 2356-63. http://dx.doi.org/10.1111/j.1537-2995.2008.01856.x
- Sullenbarger B, Bahng JH, Gruner R, Kotov N, Lasky LC. Prolonged continuous in vitro human platelet production using three-dimensional scaffolds. Exp Hematol 2009; 37: 101-10. http://dx.doi.org/10.1016/j.exphem.2008.09.009
- van de Watering L, Lorinser J, Versteegh M, Westendord R, Brand A. Effects of storage time of red blood cell transfusions on the prognosis of coronary artery bypass graft patients. Transfusion 2006; 46:1712-18. http://dx.doi.org/10.1111/j.1537-2995.2006.00958.x
- Ungerer M, Peluso M, Gillitzer A, Massberg S, Heinzmann U, Schulz C, Münch G, Gawaz M. Generation of functional culture-derived platelets from CD34+ progenitor cells to study transgenes in the platelet environment. Circ Res 2004; 95(5): e36-e44 http://dx.doi.org/10.1161/01.RES.0000141700.96085.2e
- Vassallo RR, Wagner SJ, Einarson M, Nixon J, Ziegler D, Moroff G. Maintenance of in vitro properties of leukoreduced whole blood-derived pooled platelets after a 24-hour interruption of agitation. Transfusion 2009; 49: 2131-35. http://dx.doi.org/10.1111/j.1537-2995.2009.02257.x
- Votum 38 (06.2008) Bundesgesundheitsblatt 12, 2008 S. 1484. „Festlegung der Haltbarheitsfrist von Thrombozytenkonzentraten mit dem Ziel der Reduktion lebensbedrohlicher septischer Transfusionsreaktionen durch bakterielle Kontamination“. (Reduction of septicemia risk in the use of thrombocyte concentrates) http://www.rki.de/EN/Content/Prevention/NAC_Blood/V_38E_manuscript.pdf?__blob=publicationFile
- Wandall HH, Hoffmeister KM, Sørensen AL, Rumjantseva V, Clausen H, Hartwig JH, Slichter SJ: Galactosylation does not prevent the rapid clearance of long-term, 4° C-stored platelets. Blood 2008; 15: 3249–3256. http://dx.doi.org/10.1182/blood-2007-06-097295
- Webert KE, Cserti CM, Hannon J, Lin Y, Pavenski K, Pendergrast JM, Blajchman, MA. Proceedings of a Consensus Conference: Pathogen inactivation-making decisions about new technologies. Transf Med Rev 2008; 22: 1-34. http://dx.doi.org/10.1016/j.tmrv.2007.09.001
- Krailadsiri P, Seghatchian J, Macgregor I, Drummond O, Perrin R, Spring F, Prescott R, Williamson L, Prowse C, Anstee D, Turner M. The effects of leukodepletion on the generation and removal of microvesicles and prion protein in blood components. Transfusion 2006; 46: 407-17. http://dx.doi.org/10.1111/j.1537-2995.2006.00737.x
- Wolfe LC. Oxidative injuries to the red cell membrane during conventional blood preservation. Semin Hematol 1989; 26: 307-12. http://www.ncbi.nlm.nih.gov/pubmed/2683099
- Zhang JG, Carter CJ, Culibrk B, Devine DV, Levin E, Scammell K, Weiss S, Gyongyossy-Issa MI. Buffy-coat platelet variables and metabolism during storage in additive solutions or plasma. Transfusion 2008; 48: 847-56. http://dx.doi.org/10.1111/j.1537-2995.2008.01645.x

Georges Andreu

08. TRENDS IN PLATELET PROCESSING, DELIVERY AND CLINICAL USE

Blood processing consists of separating therapeutic components from blood. This is done either from a blood bag collected from a donor in a blood establishment (BE), or directly from a blood donor during a collection process called apheresis. Processing and apheresis allow the separation of the main blood components (red blood cells, platelets, plasma) and the presentation of them in a bag ready for transfusion in patients.

To illustrate some processing issues, we chose to present the outcome of a recent survey on platelet concentrates (PC). This blood component is mainly used in patients having low platelet counts (thrombocytopenia), mostly resulting from chemotherapy for cancer. As deeply thrombocytopenic patients are at risk of serious bleeding, the PC transfusion aims at preventing or curing bleeding in these patients.

In order to investigate trends in platelet component production and use, a questionnaire was sent to Euronet TMS correspondents. Euronet TMS is a European network of scientific societies of Transfusion Medicine, created in 2002. The survey dealt with PC production, processing and storage, inventory management and delivery, economic aspects, and use of guidelines for clinical use of PCs. Eleven countries responded to the questionnaire: Czech Republic, Estonia, France, Germany, Ireland, Latvia, Luxembourg, Malta, Poland, Portugal and Romania.

The survey dealt with I) collection used for PC production (apheresis or separation from whole blood collection); II) processing and storage (leukocyte reduction, additive solution, pathogen reduction, bacterial detection, storage time); III) transfusion related acute lung injury (TRALI) prevention; IV) inventory management and delivery to patients. In addition, economic aspects were considered: V) release price structure, and VI) guidelines for clinical use of PC.

8.1 COLLECTION FOR PLATELET CONCENTRATES PRODUCTION

8.1.1 PC COLLECTED BY APHERESIS

All eleven countries collect platelets by apheresis. Only one country (Romania) collects apheresis platelets without any associated multi-component collection such as Platelets + Plasma, Platelets + red cells or Platelets + plasma + red cells. Conversely, only one country (Portugal) collects all apheresis platelets in association with another component, plasma and/or red cells. The remaining nine countries use both approaches of single and multicomponent apheresis collections.

8.1.2 PC PROCESSED FROM WHOLE BLOOD COLLECTION

All countries prepare platelet concentrates from whole blood collection. Considering the basic techniques, the "platelet rich plasma" (PRP) and the "buffy-coat" (BC) methods used are as follows:

- PRP alone: 1 country: Romania
- BC alone: 8 countries:
  - Pools of BC alone: Estonia, Germany, Ireland, Latvia, Luxembourg, Malta,
  - Pools of BC and single BC techniques: Czech Republic and France
- PRP and BC: 2 countries: Poland and Portugal

8.2 PROCESSING AND STORAGE

8.2.1 LEUKOCYTE REDUCTION

All countries produce leuko-reduced PC. However, PC leuko-reduction is universal in only seven countries: France, Germany, Ireland, Latvia, Luxembourg, Malta, Portugal. In the Czech Republic, leuko-reduction is performed in 85% of the products.

8.2.2 PLATELET ADDITIVE SOLUTIONS

All countries use platelet additive solutions. For apheresis platelet concentrates, a single country uses them for all components collected: Portugal. All other countries use them as part of the production, and two indicate the percentage of apheresis PC with platelet additive solutions: France (45%) and Germany (20%).

For PC prepared from whole blood collection, all countries use platelet additive solution, and six use them for 100% of their production: Estonia, Ireland, Latvia, Luxembourg, Malta and Portugal. Among the remaining countries, two indicate the percentage of components produced with platelet additive solutions: France (87%) and Germany (80%).

8.2.3 PATHOGEN REDUCTION

The use of a pathogen reduction technique is mentioned by three countries: France, Germany and Poland. The use of pathogen reduction is 8% of the production in France, 1% in Germany and is not mentioned in Poland.

8.2.4 BACTERIAL DETECTION IN PC

Bacterial detection is mandatory for all PC in four countries: Estonia, Ireland, Luxembourg and Malta. It may be performed either for quality control or according to local policies in other countries.

8.2.5 STORAGE TIME OF PC

Storage time is the same for all types of PC (apheresis or BC, with or without platelet additive solution) in a given country. However, it varies in the eleven countries from four to seven days:

- 4 days: Germany; a single country
- 5 days: Czech Republic, France, Luxembourg, Malta, Poland, Portugal and Romania; 7 countries
- 7 days: Estonia, Ireland, Latvia; 3 countries

Storage time may be extended in some conditions:

- From 4 to 5 days in Germany when either a pathogen reduction or bacterial detection technique is used
- From 5 to 7 days in Poland where bacterial detection is performed

8.3 TRALI PREVENTION POLICY

There is a national policy to reduce the incidence of TRALI in 5 countries: Estonia, France, Germany, Ireland and Malta. The following three TRALI prevention measures are adopted:

- reduction of plasma volume by use of platelet additive solutions in the five countries
- selection of male donors (apheresis and / or recovered PC) in Ireland
- anti-HLA and/or granulocyte antibodies detection in apheresis platelet donors in France, Germany and Ireland

8.4 INVENTORY MANAGEMENT AND DELIVERY

8.4.1 OUTDATE RATE

Seven countries documented the rate of outdated PC:

- The outdate rate of apheresis PC is highly variable, and ranges from 1 to 19% (mean 7% and median 5%): Czech Republic (2%); Estonia (7%); France (2%); Germany (10%); Ireland (19%); Luxembourg (10%); Malta (5%); and Poland (1%).
- The outdate rate of whole blood-derived PC is almost always higher than for apheresis PC, and ranges from 2 to 32% (mean 10% and median 10%): Czech Republic (28%); Estonia (20%); France (4%); Germany (10%); Ireland (24%); Luxembourg (32%); Malta (7%); and Poland (2%).

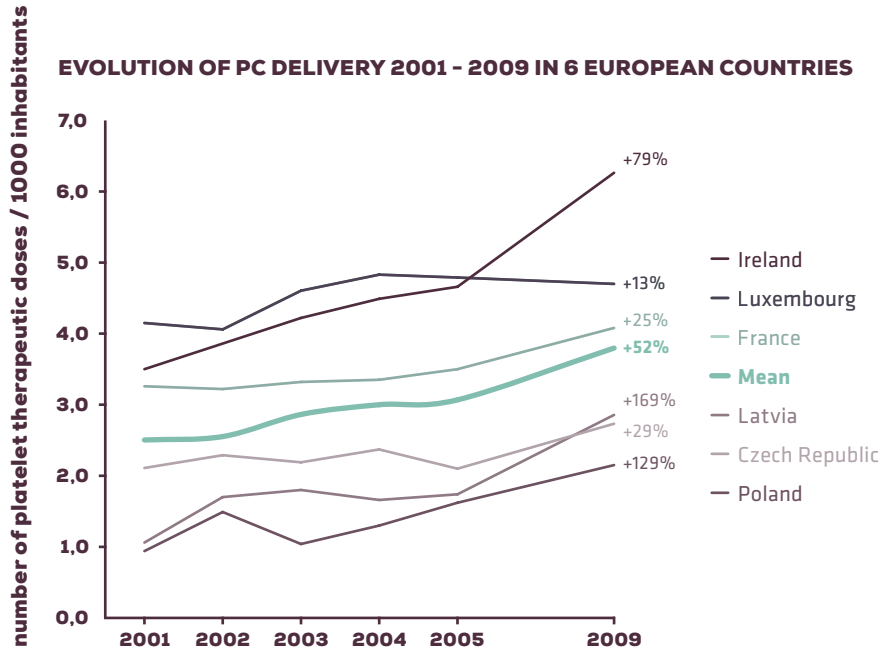
8.4.2 DELIVERY TO PATIENTS

Full data is provided by 10 countries: Czech Republic, Estonia, France, Ireland, Latvia, Luxembourg, Malta, Poland, Portugal and Romania.

The percentage of apheresis platelets is highly variable in the different countries, ranging from 0% (Romania), to 95% (Czech Republic), with a mean of 58% and a median of 40%.

As it is difficult to compare crude data from country to country, delivered PC are reported as the number of delivered therapeutic doses of platelets per 1000 inhabitants (Romania could not be evaluated according to that criterion, as there is only mention of the number of single PRP delivered): values range from 2.1 to 6.3 (median 4.1 and mean 3.8 PC per 1000 inhabitants).

As the Council of Europe already collected data of delivered platelets to patients from 2001 to 2005, it is of interest to add the year 2009 to the already available data provided by the Council of Europe. This was possible for six countries: Czech Republic, France, Ireland, Latvia, Luxembourg and Poland. Results are shown in the following table:



There is a very clear increase of platelet delivery since 2001:

- Between 2001 and 2009, the mean increase is +52%, ranging from 13% to 169%.
- Considering the more recent period, between 2005 and 2009, the trend is still toward a general increase (mean = +24%), with only one country (Luxembourg) maintaining the same activity, already belonging to the highest values, close to 5 PC per 1000 inhabitants. The trends for other countries are as follows: Czech Republic (+30%); France (+17%); Ireland (+34%); Latvia (+64%); Poland (+33%).

As all the recent studies devoted to the use of blood components show that most platelet concentrates are used in haematology [1-3], and more precisely in onco-haematology patients, there is no doubt that this increase is related, at least partly, to the expansion of heavy chemotherapy and haematopoietic stem cells transplants.

8.5 ECONOMIC ASPECTS: RELEASE PRICE STRUCTURE

8.5.1 APHERESIS PLATELET CONCENTRATES

Countries were asked whether the following factors were taken into account in order to determine the release price:

- **Multi vs. single component collection:** seven countries answered – all negative. This factor is not taken into account in Czech Republic, France, Germany, Ireland, Luxembourg, Poland and Portugal
- **Actual platelet content of the PC:** Six countries answered: one (France) said "yes" (i.e. the price is dependent of the actual platelet content of the PC); five (Germany, Ireland, Luxembourg, Poland and Portugal) said "no" (i.e. the price is not dependent of the actual platelet content of the PC)
- **Leukodepletion:** Eight countries answered: four said "yes" (The Czech Republic, Estonia, France and Poland) and four said "no" (Germany, Ireland, Luxembourg and Portugal).

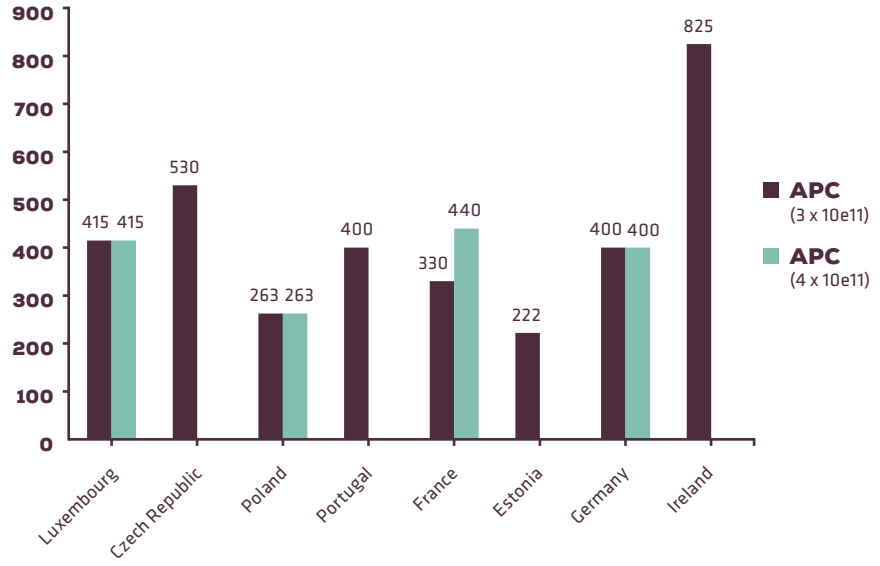
8.5.2 WHOLE BLOOD DERIVED PLATELETS

Countries were asked whether the following factors were taken into account when determining the release price:

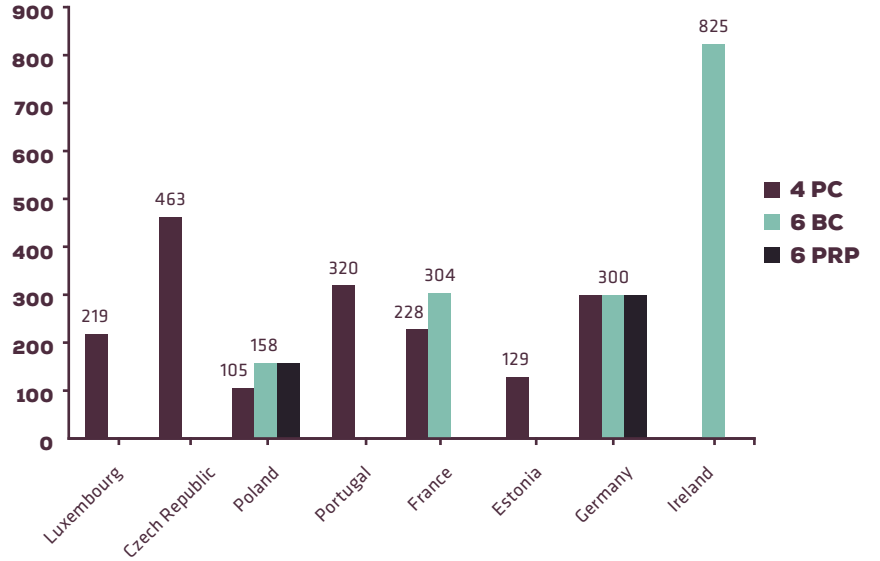
- **The technique used** (PRP vs Buffy-coat) is taken into account in a single country (Czech Republic) and not in Germany, Ireland, Luxembourg, Poland and Portugal
- **The number of units** from whole blood is taken into account in Estonia and Poland, and is not taken into account to determine the release price in Czech Republic, Germany, Ireland, Luxembourg and Portugal
- **The actual platelet content** of the PC is taken into account in France, but not in Germany, Ireland, Luxembourg, Poland or Portugal
- **Leuko – reduction** is taken into account in the Czech Republic, France, Ireland and Poland, and not in Germany, Luxembourg or Portugal.

Finally, as an "exercise", countries were asked to provide the price they would charge their hospitals for one apheresis PC (APC) with a platelet content of 3×10^{11} or 4×10^{11}. The same question was raised for whole blood derived PCs respectively prepared from 4 BC, 6 BC or 6 PRP. Data was provided in the local money, and after conversion into Euros is presented in the following figures.

RELEASE PRICE OF APC (EUROS)



RELEASE PRICE OF WHOLE BLOOD DERIVED PC (EUROS)



The release price of APC varies by a factor of four between countries (€222 in Estonia vs €825 in Ireland), and by a factor of five for whole blood derived platelets (€158 in Poland vs €825 in Ireland).

8.6 GUIDELINES FOR CLINICAL USE OF PC

Seven countries indicated that they have national clinical guidelines, and six provided information on several items indicated in the following table:

Content of guidelines	Malta	Czech Republic	Poland	France	Estonia	Germany
specific clinical indication of apheresis PC	no	yes	yes	yes	yes	no
specific clinical indication of whole blood recovered PC	no	no	yes	no	yes	no
irradiation of PC	yes	yes	yes	yes	yes	yes
CMV transmission prevention policy	yes	yes	yes	yes		yes
standardization of therapeutic dose (prophylactic transfusion)	no	no	yes	yes		no
standardization of platelet count threshold for prophylactic transfusion	yes	no	yes	yes	yes	no
definition of refractoriness to platelet transfusion	no	no	yes	yes	yes	yes
management of refractoriness to platelet transfusion	no	no	yes	yes		
platelet transfusion indication in general surgery	no	no	no	yes	yes	
platelet transfusion indication in cardiac surgery	no	no	no	yes		
platelet transfusion indication in neuro surgery	no	no	no	yes		
platelet transfusion indication in massive transfusion / trauma	no	no	no	yes	yes	

8.7 CONCLUSION

Since 2005, many changes in platelet transfusion policy have emerged. Among them we can note the following:

- A new view of the quality of whole blood derived vs apheresis PC [4,5]
- The emergence of platelet additive solutions
- The possibility of organising a prevention policy against TRALI
- The development of onco-haematology treatments enabling heavy chemotherapy procedures in older patients that result in a significant increase in the need for platelet support in these patients.
- Other factors, not explored in the survey, could also contribute to the important increase in PC use, such as the development of various surgical procedures in older patients, with a significant proportion of them taking anti-platelet drugs.

The survey we conducted, although far from being exhaustive with regard to the number of participating countries, significantly reflects this evolution.

Moreover, as shown by the development of clinical guidelines in many countries in recent years, it is clear that there is a trend to better control the clinical use of platelets.

Finally, there is a point that remains weak in most countries (9 out of 11 in our sample of responding countries): the outdate rate remains much higher than for red cell concentrates. We can hope that the experience and practices of those few countries that seem to better control their inventory and better manage their "platelet supply chain" may in future be shared with all the others. The European Blood Alliance is currently involved in benchmarking these practices and helping to improve them, for the benefit of patients, donors and healthcare providers.

REFERENCES

1. Wells AW, Chapman CE, Stainsby D, Wallis JP. Where does blood go? Transfusion in Medical patients in the North of England. Transfusion Medicine, 2002, 12 (Suppl. 1): 43. http://dx.doi.org/10.1046/j.1365-3148.12.s1.24.x
2. Cobain TJ, Vamvakas EC, Wells A, Titlestad K. A survey of the demographics of blood use. Transfusion Medicine, 2007, 17: 1-15. http://dx.doi.org/10.1111/j.1365-3148.2006.00709.x
3. Quaranta JF, Berthier F, Courbil R, Courtois F, Chenais F, Waller C, Leconte des Floris MF, Andreu G, Fontaine O, Le Niger C, Puntous M, Mercadier A, Nguyen L, Pelissier E, Gondrexon G, Staccini P. Qui sont les receveurs de produits sanguins labiles (PSL) ? Une étude nationale multicentrique - un jour donné. Établissement de transfusion sanguine (ETS) - établissements de santé (ES). Transfus Clin Biol. 2009, 16: 21-29. http://dx.doi.org/10.1016/j.tracli.2009.02.002
4. Murphy S. Platelets from pooled buffy coats: an update. Transfusion 2005, 45: 634-639. http://dx.doi.org/10.1111/j.0041-1132.2005.04467.x
5. Andreu G, Vasse J, Sandid I, Tardivel R, Semana G. [Use of random versus apheresis platelet concentrates]. Transfus Clin Biol. 2007, 14: 514-21. http://dx.doi.org/10.1016/j.tracli.2008.01.004

Michael Schmidt
Erhard Seifried

09. BLOOD TESTING: DEVELOPMENT OF NEW TECHNOLOGIES

9.1 INTRODUCTION

In recent years, the tremendous development of the human genome study has led to new methods and concepts which have revolutionised medical biology by opening large avenues for predictive and diagnostic medicine. The first step was a **genomic era**, characterised by sequencing the entire genome from humans and those from several living species used as models (yeast, amoeba, green alga, drosophilia, mouse, etc.). This was followed by a **post-genomic era**, in which it became also obvious that extensive studies of gene products (transcriptome and proteome) are essential to the understanding of molecular mechanisms underlying cell architecture and function in normal and pathological conditions. Similarly, interactions between proteins (interactome) and those from cellular metabolites (metabolome) should further extend our knowledge of cell functions. Such studies represent a significant source of progress for numerous fields in biology and medicine, including blood transfusion.

9.2 GENOMICS

9.2.1 BLOOD GROUP GENOTYPING OF DONORS AND PATIENTS

At the level of the gene, the molecular background of human blood groups is now comprehensively described and currently, on a massive scale, commercially available platforms are capable of delivering blood group genotyping. Such systems are a prerequisite for the proposal that high throughput genotyping systems will complement (rather than replace) standard serological typing of blood units.

Potential target patient groups and corresponding matched blood donors for extended typing using DNA-based approaches can be defined. The testing systems currently available are merely a "stop-gap" and eventually next generation or "next-next" (single molecule) sequencing will allow the rapid and cheap determination of all blood groups and other genetic polymorphisms.

A. MOLECULAR BACKGROUND OF BLOOD GROUP ANTIGENS

The ISBT nomenclature committee has defined over 300 blood group antigens, and has classified the majority of these into 30 different blood group systems [1-3]. Almost all clinically significant blood group systems and their alleles have been defined genetically (http://www.ncbi.nlm.nih.gov/gv/mhc/xslcgi.cgi?cmd=bgmut/home). Most blood group polymorphisms are defined by single nucleotide substitutions (SNPs) causing coding-region changes of genes encoding blood group active polypeptides. One such example is the Kell (K1) polymorphism which is caused by a C698T SNP in exon 6 of the KEL gene causing a Thr193Met amino acid exchange in the Kell glycoprotein.

Some systems, however, such as *ABO* and *RH*, are inherently complicated at the level of the gene which makes approaches to genotyping more technically challenging. Thus, whilst Rh serology is complex and often very technically difficult, ABO serology is not and does challenge the proposal that genotyping technology could directly replace serology in front-line blood group antigen testing.

ABO is, by far, the most clinically significant blood group system which is due predominantly to the existence of preformed antibodies in all but AB group individuals. In terms of serological determination of ABO status, this is comparatively simple, cheap and efficient. There has been much debate as to whether genotyping for ABO is worthwhile, as there are large numbers of ABO alleles that cause blood group O and variant A and B phenotypes. Mutations in the *ABO* gene, which encodes a glycosyltransferase that catalyze addition of either N-acetylgalactosamine (A-transferase) or galactose (B-transferase) onto developing carbohydrate moieties, can lead to nonsense or missense inactivating mutations in the enzyme. Over 60 such O alleles exist [4].

The *RH* system is the most complex of blood groups at the genetic level (for reviews see [5-7]) and many variants have been identified (http://www.uni-ulm.de/~wflegel/RH/). This is due in part to the tail to tail arrangement of the two RH genes on chromosome 1 (*RHCE* and *RHD*). The two genes appear to interact on a frequent basis with gene conversion producing RhD variants and D-negative genotypes.

Coupled with this phenomenon, there are frequent point mutations in both *RHD* and *RHCE* genes producing partial D, weak D and D-negative phenotypes (*RHD*), C^w and C^x antigens and RHCE variants (*RHCE*). In certain partial D phenotypes, hybrid *RHD-RHCE-RHD* genes are present, which are likely to have been generated by gene conversion events. These genes can be difficult to detect using standard SNP-based genotyping and require an "exon scanning" approach where all *RHD* exons are analysed simultaneously and "drop out" of certain exons detected and scored against known hybrid partial D alleles. The situation is complicated yet further by the fact that in certain *RH* alleles only part of the exon is converted (for example in the r^s type 1 phenotype).

B. POTENTIAL TARGET GROUPS AND GENOTYPING SCENARIOS

Blood group genotyping was initially applied to situations where it was dangerous to obtain blood for serological typing. This was the case in antenatal testing, which for decades had been used in the clinical management of haemolytic disease of the fetus and newborn (HDFN). In this instance, the predominant blood group system required for investigation was Rh (in particular D), but to a lesser extent Kell and Duffy genotyping is performed. With the advent of safe maternal plasma-based genotyping [8], *RHD* was one of the first completely non-invasive genotyping tests to be introduced in prenatal testing. Now, it appears most likely that all RhD negative women in certain countries in Europe will have their fetuses typed prenatally in order to determine which of them requires treatment with prophylactic anti-D [9-11].

At the blood bank

Presently, and for the foreseeable future, routine blood typing will be performed using serological reagents. This is especially true for ABO typing where a large number of O alleles complicate approaches to genotyping. In contrast, serology using anti-A and anti-B is cheap and robust. Nevertheless, there is some strong argument for the introduction of genotyping on a mass scale, perhaps at first as a "hybrid" mode. Genotyping, in particular for Rh will be able to accurately identify variant D units (quite possibly wrongly serologically defined as D-negative), detect C^x and C^w positive units, define Fy^b weak units and predict other antigens difficult or impossible to define using serological reagents.

Donation of weak or partial D units and transfusion into D-positive patients does not necessarily represent a risk, as the only immunogenic stimuli will be to low frequency antigens carried by such D variants (e.g Tar and DVII, Go^a and DIV, BARC and DVI) which are unlikely to produce an antibody of clinical relevance during repeated transfusions (unlikely with D variants).

For routine blood donors, it may make good economic sense to comprehensively genotype this cohort, as their reliability will ensure a consistent supply of this blood. This will streamline the management of blood donation, eliminate repeat testing and instantly identify antigen-negative units within the blood bank, and thus greatly enhance electronic cross matching.

It would also be of great benefit to genotype donors that may aid vulnerable patient groups (see below), and developing cohorts of donors with African ancestry may facilitate this. Some studies have advocated the use of molecular *RHD* typing to assist the quality control of D-negative units in blood banks [12]. This will eliminate potentially risky RhD variant units from the D-negative donor pool that have failed to be detected by serological reagents.

Vulnerable patient groups

Sickle cell disease (SCD) patients often are transfusion dependent which gives them a bearable value of life. However, routine blood transfusion can lead to alloimmunisation to minor blood group antigens. As a consequence, alloimmunisation to incompatible blood group antigens can be potentially life-threatening and complicate the clinical management of these patients.

It makes good sense, therefore, to comprehensively genotype SCD patients and select antigen-negative units for transfusion wherever possible [13]. Stem cell transplant patients are prone to rejection, and care must be taken to match their blood group as closely as possible with respect to the graft. During the period of engraftment, the patients are very often transfusion-dependent, and, therefore, close matching of this blood is required.

C. BLOOD GROUP GENOTYPING OR SEROLOGICAL PHENOTYPING?

It is a matter of debate as to whether DNA-based typing of blood group status will eventually replace serological phenotyping as the default method in blood banks [14]. There is little doubt that genotyping will occupy more prominence in routine blood grouping in the future than is the current practice. Whether it will completely replace serology, (which for ABO typing in particular is cheap, robust and reliable), is doubtful in the short term. However, it is the author's opinion that the widespread acceptance of genotyping in clinical genetics should make that transition in transfusion medicine.

An often quoted statement that is critical of blood group genotyping is that "*genotype does not correspond to phenotype*". This statement is misleading, as a given genotype must always have a corresponding phenotype. It is true, however, that some variants are not be detected by current genotyping technology. This situation will lead to an incorrect call by genotyping, but this is due to simple lack of knowledge rather than an inherent flaw in the ability of genotyping as a discipline. As blood group genotyping evolves into perhaps massive parallel sequencing as the prime method of choice, these new alleles or *de novo* mutations will not be invisible, and will invariably lead to robust discovery mode genotyping or "genotype to phenotype" based approaches. In this scenario, serology would play a supporting role to genotyping to confirm a predicted phenotype.

Although there has been a movement forward in the implementation of blood group genotyping, it must be progressed with necessary caution. It is imperative that large-scale studies are carried out to determine the accuracy and economic viability of blood group genotyping: a direct and frank assessment of the accuracy above and beyond serological testing must be made.

D. THE CURRENT TECHNICAL PLATFORMS – BLOOD GROUP GENOTYPING ON "GENE CHIPS"

Genotyping can be performed on several plateforms exploiting different techniques, although all used polymerase chain reaction (PCR) of the targeted DNA as a first step. Technologies to handle amplicons may include nucleic acid hybridisation on various supports (glass, plastic, beads), oligonucleotide primer extension, and size/charge determination, or a combination of them. More recently, highly flexible fluidic microarray systems have been introduced (Luminex, Biotrove). Several reviews outline these technical advances and discuss their application in the field of blood transfusion [15-18].

Bloodgen project and BLOODchip

The commercially available high-throughput DNA-based typing platform BLOODChip (Progenika, Vizcaya, Spain) has been developed by a consortium of European laboratories (Bloodgen project, www.bloodgen.com) for blood group genotyping purpose [19]. The testing platform comprises a multiplex PCR amplification of genes encoding the major clinically significant ABO, RHD, RHCE, KEL, FY, JK, MNS, CO, DO, DI blood group alleles. These PCR products are labelled with a fluorescent dye and fragmented and then hybridised to a gene chip, comprising multiple copies of probes attached to a glass slide.

Based on an algorithm that defines the strength of hybridisation as being positive, negative or heterozygous for an allele, software uses this allele-specific hybridisation approach to score the blood group genotype. Clinical trials have proved that BLOODchip is significantly superior in accuracy to serological typing, and, in particular, is much more accurate in correctly typing FY and MNS systems and identification of D variants. BLOODchip's main advantage is to handle genotyping almost all known D variants. Human platelet antigen genotyping (HPA1-11 and 15) is also available.

Bioarray HEA chip

Virtually in parallel to the development of BLOODchip, Bioarray solutions of Warren, New Jersey USA developed a bead-based genotyping platform for "human erythrocyte antigens" or HEA beadchip system. The system (HEA version 1) includes testing for the major clinically significant alleles of the MNS, KEL, FY, JK, DI, CO, DO, LU, LW, SC and HbS [20,21]. HEA-1 does not include testing for Rh or ABO alleles, although kits for *RHD* and *RHCE* typing are in development and will soon be available.

Technically, the system involves the amplification of PCR products that encompass each blood-group specific SNP, the denaturation of each PCR product and hybridisation to a probe which is covalently attached to a colour (dye) coded bead. SNPs are then identified by performing a short extension reaction and the labelled bead and attached extended products are identified after separation of the beads on an array. The main advantage of the Bioarray HEA system is throughput and has become adopted by many laboratories as an adjunct to serological testing.

Beckmann-Coulter Genome Lab SNPstream

This commercially available system includes a multiplex PCR followed by single-base extension reaction using allele-specific, tag-specific oligonucleotide primers designed to flank the SNP of interest, and fluorescent ddNTPs. Labelled extension products are hybridised to microarrays grafted with oligonucleotides complementary to the primer tags and analysed on a laser imager. Detection of RHD SNPs, RHCE, S/s, K/k, Kp(a/b), Fy(a/b), FYo (-33 promoter silencing polymorphism), Jk(a/b), Di(a/b) have been reported, as well as platelet antigen genotyping [22,23].

Fluidic microarrays

- **Luminex technology**
  The Luminex xMAP technology (Luminex Corp, Austin, USA) is already in use for other nucleic acid detection, including HLA genotyping [24]. It was been recently adapted for MNS, KEL, FY, JK, CO and LU blood group genotyping [25]. The technique is based on the use of color-coded polystyrene beads with a unique spectral signature chemically grafted with allele-specific oligonucleotides. Fluorescently labelled amplicons generated in multiplexed PCR of DNA samples carrying the targeted SNPs are captured by the appropriate beads which are interrogated individually in a rapid flowing stream by two separate lasers of a Luminex 100 analyser.

- **Biotrove Nanofluidic OpenArray**
  The OpenArray platform (Biotrove Inc, Woburn, USA), is based on high throughput PCR conducted in OpenArray microplates with 3072 through-holes pre-arrayed with primers and probes targeting a unique SNP and designed to analyze 33 nl DNA reaction volumes. Application for RH (E/e), KEL, Jsa/b, FY, FYo, JK, LU, DO, JOa and HY blood group genotyping has been recently published [26].

Of note, the two fluidic techniques are very flexible, particularly for the insertion or removal of any SNP.

Other technologies

- **Applied Biosystems SNaPshot**
  The method is based on multiplex PCRs to generate amplicons encompassing the SNPs of interest, followed by a single-base extension assay to incorporate fluorescently-labeled ddNTPs into a primer probe annealed next to the target SNP. Fluorescent extension products are size-separated by capillary electrophoresis and quantified. Applications of the ABI SNaPshot system indicating its viability in molecular blood grouping have been published for the detection of MN, S/s/U-/U+^{var}, K/k, Kp(a/b), Fy(a/b/bw), FYo (-33 promoter silencing polymorphism), Jk(a/b), Sc1/Sc2, Di(a/b), Co(a/b) and Yt(a/b) [27,28].

- **Mass spectrometry**
  Mass spectrometry has been used for fetal blood groups *RHD*, *Kell* and *HPA* genotyping from cell-free DNA present in maternal blood [29-31]. After a multiplex PCR to generate amplicons overlapping the desired SNPs, oligonuleotides primers bound adjacent to SNP positions are used to generate allele-specific single base extension products using a cocktail of unlabelled ddNTPs. In the mass spectrometer, the extension products are spotted on a silica-based chip array matrix and a desorption/ionisation process initiated by laser pulses (MALDI, matrix-assisted laser desorption/ionisation) creates ionized gas-phase DNA molecules that are accelerated in an electric field and the time-of-flight (TOF) of the molecules through a vacuum chamber to the detector is monitored. The time-of-flight is proportional to the masse-to-charge ratio (m/z) of the particles which can easily discriminate products differing by a single base. Identification of products is made through a reference database. The instrumentation is expensive and most likely limited to specialised centres handling a large number of samples for SNP analysis.

E. NEXT GENERATION (NEXT-GEN) AND "NEXT-NEXT" GENERATION SEQUENCING AND BLOOD GROUPING

In our opinion, all genotyping for blood groups will, in the future, be performed by high-throughput sequencing, otherwise known as "deep sequencing". At present, this technology involves sequence determination in a massively parallel format, and while it yields relatively short sequence reads, it generates millions of them [32-34].

Commercially available systems include those produced by 454, Solexa and Applied Biosystems (SOLiD). The implementation of such systems for routine blood group genotyping is currently hampered by cost and throughput, but there is no doubt that this

situation will change with newer technologies coming on stream. This will lead to cheaper higher throughput systems with more effective bioinformatics.

Furthermore, DNA sequencing systems is in development: known as single molecule systems, nanotechnology is able to detect the real-time generation of DNA sequences. First, single molecule sequencers (Helicos, Pacific Biosystems) can generate 100Gb of DNA sequence per hour (equivalent to a diploid human genome sequence every four minutes). Such machines will greatly reduce the cost of genome sequencing and it may well be economically viable to sequence many human genomes (primarily for assessment and study of diseases). Routine blood donors may fit in this category.

The advantages that sequencing for predicted blood group can offer is, of course, that the process, by definition, defines unknown blood group alleles, and is not inhibited by what SNPs are selected in the assay, only by what region of the genome is covered.

9.2.2 NUCLEIC ACID TESTING METHODS TO IMPROVE BLOOD SAFETY

The description of the ABO blood group system was an enormous milestone for making transfusions of whole blood or blood components feasible and safe for a broad range of indications. Blood components are needed for the successful treatment of many diseases. However, the adverse side effects, like infections, were (and still are) potentially problematic, often causing severe life-threatening disease.

To avoid infection, the most critical point is the diagnostic window period [35]. This is defined as the time period between the start of an infection and the first opportunity to recognise the infection by diagnostic testing. Shortening the diagnostic window period has been the focus of the last three decades of transfusion medicine. Therefore, many general safety procedures were implemented in blood donor screening, including critical donor selection [36], a donor self-exclusion opportunity [37], the storage of quarantined plasma and the development of new screening systems like nucleic amplification technology (NAT).

Blood donor screening for pathogens NAT can be divided into four groups:

I. transfusion-relevant pathogens that are generally tested for in many countries (HBV, HCV and HIV-1)
II. transfusion-relevant pathogens that are tested for only in some countries with special circumstances (WNV, HAV, B19V, Chikungunya virus and HIV-2)
III. pathogens that are probably transfusion-relevant but that are currently not indicated as special risks for blood transfusions and not tested for in blood donor screening programmes (SARS CoV and Influenza viruses)
IV. bacterial screening by NAT.

Blood safety was significantly improved by the introduction of NAT systems through the reduction of the diagnostic window period, especially for transfusion-transmitted virus infections. Nevertheless, the new technologies are not risk free [38].

A. CURRENT TECHNOLOGIES

The methods for screening of transfusion-transmissible infectious agents in donated blood have improved over the years at a somewhat unsteady pace, by including new molecular biology technologies and automated devices. For instance, since its introduction in the blood testing technology, the enzyme-linked immuno assay (ELISA), generally performed under a 96-well format, have benefitted from constant technological evolution, leading to quality improvement. The assay has, to some extent, adapted to automated devices for the screening of large numbers of samples.

But the major step forward in blood screening over the past years has been the introduction of the PCR technology for direct detection of viral genomes, such as HIV RNA, HCV RNA and HBV DNA. Today, this technology enables the detection of very low levels of viruses in a biological sample, and it improves both sensitivity and specificity.

Nucleic acid amplification technology (NAT) can be performed on individual donations or on pools and be fully automated. The risk of transmission through transfusion of a well-recognised virus has become minimal because of donor screening and testing, and it is solely associated to donations collected during the window period (short period after contamination during which markers of infection are not yet detectable in the blood). The challenges now lie rather in the detection of emerging pathogens, such as West Nile or Chikungunya viruses. These challenges can be overcome by including new devices and innovations to the current techniques.

B. BLOOD DONOR SCREENING BY NAT WORLDWIDE

All over the world, blood donor services are responsible for releasing life-saving blood components for many kinds of different therapeutic strategies. Therefore, some countries centralise all blood donor screening tests in one or two laboratories. These test centres have to screen up to 10,000 samples per day.

Analysing such a large number of samples by NAT daily is a big challenge. Therefore, pooling procedures were developed to reduce the total number of samples. Countries like Japan started in 1999 with mini-pools of up to 50 samples per pool for HBV, HCV and HIV-1 [39]. Other countries like Germany developed a mini-pool NAT (MP-NAT) system with up 96 samples per pool [40-42]. After the pooling process, high-speed centrifugation is used to enrich viruses to the bottom of a centrifugation tube, followed by a manual extraction procedure using chaotropic salts [43].

At the beginning of blood donor screening by NAT, no commercial systems were available. Therefore, blood banks developed their own "in-house" systems to improve blood safety by this new technology [40,43]. Now, after more than ten years of experience with NAT, the situation has completely changed. Fully automated barcode-controlled NAT systems based on bead extraction technologies are on the market and make the introduction of these screening systems as easy as blood donor screening for antibodies.

More and more countries have already implemented NAT in blood donor screening or are currently in the process of implementation. The introduction of NAT systems into blood donor screening was able to reduce the diagnostic window period to only a few days for HCV and HIV-1. Many countries currently have approximately 10 years of experience with NAT. Starting with "in-house" PCRs, the methods are currently CE-certified or FDA-approved.

Most countries use fully automated NAT systems, and their handling is currently as easy as using serological systems. With these automated systems, the pool size is reduced to six samples per pool or even to ID-NAT. Only Germany, Austria and Luxemburg continue to screen blood donor samples in mini-pools, with a maximum pool size of 96.

Blood donor screening by NAT for at least HIV-1 and HCV has been, as far as is known, implemented in the USA, Canada, parts of Brazil, Spain, France, the UK, Denmark, Germany, the Netherlands, Belgium, Greece, the Czech Republic, South Africa, Ghana, Luxembourg, Switzerland, Italy, Japan, parts of China, Australia, Poland, Norway, Finland and New Zealand.

Based on the very low incidence of HIV-1 and HCV in their donor population, Sweden decided to stop blood donor screening by NAT. Although such screening is able to reduce the diagnostic window period and improve blood safety, it is still at risk of producing false negative test results due to genomic mutation within the primer and probe binding region. To diminish this risk, manufacturers of NAT screening system were advised to develop screening systems with an amplification of at least two genomic regions (dual targeting).

C. NAT ALTERNATIVES

Within the last five years, new combination assays for the parallel detection of antigens and antibodies were developed for HCV and HIV, respectively. Barbara et al [44] compared the analytical sensitivities of different assays. The optimised antigen test for HCV requires an additional three days for the diagnostic window period compared to NAT. The best combo test was reactive at five days after NAT. Such data will be comparable for HIV. These data clearly demonstrate that blood donor screening by NAT will reduce the diagnostic window to a minimum. If NAT technology cannot be implemented, a combo test could be a fairly good alternative to improve blood safety and should be, in these cases, considered to be the preferred state-of-the-art method.

D. FUTURE TECHNOLOGIES

It is expected that scientific and technological developments will keep bringing new technologies to blood screening programmes, especially for better detection of new or emerging viruses [45]. The advent of nanotechnologies is a prime example of such promising evolution.

Nanotechnologies are based on devices that are amenable to physical chemical and biological designs at the nanometer range [46]. Nanostructures are assembled at the molecular scale, thereby allowing a major step forward in the progression toward miniaturisation of screening assays. Through the use of nanotechnologies for blood screening, detecting a single infectious particle in a biological sample now becomes a foreseeable possibility. A number of nanodevices have been developed already, such as fluorescent nanocrystals or quantum dots, gold nanoparticles, magnetic nanoparticles.

The bio-barcodes technology is a good example of the possibilities offered by nanotechnologies. It is based on the association of magnetic and gold nanoparticles [47]. For the detection of a given target molecule, for instance, a viral nucleic acid, dedicated magnetic particles are covered with oligonucleotide probes specific for the target nucleic acid sequence. The gold particles bear oligonucleotides that are complementary to a distinct sequence of the target nucleic acid, and also to multiple copies of non-viral oligonucletides that serve as barcodes.

After incubation of a biological sample in the presence of the magnetic and gold nanoparticles, the complexes consisting of magnetic beads - viral DNA - gold beads are captured in a magnetic field, and the identity of the viral DNA is revealed through reading the barcodes. The same device can be generated for the detection of pathogen-associated proteins by the association of specific monoclonal antibodies to nanoparticles. Recent studies have demonstrated the feasibility of such devices, in particular, for the detection of the hepatitis B, Ebola, or human immunodeficiency viruses.

Other types of nanoparticles, such as fluorescent nanocrystals, may have future application in blood screening technology [48]. Fluorescent nanocrystals are inorganic semiconductors of nanometric size, made of cadmium and selenium, which, in response to UV light absorption, become fluorescent with a narrow spectrum of emission. The emission wavelength is dependent upon the chemical composition and size of the nanocrystal, offering the possibility of designing a large array of nanocrystals that cover the entire color spectrum. Nanocrystals can be functionalised with specific DNA or protein probes, and through excitement with a single source of UV light, markers associated to each color-specific nanocrystal can be easily quantified.

Another technology, with potential application in blood screening for pathogens is called lab-on-chip system. It consists of microfluidic systems integrated on a chip, including microcanals and reservoirs, and is designed to carry out complex reactions. It may include gold nanoparticles for direct detection of a biological marker with a specificity equivalent to conventional ELISA, and it has the potential for detecting biomarkers at very low concentrations within a biologic sample.

Bio-barcodes can also be integrated into a microfluidic chip for better automation and multiplex detection of viruses or virus-specific antibodies. Future microfluidic platforms may be designed to automatically collect, concentrate and purify target markers in addition to conducting the detection reaction.

One can expect these new technologies to make a significant impact on the efficacy and safety of blood screening for infectious agents. The pace of this evolution is as yet uncertain, but it clearly tends to evolve toward increased miniaturisation of blood test devices for higher throughput – and better cost-effectiveness – with improved sensitivity and specificity.

9.3 PROTEOMICS

Although the human genome is composed of 25-30,000 genes, current estimates suggest that at least 300,000 proteins, including their isoforms and post-translational modifications, can be expressed from these genes. In the **post-genomics** age which followed that of **genomics**, all possible cellular gene products (RNA and proteins) are to be extensively analyzed and characterised. The large-scale analysis of the entire collection of mRNAs, which targets the active genes in a given cell, defines the **transcriptome**, whereas analysis of all proteins, defines the **proteome**. Both analyses are dependent on environmental factors, developmental or growth conditions, drugs, stress and more generally, physiological and pathological status.

A. TRANSCRIPTOME AND PROTEOME

The most widely used technique for transcriptome analysis relies on the use of DNA microarrays on which all cDNA (or oligonucleotides) to be analyzed are spotted at high density on a solid support. Microarrays are next hybridized with mRNAs (complementary DNA labelled with a tracer, generally a fluorescent dye) extracted from cells or tissues under study and hydridisation products detected by fluorescence are analyzed as described above for genotyping.

High throughput sequencing of all possible transcripts is another technical option not limited by the choice of oligonucleotides (or cDNA) spotted on microarrays. In most instances, comparative studies are performed, for instance, by analyzing expression levels of cell transcripts before and after treatment with a drug or an inducer of cell differentiation. Real-time quantitative PCR analysis is often used as a validation tool of the results derived from DNA microarrays.

Proteomic analysis is more complex as it requires detection of isoforms and post-translational modifications (glycosylation, phosphorylation, acylation, ubiquitination, etc.) of proteins present in a wide range of concentration. Qualitative analysis, which lists the expressed proteins at a given time in a given cell or tissue, can be performed by approaches comprising several steps such as: (I) extraction of protein components from a biological fluid or homogenous population of cells, (II) separation/purification of proteins by 2D gel electrophoresis (according to mass and isoelectric point) or high-performance liquid chromatography, (III) identification and characterisation of each protein by mass spectrometry.

In this technique, peptides derived from proteins by partial proteolytic cleavage are separated according to their mass-to-charge ratio (m/z). Current methods include the generation of gas-ions by electrospray ionisation (ESI) or matrix-assisted laser desorption/ionisation (MALDI) of molecules before ion separation by either space (ion trap) or time (time-of-flight, TOF) in the mass analyser, and recording the number of ions at each m/z value. A frequently used technique for protein and peptide sequencing is tandem mass spectrometry (MS-MS) which separates compound fragments by magnetic field followed by identification by mass. Peptide identification in the sample is made *in silico* using bioinformatics and specialised softwares by comparison with computerised peptide spectrum of proteins present in databases. The purity of products submitted for analysis is critical to avoid contaminants.

Another challenge is the dynamic range of proteins in the sample, as concentrations may differ by several orders of magnitude from one protein to another. For instance, in red blood concentrates (RBCs), Band 3 is about 2,000 more abundant than CR1. To overcome this problem, purification steps to deplete abundant components can be introduced (chromatography, differential expression, combinatorial peptide libraries etc.), but this may potentially remove minor components.

To the qualitative feature of these studies, one should add a quantitative dimension to appreciate the expression level of proteins, but more complex techniques have to be performed (for instance, the use of stable isotope-modified peptides). Overall, proteomic science is rapidly growing but the cost and complexity of these technologies and instrumentation still represent limiting factors and call for collaborative strategies for their development.

B. PROTEOME AND TRANSFUSION MEDICINE

Proteomic analysis has many applications in all area of biological sciences and medicine as it is a powerful tool for studying the structure and functions of proteins and their interactions, cell signalling pathways and networks, as well as for searching, identifying an analyzing systemic disease-associated markers, and monitoring the impact of toxicity and drug therapy on cellular systems [49].

Several applications under development in transfusion medicine have been published in special issues of the Journal of Proteomics [50] and Blood Transfusion [51] and in several reviews [52-54]. Current topics, focus on the following analyses: (I) cellular blood constituents or derivatives including haematopoietic stem cells, and blood components derived from plasma or recombinant technology, (II) changes in biological fluids or blood cells under various physiological and pathological conditions (sickle cell anemia), (III) changes that accompany storage and ageing of blood cells, (IV) composition of microparticles released by various blood cells undergoing apoptosis and membrane-remodelling as markers of cell activation or degradation and as transcellular effectors; (V) adverse events associated with transfusions (pro-inflammatory or immunosuppressive effects, TRALI, platelet and vascular endothelial cell « response » by the recipient, release of bioactive mediators, pro-coagulant effect of microparticles, non haemolytic reactions, etc), (VI) alteration pattern of plasma proteins and cell damages caused by pathogen reduction techniques.

Other important applications include monitoring the quality of blood products as part of the quality-control process to check the identity, purity, safety and potency of blood components for better clinical applications.

SELECTED REFERENCES

1. Daniels G. The molecular genetics of blood group polymorphism. Hum Genet 2009; 126:729-742. http://dx.doi.org/10.1007/s00439-009-0738-2
2. Cartron JP. Blood groups : genetics and physiology. ISBT Science Series (Vox Sang) 2010 ; 5:27-45. http://dx.doi.org/10.1111/j.1751-2824.2010.01388.x
3. Anstee DJ. The functional importance of blood group active molecules in human red blood cells. Vox Sang 2011; 100:140-149. http://dx.doi.org/10.1111/j.1423-0410.2010.01388.x
4. Storry JR, Olsson ML. The ABO blood group system revisited: a review and update. Immunohematol 2009; 25:48-59. http://dms.efsra.pagesperso-orange.fr/IH092502.pdf#page=14
5. Avent ND, Reid ME. The Rh blood group system: a review. Blood 2000; 95:375-387. http://bloodjournal.hematologylibrary.org/content/95/2/375.full.pdf+html
6. Le van Kim C, Colin Y, Cartron JP. Rh proteins: Key structural and functional components of the red cell membrane. Blood Rev 2006; 20:93-110. http://www.bloodreviews.com/article/S0268-960X%2805%2900029-9/abstract
7. Westhoff CM. The structure and function of the Rh antigen complex. Semin Hematol 2007; 44:42-50. http://dx.doi.org/10.1053/j.seminhematol.2006.09.010
8. Lo YM, Hjelm NM, Fidler C, Sargent IL, Murphy MF, Chamberlain PF et al. Prenatal diagnosis of fetal RhD status by molecular analysis of maternal plasma. N Engl J Med 1998; 339:1734-1738. http://www.nejm.org/doi/pdf/10.1056/NEJM199812103392402
9. Finning K, Martin P, Summers J, Massey E, Poole G, Daniels G. Effect of high throughput RHD typing of fetal DNA in maternal plasma on use of anti-RhD immunoglobulin in RhD negative pregnant women: prospective feasibility study. BMJ 2008; 336:816-818. http://www.bloodreviews.com/article/S0268-960X%2805%2900029-9/abstract
10. Rouillac-Le Sciellour C, Sérazin V, Brossard Y, Oudin O, Le Van Kim C, Colin Y, et al. Noninvasive fetal RHD genotyping from maternal plasma. Use of a new developed Free DNA Fetal Kit RhD. Transfus Clin Biol 2007;14:572-577. http://www.ncbi.nlm.nih.gov/pubmed/18375165
11. van der Schoot CE, Soussan AA, Koelewijn J, Bonsel G, Paget-Christiaens LG, de Haas, M. Non-invasive antenatal RHD typing. Transfus Clin Biol 2006; 13:53-57. http://www.ncbi.nlm.nih.gov/pubmed/16564727
12. Flegel WA, von Zabern I, Wagner FF. Six years' experience performing RHD genotyping to confirm D- red blood cell units in Germany for preventing anti-D immunizations. Transfusion 2009; 49:465-471. http://dx.doi.org/10.1111/j.1537-2995.2008.01975.x
13. Ribeiro KR, Guarnieri MH, da Costa DC, Costa FF, Pellegrino J, Jr., Castilho L. DNA array analysis for red blood cell antigens facilitates the transfusion support with antigen-matched blood in patients with sickle cell disease. Vox Sang 2009; 97:147-152. http://dx.doi.org/10.1111/j.1423-0410.2009.01185.x
14. Anstee DJ. Red cell genotyping and the future of pretransfusion testing. Blood 2009 ;114:248-56. http://dx.doi.org/10.1182/blood-2008-11-146860
15. Avent, N.D. Large-scale blood group genotyping: clinical implications. Br J Haematol 2009; 144:3-13. http:dx.doi.org/10.1111/j.1365-2141.2008.07285.x
16. Veldhuisen B, van der Schoot CE, de Haas M. Blood group genotyping: from patient to high-throughput donor screening. Vox Sang 2009; 97:198-206. http://dx.doi.org/10.1111/j.1423-0410.2009.01209.x
17. Moulds JM. Future of molecular testing for red blood cell antigens. Clin Lab Med 2010; 30:419-429. http://dx.doi.org/10.1016/j.cll.2010.02.004
18. Denomme GA, Johnson ST, Pietz BC. Mass-scale red cell genotyping of blood donors. Transfus Apher Sci 2011; 44:93-99. http://dx.doi.org/10.1016/j.transci.2010.12.012
19. Avent ND, Martinez A, Flegel WA, Olsson ML, Scott ML, Nogues N, et al. The Bloodgen Project of the European Union, 2003-2009. Transf Med Hemother 2009; 36:162-167. http://dx.doi.org/10.1159/000218192
20. Hashmi G, Shariff T, Seul M, Vissavajjhala P, Hue-Roye K, Charles-Pierre D, et al. A flexible array format for large-scale, rapid blood group DNA typing. Transfusion 2005; 45:680-688. http://dx.doi.org/10.1111/j.1537-2995.2007.01178.x
21. Hashmi G, Shariff T, Zhang Y, Cristobal J, Chau C, Seul M, et al. Determination of 24 minor red blood cell antigens for more than 2000 blood donors by high-throughput DNA analysis. Transfusion 2007; 47:736-747. http://dx.doi.org/10.1111/j.1537-2995.2007.01178.x
22. Denomme GA, Van Oene M. High-throughput multiplex single-nucleotide polymorphism analysis for red cell and platelet antigen genotypes. Transfusion 2005; 45:660-666. http://dx.doi.org/10.1111/j.1537-2995.2005.04365.x
23. Perreault J, Lavoie J, Painchaud P, Cote M, Constanzo-Yanez J, Cote R, et al. Set-up and routine use of a database of 10,555 genotyped blood donors to facilitate the screening of compatible blood components for alloimmunized patients. Vox Sang 2009; 97:61-68. http:/dx.doi.org/10.1111/j.1423-0410.2009.01177.x
24. Dunbar SA. Applications of Luminex xMAP technology for rapid, high-troughput multiplexed nucleic acid detection. Clin Chim Acta 2006; 363:71-82. http://dx.doi.org/10.1016/j.cccn.2005.06.023
25. Karpasitou K, Drago F, Crespiatico L, Paccapelo C, Truglio F, Frison S, et al. Blood group genotyping for Jk(a)/Jk(b), Fy(a)/Fy(b), S/s, K/k, Kp(a)/Kp(b), Js(a)/Js(b), Co(a)/Co(b), and Lu(a)/Lu(b) with microarray beads. Transfusion. 2008; 48:505-512. http:/dx.doi.org/10.1111/j.1537-2995.2007.01555.x
26. Hopp K, Weber K, Bellissimo D, Johnson ST, Pietz B. High-throughput red blood cell antigen genotyping using a nanofluidic real-time polymerase chain reaction platform. Transfusion 2010; 50:40-46. http:/dx.doi.org/10.1111/j.1537-2995.2009.02377.x
27. Palacajornsuk P, Halter C, Isakova V, Tarnawski M, Farmar J, Reid ME, Chaudhuri A. Detection of blood group genes using multiplex SNaPshot method. Transfusion 2009; 49:740-749. http:/dx.doi.org/10.1111/j.1537-2995.2008.02053.x
28. Di Cristofaro J, Silvy M, Chiaroni J, Bailly P. Single PCR multiplex SNaPshot reaction for detection of eleven blood group nucleotide polymorphisms: optimization, validation, and one year of routine clinical use. J Mol Diagn. 2010; 12:453-460. http:/dx.doi.org/10.2353/jmoldx.2010.090222
29. Li Y, Finning K, Daniels G, Hahn S, Zhong X, Holzgreve W. Noninvasive genotyping fetal Kell blood group (KEL1) using cell-free fetal DNA in maternal plasma by MALDI-TOF mass spectrometry Prenat Diagn 2008; 28:203-208. http:/dx.doi.org/10.1002/pd.1936
30. Garritsen HS, Xiu-Cheng Fan A, Lenz D, Hannig H, Yan Zhong X, Geffers R, et al. Molecular Diagnostics in Transfusion Medicine: in capillary, on a chip, in silico, or in flight ? Transfus Med Hemother 2009; 36:181-187. http:/dx.doi.org/10.1159/000217719
31. Grill S, Banzola I, Li Y, Rekhviashvili T, Legler TJ, Müller SP, et al. High throughput non-invasive determination of foetal Rhesus D status using automated extraction of cell-free foetal DNA in maternal plasma and mass spectrometry. Arch Gynecol Obstet 2009; 279:533-537. http:/dx.doi.org/10.1007/s00404-008-0774-5
32. Ansorge WJ. Next-generation DNA sequencing techniques. N Biotechnol 2009, 25:195-203. http:/dx.doi.org/10.1016/j.nbt.2008.12.009
33. Kircher M, Kelso J. High-throughput DNA sequencing - concepts and limitations. Bioessays 2010; 32:524-36. http:/dx.doi.org/10.1002/bies.200900181
34. Zhao J, Grant SF. Advances in whole genome sequencing technology. Curr Pharm Biotechnol 2011; 12:293-305. http://www.ncbi.nlm.nih.gov/pubmed/21050163
35. Dodd R, Kurt Roth W, Ashford P, Dax EM, Vyas G. Transfusion medicine and safety. Biologicals 2009; 37:62-70. http:/dx.doi.org/10.1016/j.biologicals.2009.01.006
36. Epstein JS. Alternative strategies in assuring blood safety: An Overview. Biologicals 2010; 38:31-35. http:/dx.doi.org/10.1016/j.biologicals.2009.10.009

37. Brennan MT, Hewitt PE, Moore C, Hall G, Barbara JA. Confidential unit exclusion: the North London Blood Transfusion Centre's experience. Transfus Med 1995; 5:51-56. http:/dx.doi.org/10.1111/j.1365-3148.1995.tb00185.x
38. Schmidt M, Seifried E. Improving blood donor screening by nucleic acid technology (NAT). ISBT Science Series 2010; 5:219-229. http:/dx.doi.org/10.1111/j.1751-2824.2010.01410.x
39. Mine H, Emura H, Miyamoto M, *et al.* High throughput screening of 16 million serologically negative blood donors for hepatitis B virus, hepatitis C virus and human immunodeficiency virus type-1 by nucleic acid amplification testing with specific and sensitive multiplex reagent in Japan. J Virol Methods 2003; 112:145-151. http:/dx.doi.org/10.1016/S0166-0934(03)00215-5
40. Roth WK, Weber M, Seifried E. Feasibility and efficacy of routine PCR screening of blood donations for hepatitis C virus, hepatitis B virus, and HIV-1 in a blood-bank setting. Lancet 1999; 353:359-363. http:/dx.doi.org/10.1016/S0140-6736(98)06318-1
41. Roth WK, Weber M, Buhr S, Drosten C, Weichert W, Sireis W *et al.* Yield of HCV and HIV-1 NAT after screening of 3.6 million blood donations in central Europe. Transfusion 2002; 42:862-868. http:/dx.doi.org/10.1046/j.1537-2995.2002.00129.x
42. Roth WK, Seifried E. The German experience with NAT. Transfus Med 2002; 12:255-258. http:/dx.doi.org/10.1046/j.1365-3148.2002.00383.x
43. Roth WK, Buhr S, Drosten C, Seifried E. NAT and viral safety in blood transfusion. Vox Sang 2000; 78(Suppl 2): 257-259. http://www.ncbi.nlm.nih.gov/pubmed/10938964
44. Barbara J, Ramskill S, Perry K, Parry J, Nightingale M. The National Blood Service (England) approach to evaluation of kits for detecting infectious agents. Transfus Med Rev 2007; 21:147-158. http:/dx.doi.org/doi:10.1016/j.tmrv.2006.11.007
45. Caygill R.L. Blair G.E., Millner P.A. A review on viral biosensors to detect human pathogens. Analytica Chimica Acta 2010; 681:8-15. http:/dx.doi.org/10.1016/j.aca.2010.09.038
46. Fournier-Wirth C, Jaffrezic-Renault N, Coste J. Detection of blood-transmissible agents: can screening be miniaturized ? Transfusion 2010; 50:2032-2045. http:/dx.doi.org/10.1111/j.1537-2995.2010.02678.x
47. Kim EY, Stanton J, Korber BT, Krebs K, Bogdan D, Kunstman K, Wu S, Phair JP, Mirkin CA, Wolinsky SM. Detection of HIV-1 p24 Gag in plasma by a nanoparticle-based bio-barcode-amplification method. Nanomedicine 2008; 3:293-303. http:/dx.doi.org/10.2217/17435889.3.3.293
48. Myyryläinen T, Talha SM, Swaminathan S, Vainionpää R, Soukka T, Khanna N, Pettersson K.Simultaneous detection of human immunodeficiency virus 1 and hepatitis B virus infections using a dual-label time-resolved fluorometric assay. J. Nanotechnol 2010, 26:8-27. http:/dx.doi.org/10.1186/1477-3155-8-27
49. Brewis IA, Brennan P. Proteomics technologies for the global identification and quantification of proteins. Adv Protein Chem Struct Biol 2010; 80:1-44. http:/dx.doi.org/10.1016/B978-0-12-381264-3.00001-1
50. Special issue of / *Proteomics* 2010 ; 73(3), pp. 361 to 696 « Blood Proteomics », edited by Lello Zolla. http://www.eupa.org/index2.php?option=com_content&do_pdf=1&id=296
51. Special issue of *Blood Transfusion* 2010 ; 8(suppl 3), pp. s1 to s92 « Blood proteomics : applications relevant to transfusion medicine », edited by Lello Zolla. http://www.lumc.nl/con/1040/81028091348221/811071049172556/903020113062557/1002191043402557/
52. Liumbruno G, D'Alessandro A, Grazzini G, Zolla L. How has proteomics informed transfusion biology so far ? Crit Rev Oncol Hematol 2010 ;76:153-172. http:/dx.doi.org/10.2450/2010.002S
53. Pasini EM, Mann M., Thomas AW. Proteomics, the red blood cell and transfusion medicine. ISBT Science Series 2010 ; 5:63-72. http:/dx.doi.org/10.1111/j.1751-2824.2010.01365.x
54. Devine DV, Schubert P. Proteomic applications in blood transfusion: working the jigsaw puzzle. Vox Sang 2011; 100:84-91. http:/dx.doi.org/10.1111/j.1423-0410.2010.01433.x

Gilles Folléa
Liz Pirie
Claudio Velati

10. HOSPITAL AND BLOOD ESTABLISHMENT RELATIONSHIPS AND RESPECTIVE ROLES

10.1 INTRODUCTION

In-hospital patients mostly are at the heart of the transfusion medicine activities, all aimed at providing them with the missing vital blood component(s). This patient-centred vision leads to conceiving all transfusion medicine activities as a "blood supply chain", starting with patients' needs and ending with transfusion of needed blood components to patients. This blood supply chain comprises two main sectors: the hospitals – where transfusion is ordered by clinicians and administered to patients; and the suppliers, from donors to blood components, usually blood establishments (BE).

Cooperation between hospitals and BEs for transfusion related matters is vital to ensure that the end user is satisfied with the products and services provided. The customers of the BEs (or of any blood supplier), which encompass all the actors concerned with transfusion related matters in hospitals (patients, physicians, nurses) should be satisfied with the products and services supplied by the BE.

A common objective for hospitals and suppliers is also to comply with the requirements of the Health Authorities. BEs and hospital blood banks operate in highly regulated environments, and have to comply with the requirements of the National Health Authority. These ensure that patients who require blood transfusion are transfused using the guiding principles of safe, appropriate, effective and optimal use of blood.

Optimizing the use of blood comprises a specific dimension of this particular customer-supplier relationship. To achieve these goals for the patients, interaction between the suppliers and hospital clinicians is essential and each must be aware of the need for continuous improvement.

This chapter aims at briefly describing the main types of hospital–BE relationships in Europe, and illustrating the main principles which should guide cooperation between hospitals and BEs for continuously improving the use of blood and securing the blood supply. We'll first focus on the quantitative aspects of the optimisation of blood use rather than qualitative aspects, which have been excellently presented in a manual coming from the EU funded – EBA promoted study on optimal blood use [1]. The cooperation principles aiming at optimising blood utilisation will be reviewed in the following order: transfusion specialist advice (counselling); training and education; blood utilisation monitoring and benchmarking. Then we'll describe the key mission of blood supply management requiring active collaboration between blood component suppliers and hospitals transfusing blood components to patients.

10.2 MAIN TYPES OF ORGANISATION

There are several different models of relationships between blood providers and hospitals. From the Donor Management in Europe (DOMAINE) survey, issued in 2009 [2], we know that there are also three main types of organisations.

I. In some countries one National BE distributes all the blood components to hospital blood banks in which they are stored and then issued to patients in response to orders from clinicians *(Fig. 1)*;
II. In a few countries the transfusion activities are all included in hospitals that are responsible for all activities from donors to patients *(Fig 2)*;
III. In the majority of countries, the organisation comprises a mix of different types of bodies that could either collaborate or compete.

Competition could occur when there are one or several commercial organisations.

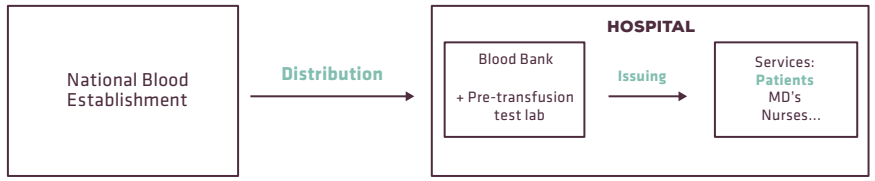


Figure 1: National BE based Blood supply organisation.

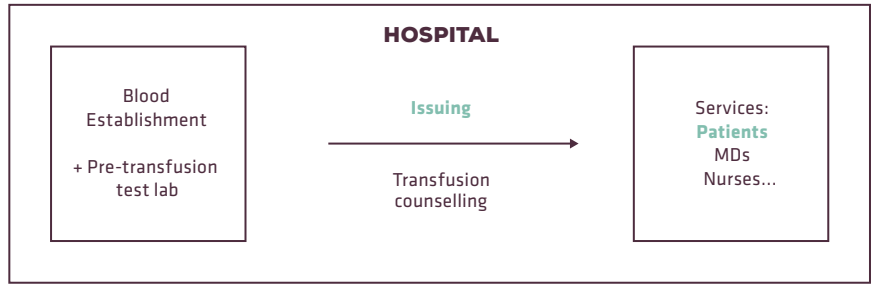


Figure 2: Hospital based Blood supply organisation.

In order to avoid confusion, it is important to use the terminology defined in the EU Directives 2002/98/EC [3] and 2005/61/EC [4].

"Distribution" shall mean the act of delivery of blood and blood components to other blood establishments, hospital blood banks ...It does not include the issuing of blood or blood components for transfusion.

"Issue" means the provision of blood or blood components by a blood establishment or a hospital blood bank for transfusion to a recipient. It is synonym of "delivery", meaning the process in which blood components are transferred to the clinical area where they are to be transfused [1].

Details of the clinical transfusion process vary among the EU member states, but there are essential steps that are common to most. These are shown in Fig. 3, and more detail could be found in the *Manual of Optimal Blood Use* [1].

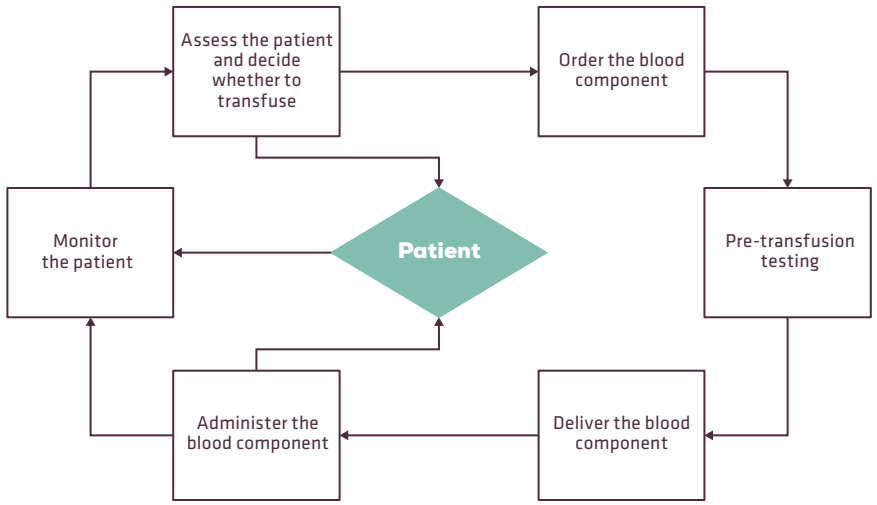


Figure 3: Essential steps of the clinical transfusion process

10.3 OPTIMISING BLOOD COMPONENT UTILISATION

10.3.1 TRANSFUSION SPECIALIST ADVICE (COUNSELLING)

The provision of specialist transfusion advice should be available 24 hours a day, every day of the year, and should cover patient care, such as transfusion support to paediatrics and neonatology and the care of patients with transfusion dependent and immunohaematological disorders. In addition, advice should be provided for transfusion adverse events, existing and new product information, correct use and handling of products, storage procedures, safe and appropriate product use, and advice on consent and risk management. Support with interpretive laboratory reporting can also result in avoidance of inappropriate therapies and shorten hospital stay.

Providing specialist transfusion advice is a team effort and can involve the blood centre consultant, and haematology consultant in addition to the biomedical scientist/technician and transfusion nurse/practitioner. An interesting experience advocating the importance of providing a team approach has been reported [5].

The author wished to empower the blood bank staff to become involved in querying decision-making about the use of blood. The method used was that of taking doctors through agreed algorithms for blood use and providing them with simple decision-support to determine whether the transfusion was justified or not. This study was successful in demonstrating the case for using the expertise of the BE staff to promote appropriate clinical use of blood and assist with monitoring of blood utilisation.

Developing 'aide-mémoires', which give advice on the clinical indications for blood components, and offering written literature such as leaflets and posters to hospital staff are other simple ways of providing practical information and advice around blood transfusion. In summary: providing specialist advice and expertise to clinicians and other healthcare practitioners links with education and can have a major impact on transfusion practices and blood utilisation.

10.3.2 TRAINING AND EDUCATION

Most of the activities of transfusion medicine involve human interventions. As the risk of transfusion therapy relate mainly to human error, education and training is fundamental to every aspect of blood safety.

In some EU countries, blood services and hospitals work in partnership to develop training programmes for professionals involved in blood transfusion. For example, a continuing education programme in transfusion, including an e-learning resource was developed by the Scottish National Blood Transfusion Service *learnbloodtransfusion.org.uk.* The programme is made available to all NHS hospitals in the four UK countries and also the Republic of Ireland. In 2006 there were 32,000 registered users and 29,279 staff had completed module one of the programme using a blended approach of face to face teaching and e-learning.

In some cases, a transfusion nurse specialist/ practitioner employed by the blood centre, but based within the hospital setting in order to support an education programme, was demonstrated to improve the safety and outcomes of transfused patients [6]. Experience in one teaching hospital of having such a nurse in place was that this allowed audits of compliance of ward based nurses with transfusion guidelines followed by dissemination of the education of blood transfusion. A significant improvement in compliance with the national guidelines to over 95% in six out of seven of the key recommendations on best practice was observed 18 months after the initial intervention [7]. This experience has been repeated in other hospitals in the UK and also has been described in France [8].

Another interesting example and evaluation of continuous education in transfusion for professionals in hospitals and clinics has been reported by one BE in France [9]. This blood establishment, in cooperation with the directorate of sanitary and social affairs of region Auvergne-Loire has set up a proximity based continuous education course for more than three years. Their teaching experience concerned 127 individual professionals in eight one-day sessions and 95% gave full appreciation. This experience reached 53% of the public and private hospitals with transfusion services in the concerned region and 90% of hospitals having blood banks remote from the EFS sites. It is a good example of a fruitful cooperation between the BE and the hospitals in one region.

Various techniques used to bring about behavioral changes in the transfusion practices of clinicians, including implementation of transfusion guidelines, audit with feedback, audit with approval, a new transfusion form and education, have been studied. Tinmouth et al. [10] reviewed 19 of these studies, many of which involved both blood services and hospitals. They demonstrated a relative reduction in the number of blood units given or the proportion of patients receiving transfusions in 18 of the 19 studies reviewed.

Another study compared processes of care and outcomes during the two-three months periods before and after the introduction of a multidisciplinary quality improvement intervention [11]. Using the computerized provider order entry, the authors developed an evidence-based decision algorithm for red cell transfusion in adult intensive care units. The implementation of this institutional protocol resulted in a significant decrease in the mean number of red cell transfusions per intensive care unit admission (1.08 ± 2.3 versus 0.86 ± 2.3 units after the protocol, $p < 0.001$). A marked decrease in the percentage of patients receiving inappropriate transfusions (17.7% versus 4.5%, $p < 0.001$) was also observed. A similar protocol was assessed by another team for non-emergency blood transfusions [12]. Although the results seemed to be less successful, the percentage of inappropriate orders was significantly reduced after conventional education.

10.3.3 BLOOD UTILISATION MONITORING AND BENCHMARKING

BEs within EU countries aim to provide a life-saving service by ensuring an adequate supply of safe blood. But in addition, BEs should regularly provide each local hospital with the number of blood products issued and, in return, each hospital should provide the blood centre with the number of actual transfused blood products and the number of unused blood products, either returned to the blood centre or destroyed for any reason.

A recent international survey [13], involving 37 organisations distributing 30 million blood components in 30 countries, has shown that many providers had only one end of the rope: that which is attached to the inventory around the production and distribution processes. Only five responding BEs had received information back from the hospital customers as to the disposition of the products provided giving information as to when, (or even if they were) transfused. This lack of information hampers the ability to drive down the rate of avoidable discards; to determine whether the manner in which the blood provider manages inventory is optimal for patient safety; or to provide ready access to transfusion products.

This information gap was also frequently observed in the EU responding countries despite the EC regulatory obligation for traceability of blood and blood components, from donor to recipient and vice versa [3,4]. In only a few EU countries effective traceability procedures exist covering more than 99.5 % of blood components distributed by the BEs, and then received, eventually stored, and transfused (or unused) in the hospitals. Such traceability allows closely following the blood component transfusion numbers and rates, and rapid alert in the case of significant deviation from the current blood component utilisation and/or guidelines for blood transfusion.

In most countries, the blood component utilisation monitoring is thus limited only to the components distributed by the BEs, and could not cover the subsequent use of these products in the hospitals concerned. Nonetheless, the comparison of this national data for blood use regularly shows a wide inter-country variation. As an example, in 2008 in Europe, the number of red blood cell concentrates (RBC) used per 1,000 population averaged 41 and ranged from 19.5 to 60.0 [14]. This wide variation most probably could not be attributed to large differences in the numbers of patients needing transfusions between countries. It stimulated several countries to benchmark the transfusion practices and blood component utilisation between the hospitals of a given country, and also according to diagnostic related groups (DRG).

The methods used for this specific benchmarking share the following common characteristics. They use existing electronically based registers to describe transfusion practices from local to national levels: hospital, laboratory and administrative patient registers and BE registers. The objective of such an approach is to create a basis for decision, audit, and education regarding best practice; for cost benefit analysis; and for long-term planning of blood collection.

The experiences of Denmark [15,16], Finland [17,18], Belgium [19] and Austria [20], showed that development of a sustainable system that provides information about the clinical use of blood by relating blood utilisation to DRGs, with existing computerized databases, is a powerful tool to monitor the blood utilisation. This approach can help by identifing variations in practice and encouraging clinical review of blood use: all these studies demonstrated high inter-centre variability in RBC transfusions.

Recently this inter-hospital benchmarking has been further refined down to inter-clinician benchmarking of blood use, in association with cost impacts [21]. For example, the RBC transfusion practice among orthopedic surgeons who perform total hip arthroplasties (THAs) has been shown to be highly variable, ranging from a few surgeons who rarely transfuse RBCs to others who routinely transfuse most of their patients with large numbers of RBCs.

Graphs plotting all surgeons who perform THA surgeries by the mean number of RBCs that are transfused per patient help in identifying the surgeons who repeatedly transfuse

large quantities of RBCs and provide specific feedback and education to these "outliers" when they see how they compare to their peers *(Fig. 4)*. Hospital transfusion committee meetings usually offer good opportunities to share this kind of experience, to promote the optimal use of blood, and assess the effectiveness and efficiency of corrective measures.

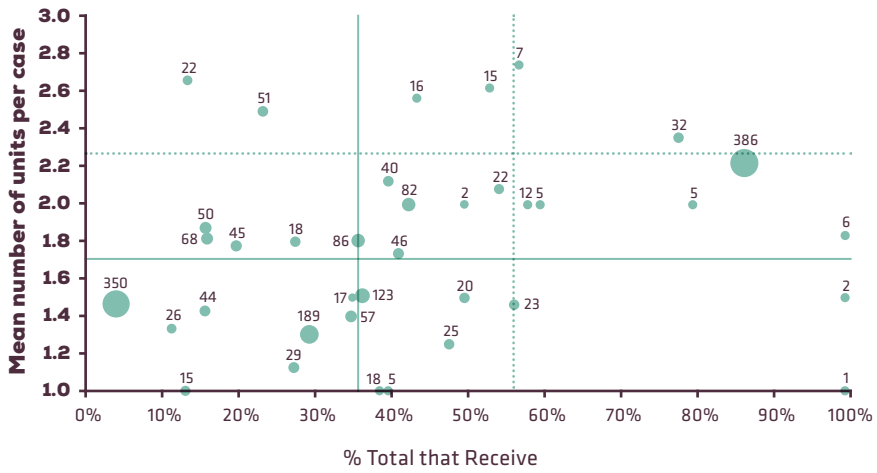


Figure 4: "Bubble graph" plotting surgeons performing total hip arthroplasty surgeries by the frequency with which they transfuse RBCs to their patients and the mean number of RBCs that are transfused per patient (courtesy M. Yazer, ref. 21).

As preoperative anemia is a major risk factor for requiring perioperative allogeneic RBCs, as advocated by World Health Assembly resolution [22], patient blood management is another complementary way to optimise blood use in patients needing elective surgery, with a sufficient length of time between the scheduling of the surgery and its actual date. This permits the diagnosis and, when appropriate, treatment of preoperative anaemia, the frequency of which has been found to be high in general populations, around 27 – 30.4 % [21,23].

10.4 BLOOD SUPPLY MANAGEMENT

Although optimising blood utilisation, as developed above, greatly impacts both patient safety and blood supply security, the blood supply management (BSM) itself is the top mission exerted both by BEs, supplying blood components, and hospitals, storing, delivering, prescribing and transfusing blood components to patients, to make safe blood supply available for patients. This subject has been investigated by a working group of the Committee (partial agreement) on blood transfusion of the Council of Europe (CD-P-TS, TS003 WG), with the objective to help countries to assess and improve their BSM.

Based on a review of the literature and current members' experiences, the CD-P-TS WG confirmed that information on blood component use received back from hospitals was missing for the majority of BEs. This observation and an analysis of the main factors affecting blood supply led the WG to conceive the BSM as a real process with the following steps for RBC supply management:

I. assess past hospital RBC use for patients
II. establish a forecast for overall annual supply (BEs) and use (hospitals)
III. establish annual blood collection program (BEs)
IV. weekly balance RBC use and supply in both BEs and hospitals
V. review and update the patients' RBC needs and their satisfaction.

Starting from this process definition, the TS003 WG elaborated a methodological approach including an analysis based on a self-assessment questionnaire to help countries, and particularly BEs, to identify the gaps between their present situation and an optimal BSM, and elaborate appropriate measures.

A survey using this questionnaire has been performed in the Council of Europe countries and observers (Australia, Canada, New Zealand, and USA). A symposium organised by the Council of Europe with interested parties, in October 2012, has allowed the presentation and discussion of the results of the survey, and initiated the elaboration of recommendations. The follow up work after the symposium will lead to a Council of Europe manual on BSM with the following content: I) finalised results of the survey; II) report of the symposium; III) international "good practices of BSM". The manual is scheduled to be published in 2013.

The main outcomes from the symposium agreed by all participants was to use the survey questionnaire, after a few modifications, as a self-assessment tool, and to present modalities to improve collaboration between hospitals and BEs, as a key factor for continuous improvement of BSM. Sharing expertise on emergent "vein to vein" IT tools will certainly help to improve both collaboration between BEs and hospitals, and optimise the BSM process.

10.5 CONCLUSIONS

Close cooperation between hospitals and BEs is essential to ensure that hospital clinicians are supported to deliver best transfusion care to patients. There is evidence to show that monitoring blood use, transfusion counselling, teaching and education of healthcare professionals can all achieve significant transfusion practice improvements and optimisation of blood utilisation. The use of the tools presented and illustrated in this chapter should be encouraged.

Improving the blood supply management in European countries is another major goal, also requiring more cooperation between BEs, hospitals and end users to guarantee the ongoing development and implementation of innovative solutions for optimising the use of blood to ensure that the blood supply is maintained and improved. In this perspective, developing a BE – hospital partnership will first benefit the patients and also all involved stakeholders, donors, BEs, hospitals, and healthcare providers.

Ultimately these efforts will improve efficiency, the importance of which is growing, due to the current economic constraints met everywhere in Europe.

REFERENCES

1. McClelland DBL, Pirie E, Franklin IM for the EU Optimal Use of Blood Project Partners. Manual of Optimal Blood Use. Scottish National Blood Transfusion Service ed. 2010, p. 1 – 64. ISBN 978-0-9564680-0-0. www.optimalblooduse.eu
2. De Kort W, Veldhuizen I, for the EU Donor Management in Europe Project Partners. Donor management manual. Architecture and infrastructure. 2010, p. 31 – 54. ISBN 978-90-815585-1-8. http://www.domaine-europe.eu
3. Directive 2002/98/EC of the European Parliament and of the Council of 27 January 2003 setting standards of quality and safety for the collection, testing, processing, storage and distribution of human blood and blood components and amending Directive 2001/83/EC. http://eur-lex.europa.eu/LexUriServ/LexUriServ.do?uri=OJ:L:2003:033:0030:0040:EN:PDF
4. Commission Directive 2005/61/EC of 30 September 2005 implementing Directive 2002/98/EC of the European Parliament and of the Council as regards traceability requirements and notification of serious adverse reactions and events. http://eur-lex.europa.eu/LexUriServ/LexUriServ.do?uri=OJ:L:2005:256:0032:0040:EN:PDF
5. Murphy MF. Reducing blood use: how we did it. Transfusion 2007, 47:149S-151S. http://dx.doi.org/10.1111/j.1537-2995.2007.01373.x.
6. Gray A, Buchanan S (2003) Safe and Effective Transfusion: The Role of Nurse Specialist in Scottish Hospitals. Report for Scottish National Blood Transfusion Service, published 1 July 2004. http://www.healthcareimprovementscotland.org/previous_resources/audit_report/transfusion_nurse_specialist.aspx
7. Clark P, Rennie L, Rawlinson S. Quality improvement report: Effect of a formal education programme on safety of transfusions. Brit Med J 2001, 323: 1118-20. http://dx.doi.org/10.1136/bmj.323.7321.1118
8. Tramalloni D, Auperin A, Oubouzar N, Lapierre V. Implication of nurses in transfusion safety: knowledge assessment and practice evaluation at the Gustave-Roussy institute. Transfus Clin Biol 2005, 12: 427-432. http://dx.doi.org/10.1016/j.tracli.2006.02.024
9. Courbil R, Fabrigli P, Odent-Malaure H, Carrières J, Chartier M, Fressy P, Quaranta JF, Garraud O. Evaluation of continuous education in transfusion for professionals in hospitals and clinics. Transfus Clin Biol 200714: 429-32. http://dx.doi.org/10.1016/j.tracli.2007.08.001
10. Tinmouth A, MacDougall L, Fergusson D, Amin M, Graham ID, Hebert PC, Wilson K. Reducing the amount of blood transfused. A systematic review of behavioral interventions to change physicians' transfusion practices. Arch Intern Med 2005, 165: 845-52. http://dx.doi.org/10.1001/archinte.165.8.845
11. Rana R, Afessa B, Keegan MT, Whalen FXjr, Nuttall GA, Evenson LK, Peters SG, Winters JL, Hubmayr RD, Moore SB, Gajic O. Evidence-based red cell transfusion in the critically ill: quality improvement using computerized physician order entry. Crit Care Med 2006, 34: 1892-97. http://dx.doi.org/10.1097/01.CCM.0000220766.13623.FE
12. Rothschild JM, McGurk S, Honour M, Lu L, McClendon AA, Srivastava P, Churchill WH, Avorn J, Cook EF, Bates DW. Assessment of education and computerized decision support interventions for improving transfusion practice. Transfusion 2007; 47: 228-39. http://dx.doi.org/10.1111/j.1537-2995.2007.01093.x
13. Devine DV, Sher GD, Reesink HW et al. International Forum. Inventory Management. Vox Sang 2010, 98: e295-363. http://dx.doi.org/10.1111/j.1423-0410.2009.01252.x
14. van der Poel CL, Janssen MP, Borkent-Raven B. Report on the collection, testing and the use of blood and blood components in Europe in 2008. Committee (Partial Agreement) on Blood Transfusion (CD-P-TS) of the Council of Europe, 2010. http://www.edqm.eu/medias/fichiers/The_Collection_Testing_and_Use_of_Blood_and_Blood_3.pdf
15. Titlestad K, Georgsen J, Jorgensen J, Kristensen T. Monitoring transfusion practices at two university hospitals. Vox Sang. 2001, 80: 40-7. http://dx.doi.org/10.1046/j.1423-0410.2001.00001.x

16. Titlestad K, Kristensen T, Jorgensen J, Georgsen J. Monitoring transfusion practice – a computerized procedure. Transfus Med 2002, 12: 25-34. http://dx.doi.org/10.1046/j.1365-3148.2002.00352.x
17. Palo R, Ali-Melkkilä T, Hanhela R, Jäntti V, Krusius T, et al. Development of permanent national register of blood component use utilizing electronic hospital information systems. Vox Sang. 2006, 91: 140-7. http://dx.doi.org/10.1111/j.1423-0410.2006.00814.x
18. Maki T. Optimizing blood usage through benchmarking. Transfusion 2007, 47:145S-148S. http://dx.doi.org/10.1111/j.1537-2995.2007.01372.x
19. Béguin C, Closon MC, Vandekerckhove P, Baele P. Concentration of transfusion resources on a few pathologies and a few patients: analysis of the comprehensive in-hospital patient database. Transfusion 2007, 47: 217-27. http://dx.doi.org/10.1111/j.1537-2995.2007.01092.x
20. Gombotz H, Rehak PH, Shander A, Hofmann A. Blood use in elective surgery: the Austrian benchmark study. Transfusion 2007, 47: 1468-80. http://dx.doi.org/10.1111/j.1537-2995.2007.01286.x
21. Yazer MH, Waters JH. How do I implement a hospital-based blood management program? Transfusion 2012, 52: 1640-45. http://dx.doi.org/10.1111/j.1537-2995.2011.03451.x
22. Musallam KM, Tamim HM, Richards T, Spahn DR et al. Preoperative anaemia and postoperative outcomes in non-cardiac surgery: a retrospective cohort study. Lancet 2011, 378: 1396–407. http://dx.doi.org/10.1016/S0140-6736(11)61381-0
23. World Health Assembly. Resolution WHA 63.12 on Availability, safety and quality of blood products. 2010. http://apps.who.int/gb/ebwha/pdf_files/WHA63/A63_R12-en.pdf

Christian Seidl
Erhard Seifried

11. QUALITY MANAGEMENT AND INSPEC-TION IN BLOOD TRANSFUSION MEDICINE

11.1 INTRODUCTION

Quality management in blood transfusion is one of the key elements in governing best practice for the blood transfusion service. It takes into account legal requirements, technical aspects, and also respects cost-benefit analysis in order to achieve and sustain optimal blood safety. Quality management of blood establishment requires a broad knowledge of commonly used standards and criteria. In order to safeguard the transfusion process, the task for an optimal quality management system will be to combine these standards and legal requirements and to construct an efficient and smooth running system for the daily routine work.

Throughout European member states the activity profiles of blood establishments have gained considerable complexity covering blood, medicinal products and tissues and cells [1,2]. As a result, in most blood establishments there has been a move away from quality systems (as required by the EU Directives) to 'total' quality management. This movement can be described by the five 'C' (5C) as **C**ompetence, **C**omplexity, **C**ontinuity, **C**omponents and **C**ost-Benefit.

11.2 COMPETENCE AND COMPLEXITY IN TRANSFUSION MEDICINE

The collection, processing, testing, storage and distribution of blood and blood components are steps in delivering life saving blood and blood components for the treatment of patients. The quality and safety of these blood components involves manufacturing standards that have continuously improved during the last decades. These include the development of technical equipment and most sophisticated technologies in testing and manufacturing. When issuing blood and blood components to the patient, decisions must be made regarding giving the right amount of blood to the right patient, at the right time, and under the right conditions, completing the 'vein-to-vein' chain from the donor to the patient.

Blood transfusion medicine includes, therefore, an interdisciplinary approach to develop and sustain the best therapeutic outcome. This includes clinical cooperation between internal medicine, surgery, gynaecology, pediatric medicine, neonatology and many other medical disciplines using blood and blood components. The transfusion service will be involved directly or indirectly in the treatment of patients by offering facilities, e.g. for therapeutic apheresis, or intervention procedures including special components, e.g blood stem cells, granulocytes or donor lymphocytes. The transfusion service offers also clinical diagnostics covering blood group and antibody testing to define the compatibility of the blood issued. This includes also the testing of non-blood group systems relevant for the transfusion of platelets, granulocytes and stem cells.

Furthermore, the laboratory activities cover quality control measurements to test the collected blood units for blood group antigens, preformed antibodies, infectious disease markers and quality indicators. These activities will follow the licence requirements and correct specifications for blood, blood components or cells that have been given by the competent authority to the blood transfusion service or as defined by the EU legislation to the blood establishment [3,4]. Quality control measures will also include additional testing procedures defined by the blood transfusion service in order to safeguard the 'vein-to-vein' process.

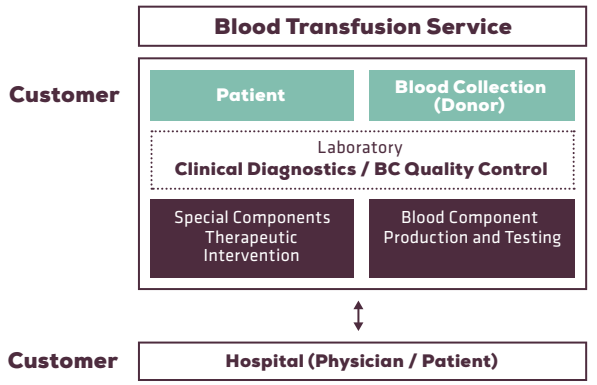


Figure 1: Competence in Transfusion medicine

Table 1: Complexity in transfusion medicine.
Common regulatory and legal aspects involved in the quality management with respect to the activity profile

Level	Common Quality Management Requirements
European	· Blood and blood components: · EU Directive 2002/98/EC and its implementing directives (Directives 2004/33/EC; 2005/61/EC and 2005/62/EC)
	· Medicinal products: EU Directive 2001/83/EC related to EU-GMP
	· Tissue and cells*: EU Directive 2004/23/EC an its implementing directives (Directives 2006/17/EC and 2006/86/EC) · Organ donation and transplantation* Directive 2010/53/EC
International	· Good Manufacturing Practice (GMP) · PIC/S, · EDQM guide (Council of Europe)
National	· Legal requirements by transposition of EU directive to national law. · Additional national legal requirements set by transfusion laws. · Technical standards and medical guidelines (defined by the Ministry of Health, National Board of Physicians), such as the Red Book (UK) or the haemotherapy recommendations (DE) · Reference given by several EU member states to the EDQM guide
Additional*	· ISO accreditation (ISO15189, ISO17025) · ISO certification (ISO9001, ISO13485)
	Additional international standards for tissues, cells and organs: · European Federation for Immunogenetics (EFI), · Joint Accreditation Committee of ISCT and EBMT (JACIE) · Foundation for the accreditation of cellular therapies (FACT)
* depending on the activity profile of the blood establishment	

11.3 CONTINUITY IN TRANSFUSION MEDICINE

The progress made in developing new therapies for curative and palliative treatment has improved public health throughout Europe and the developed countries. This is reflected in an increase in the average life span of people in these regions of the world. Besides many other issues, the challenge to collect enough blood to cover the supply in the 'vein-to-vein' chain has been an important topic in modern quality management of blood transfusion services. The function of quality management is this respect is to coordinate the quality policy in delivering 24-hours-a-day safe blood and blood components in the required amount needed for transfusion and to guarantee self-sufficiency based on non-remunerated donations. This will also address donor management in relation to alterations in population age and mobility.

In particular, continuity in transfusion medicine includes research and development to improve testing procedures, the validation of manufacturing steps, and the cross link between the collection of blood and the preparation of cellular components covering modern aspects of cellular therapies, including gene-based approaches in curing disease.

11.4 COMPONENTS AND COST-BENEFIT

In the last decade, blood establishments have been actively involved in, not only the collection of blood, but also in the collection of blood stem cells and tissue. In European Member States and the developed countries worldwide, advances in the therapeutic use of blood derived cells has led to a considerable increase in the interdisciplinary approaches to using these cell preparations.

Quality and regulatory aspects of these human substances are covered by the European Directives on blood and blood components as well as on tissue and cells, These directives have increased the quality requirements related to the collection, preparation, testing and distribution of these components [3].

Based on good manufacturing standards, blood establishments have taken a key role in these processes [4,5]. The long-standing know-how in donor management, licensing requirements and regulatory aspects for blood, and the setting up of clinical study designs improving the quality of these components, makes new demands on blood establishments involved in translational research. Modern techniques by apheresis, magnetic bead cell sorting and streptamer based selection have increased the potential for selecting various cells subpopulation from peripheral blood. This includes granulocytes for treatment of septical patient, donor lymphocytes for relapse treatment in malignant haematopoetic diseases, blood stem cells for transplantation and the preparation of antigen-specific T cells for infectious diseases, such as CMV. Current challenges in cell based therapies focus on the refinement of donor lymphocyte infusions by the preparation and in-vitro expansion of natural killer (NK) cells, with the potential to support the innate immune response in stem cells transplantation and treatment of malignancies.

The prevention of transfusion related infectious disease has made enormous progress during the last decades, having drastically minimised the risk of hepatitis and HIV Infections. Current challenges such as the need to minimise the risk of bacterial infections and new virus diseases requires the refinement of manufacturing and testing procedures for blood components.

Cost benefit relation with respect to the national budgets for health costs are an important factor for I) the supply of patient with standard blood components and cell preparations, II) in establishing advanced blood, cell and tissue components and III) implementing new approaches for risk minimising of transfusion related infectious diseases.

Quality management is involved in the management of the available resources by optimising processes, training of staff, and setting appropriate quality indicators. Manufacturing of medicinal products from human plasma has demonstrated the importance of collaboration between blood establishments and the pharmaceutical industry. In this context, quality management has the task of preparing the interface in the production processes. In addition, national health insurance systems require transparency of quality processes and the related costs. This has led to an increased demand in accreditation and/or certification of hospitals, and related hospital blood bank and blood establishments [4]. Quality management has to address these requirements by including these standards in the overall quality policy.

11.5 THE EUROPEAN BLOOD LEGISLATION REQUIREMENTS

Directive 2002/98/EC requires that each blood establishment must provide specified information to the competent authority in order to be designated, authorised, accredited or licensed (Article 5 [2]).

The required information related to a quality system is set out in its Annex I, Part B and has to include the following:

1. Documentation, such as an organisation chart setting out staffing responsibilities and reporting relationships
2. Documentation such as a site master file or quality manual describing the quality system based on the principles of good practice
3. Number and qualifications of personnel
4. Hygiene provisions
5. Premises and equipment
6. List of standard operating procedures (SOP) for the following:
   - Donor recruitment
   - Retention and assessment of donors
   - Processing and testing
   - Distribution and recall of blood and blood components
   - Reporting and recording of serious adverse reactions and events.

Directive 2005/62/EC sets out the standards and specifications related to a quality system for blood establishments, based on Directive 2002/98/EC, which will help to ensure the safety of blood throughout the European Union. Recital 3 states that:

'*A quality system for blood establishments should embrace the principles of quality management, quality assurance, and continuous quality improvement, and should include personnel, premises and equipment, documentation, collection, testing and processing, storage and distribution, contract management, non-conformance and self-inspection, quality control, blood component recall, and external and internal auditing*.' (refer to Directive 2005/62/EC)

A quality system for blood establishments is considered to be a key element in the implementation of good practice.

A quality management system is used for the purposes of compliance with regulations and guidelines. It should ensure a systematic approach towards quality and the implementation and maintenance of a quality system. It should involve all persons and processes in the blood establishment *(Annex 1.1)* and lead to a system for the evaluation of processes and continuous quality improvement.

There are no absolute criteria for framing the quality management system. In general, it comprises a number of tools defined by the individual institution, in order to allow for the flexibility to adjust to various regulations and guidelines. In meeting the requirements of Directive 2005/62/EC, individual Member States must take into account their own additional specific regulations and guidelines.

According to Directive 2005/62/EC quality systems for blood establishments should be based on 'good practice' (GP).

'*In order to ensure the highest quality and safety for blood and blood components, guidance on good practice should be developed to support the quality system requirements for blood establishments taking fully into account the detailed guidelines referred to in Article 47 of Directive 2001/83/EC so as to ensure that the standards required for medicinal products are maintained.' (Recital 5)*

Such good practice guidelines for blood establishment are to be developed by the European Commission *(Article 2, Para 2)* taking fully into account the principles and guidelines of Good Manufacturing Practice (GMP)

Annex I requires that the quality system ensures that all critical processes are specified in suitable instructions. The system must be reviewed by management at regular intervals to verify its effectiveness and measures introduced if deemed necessary *(Section 1.1 Para 3)*.

In order to fulfil these requirements, a blood establishment needs to establish a documentation system. It should be organised at different levels of document responsibility with the top level being those 'legislative instruments' (e.g. legislation and laws), regulations and guidelines the individual blood establishment has to follow. These regulations should be incorporated into the quality management system and be reflected throughout the entire quality documentation system.

11.6 COMMONLY USED STANDARDS AND CRITERIA

11.6.1 EU-GMP (EUDRALEX)

The EU-GMP standard (Eudralex) gives detailed and very specific standards for the production of pharmaceutical components [6]. In particular, blood establishments that perform cryoprecipitation or the collection of source plasma for fractionation have established quality management systems that relate to these standards. In some Member States, e.g. Germany, where pharmaceutical legislation applies to all blood components, the EU-GMP standard is mandatory.

Chapters 1 – 9 of the EU-GMP standard give detailed specifications for quality management, personnel, premises and equipment, documentation, production, quality control, contract manufacturers and analysis, complaints and recall and self inspections. In addition, Annex 2 (biological products) and Annex 14 (blood components) of the EU-GMP standard are used as specifications for plasma fractionation.

Both EU-GMP annexes contain requirements and specifications that can be adapted to the production of standard blood components and are used *inter-alia* by blood establishments. In contrast, several standards defined by EU-GMP are derived from specific production, storage and distribution characteristics of pharmaceutical production processes. These include process monitoring of intermediate and bulk products, batch processing records or ongoing stability programmes that monitor the product over its shelf life. These EU-GMP standard requirements are more suited to the manufacturing facilities and production processes for medicinal products by the pharmaceutical industry and are difficult to adapt to standard blood component collection, preparation and distribution as covered by Directive 2002/98/EC.

11.6.2 EDQM - COUNCIL OF EUROPE (CD-P-TS)

The Council of Europe, which has been involved in issues related to blood transfusion since the early 1950s, has long advocated the principle of voluntary non-remunerated blood donation and promoted mutual assistance, optimal use, and protection of the donor and recipient. Complementary to the GMP guidelines, the Council of Europe has developed a 'Guide to the preparation, use and quality assurance of blood components' [Recommendation No. R (95) 15]. The CoE guide is developed under the European Directorate for the quality of medicines and health care (EDQM) and is commonly used among blood establishments throughout the EU Member States. Only in some Member States, e.g. United Kingdom or Germany, do national recommendations surpass the CoE guide in its application for routine work.

Recommendation No. R (95) 15 is updated regularly by the European Committee on Blood Transfusion (CD-P-TS), the Steering Committee in charge of blood transfusion activities for the European Directorate for the Quality of Medicines and HealthCare (EDQM) of the Council of Europe, assisted by leading European experts, keeping it in line with scientific progress and EU legislation. The guide, now in its 16th edition (2010) is divided into two sections: principles and standards [7]. These sections give guidelines for quality systems, principles of validation and qualification, control of equipment, data processing systems, record keeping and statistical process control. The standard section comprises 11 chapters on the following topics:

- quality system for blood establishments
- selection of donors
- blood collection
- blood component preparation, storage and distribution
- component specifications (whole blood, red cell, platelet, plasma, white cell)
- blood components for intrauterine, neonatal and infant use
- autologous pre-deposit transfusion
- blood group serology
- screening for infectious markers
- transfusion practice and haemovigilance

11.6.3 INTERNATIONAL STANDARD ORGANISATION (ISO)

In addition to EU-GMP and the Council of Europe (CD-P-TS) Guide, the International Standard Organisation (ISO) 9000 standards are commonly used by blood establishments in order to comply with European requirements for diagnostic procedures and/or to harmonise their process with the increasing number of ISO9000 certified hospitals [8]. ISO 9001 specifies requirements for a quality management system where an organisation:

- Needs to demonstrate its ability to consistently provide products that meet customer and applicable regulatory requirements.
- Aims to enhance customer satisfaction through the effective application of the system, including processes for continual improvement of the system and the assurance of conformity to customer and applicable regulatory requirements.

Blood establishments using ISO 9001 are required to address the effectiveness of their quality management system. In the context of ISO 9001, effectiveness means the extent to which planned activities are realised and planned results achieved. Further requirements specify the need for continual improvements to the quality management system and not for sporadic or irregular evaluations or campaigns. ISO standards require that the suitability and effectiveness of the quality management system shall be determined. The standards given by ISO 9001 specify requirements for quality management systems that can be used for internal application by organisations, or for certification, or contractual purposes. In this context, ISO 9001 focuses on the effectiveness of the quality management system in meeting customer requirements.

11.6.4 PHARMACEUTICAL INSPECTION CO-OPERATION SCHEME (PIC/S)

PIC/S is the acronym for the Pharmaceutical Inspection Convention / Pharmaceutical Inspection Co-operation Scheme. These are 'instruments' between countries and pharmaceutical inspection authorities, which together provide active and constructive co-operation in the field of Good Manufacturing Practice (GMP). PIC/S has as its mission 'to lead the international development, implementation and maintenance of harmonised (GMP) standards and quality systems of inspectorates in the field of medicinal products.' It aims to do this 'by developing and promoting harmonised GMP standards and guidance

documents; training competent authorities, in particular inspectors; assessing (and reassessing) inspectorates; and facilitating the co-operation and networking for competent authorities and international organisations.' There are currently 41 participating authorities from around the world in PIC/S.

In response to the need for a modification of EU-GMP standards, the expert circle on blood and tissues developed a GMP 'Guide for blood establishments'. This PIC/S GMP Guide intends to facilitate the introduction of GMP standards for blood and apheresis establishments and is used by PIC/S inspectors in assessing the quality management systems of those establishments. Although the Guide follows the structure of the EU GMP standard, it addresses specific processes to be covered in the collection, preparation and distribution of blood and apheresis components, such as blood donor areas, mobile donor sessions, irradiation of blood components or whole blood collection and component preparation.

The PIC/S expert circle on blood and tissues has also developed an 'aide-mémoire' for the inspection of blood establishments [9], a PIC/S guide to the inspection of source plasma establishments and plasma warehouses, site master files for source plasma establishments and plasma warehouses and training guidelines for the qualification of inspectors.

11.6.5 EUBIS STANDARDS AND CRITERIA FOR QUALITY MANAGEMENT AND INSPECTION

The increasing diversity of processes covered by blood establishments, from blood components, pharmaceutical products, to tissue and cells, requires that quality systems need to be flexible in order to adapt to national and European quality requirements. Harmonisation of standards, therefore, would be useful [13]. However, this has to take into account the different legal requirements of the European Union for pharmaceutical products, blood components and tissues and cells. In addition, despite transposition of EU Directives to the Member State level, national laws may require additional modifications for quality management systems.

The European Commission has, therefore, co-funded two activities under the Public Health Programme related to the development of standards and requirements for quality management systems aimed to assist the implementation of the European blood legislation [10-12]:

- The EU-Q-Blood-SOP
- The EuBIS standards and criteria for inspection

The experts involved in these projects are from 19 European Members States representing blood establishments, governmental institutions and competent authorities and have linked their activities to the European Blood Alliance, the Pharmaceutical Inspection Co-operation Scheme (PIC/S) and through its experts to the EDQM Council of Europe (CD-P-TS).

In order to assist the implementation of the European blood legislation, three manuals have been developed. The EU-Blood-SOP manual summarised the principles required for a document system. It contains common requirements for standard operating procedures (SOP) and gives EU template formats as well as practical guidance on how to write an SOP [14]. The EuBIS manual and training manual has been developed to define quality management requirements based on the European blood legislation and to assist for self-inspections and regulatory inspection in order to verify the implementation of the standards required [15].

The EU-Blood-SOP manual gives a methodology for creating an SOP which comprises the relative basic quality elements [16]. It is intended to set out a practical template for the preparation of SOPs and aims to assist blood establishments in preparing for governmental inspections under blood legislation. It could also be used to adapt existing procedures to comply with current EU requirements.

The SOPs are integrated in a documentation system that should be organised at different levels of document responsibility with the top level being those 'legislative instruments' (e.g. legislation and laws), regulations and guidelines, which the individual blood establishment has to follow. These regulations should be incorporated into the quality management system and be reflected throughout the entire quality documentation system.

A description of the quality system itself should be presented in the document level directly below. Documentation on the manual and/or site-master file (See Definitions) has to be in accordance with Article 11 [1] of Directive 2002/98/EC (Annex I, Part B, indent 2). In addition, standard operating procedures (SOPs) have to be prepared by the blood establishment (Annex I, Part B, indent 6). These SOPs are an important part of the quality system and have to cover all the establishment's critical activities *(Figure 2)*.

In preparing the site master file and the SOPs, the blood establishment needs to address the main aspects of the quality system standards and specifications set out in the Annex of Directive 2005/62/EC:

- General Principles (Part 1)
- Personnel and Organisation (Part 2)
- Premises (Part 3)
- Equipment and Materials (Part 4)
- Documentation (Part 5)
- Blood collection, testing and Storage (Part 6), including
  6.1 Donor Eligibility, 6.2 Collection, 6.3 Laboratory testing, 6.4 Processing and validation, 6.5 Labelling, 6.6 Release of blood and blood components
- Storage (Part 7)
- Contract Management (Part 8)
- Non-Conformance (Part 9), including
  9.1 Deviations, 9.2 Complaints, 9.3 Recall, 9.4 Corrective and preventive actions
- Self-inspection, audits and improvements (Part 10)

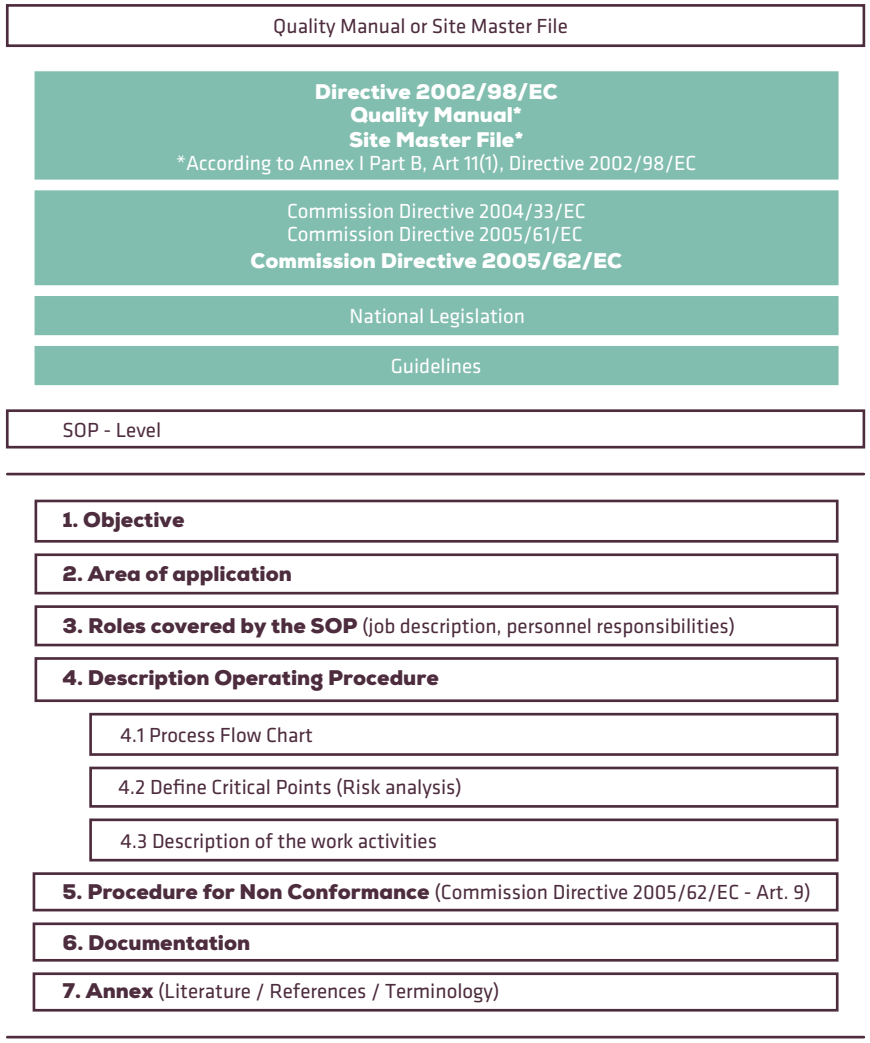
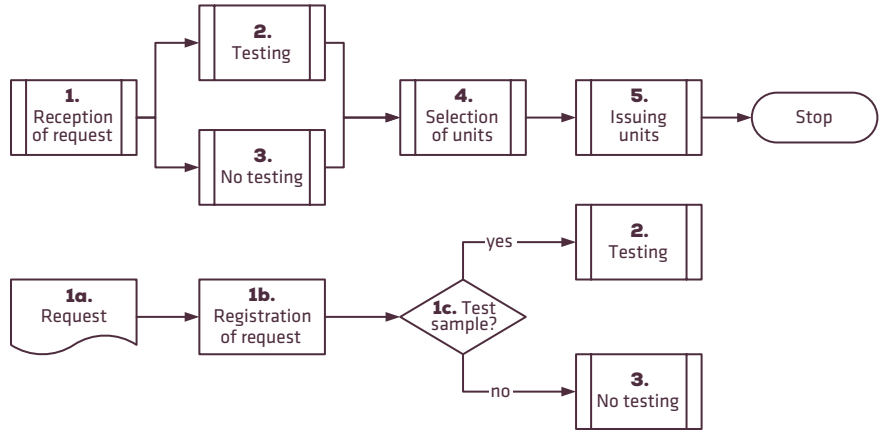


Figure 2: Schematic presentation of the minimum list required by an SOP

In order to ensure standardised practice across the blood establishment, it is advisable to introduce general procedures to describe common processes. These procedures should cover operational activities (e.g. sample receipt, collection, etc.), support services (e.g. human resources, etc.) and management processes (e.g. objective setting, non-conformances, internal audit, etc.).

Flow-Chart for testing request for blood components



Using the example in *figure 3.3.1*, this could be done as follows:

Procedure		
Step	**Action**	**Responsibility**
1	Receive the request	technician
1a	Check if the request is complete and valid · address of the customer · type of test requested · testing material and labelling	
1b	Register the sample information in your laboratory information system (LIMS)	technician
1c	If all information is complete proceed to step 2; if the request/test material/sample identification is incomplete go to step 3	
2	Start to perform the analytical test	technician
3	No testing performed. Document the type of non conformance and return relevant information to the customer	technician + physician

Figure 3: Example of a flow chart using international symbols to describe the testing request for blood component.

Writing of an SOP very often requires the interaction of different users / departments involved in the processes described *(Figure 3)*. Flow charts are an ideal way to describe a process step-by-step, including the critical decision points. Inclusion of the responsible persons for those decision points defines the action performed under practical work conditions and ensures that best practice is followed throughout the various processes performed by blood establishments.

Very importantly, proper training of the responsible staff using the SOP is mandatory. An SOP is a compulsory instruction. If deviations from an established SOP are necessary, the entire process should be amended appropriately and the change(s) fully documented. This documentation should include a description of the corrective actions and a clear identification as to who had authorised them.

Quality management and inspection standards and criteria have been further defined by the EuBIS manual and training guide *(Figure 4)*. The EuBIS manuals contain principal requirements for the self-inspection process of blood establishments and common standards, and criteria for regulatory inspection performed by competent authorities. The training guide is developed based on the quality directive 2005/61/EC including the directive 2002/98/EC and the directive 2004/33/EC and 2005/62/EC [15].

In order to facilitate the implementation of common requirements for quality management and technical aspects in the collection, manufacturing, testing, distribution and storage of blood and blood components the EuBIS training guide gives cross-reference to the EU-GMP standards, the PIC/S GMP for blood establishments and the EDQM (CoE) Guide. By cross-referencing the relevant quality requirements to Directive 2005/62/EC, commonalities between these standards can be identified.

The EuBIS manual comprises common European standards and criteria used for the process of inspection and self-inspection of blood establishments [17].

There are separate sections on these topics *(Chapter 4 'Self-inspection' and Chapter 5 'Inspection by competent authority')* including chapters on the conduct of an inspection *(Chapter 6)*, the inspection procedures after the inspection *(Chapter 7)* and the evaluation of the inspection system *(Chapter 8)*. The manual contains in its Annex a Site-master-file for blood establishments and an inspection report format with requirements commonly used by competent authorities.

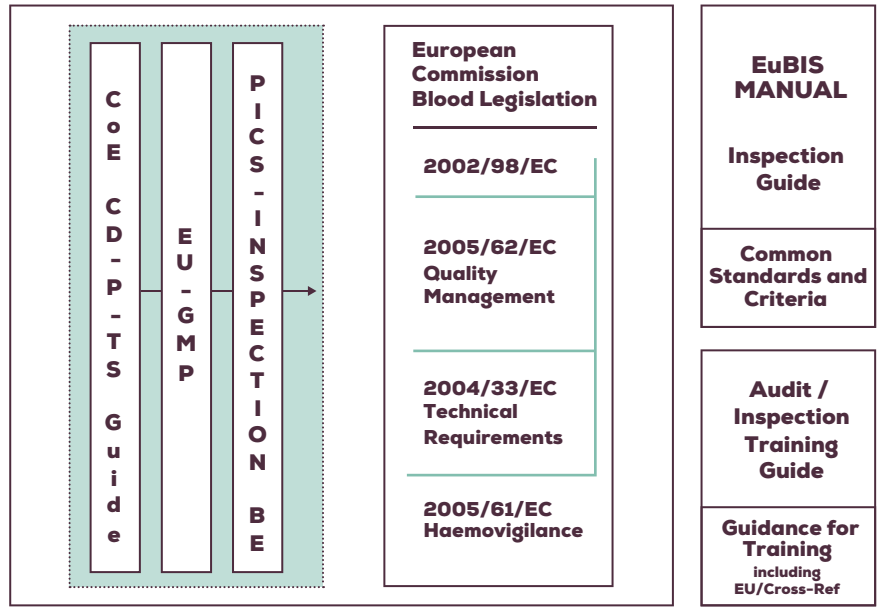


Figure 4: The EuBIS Project expert circle developing a manual for common European standards and criteria for the inspection of blood establishments (Inspection guide) for good practice following the EC blood legislation. The manual is supplemented by an audit / inspection – training guide on the relevant aspects to be addressed during the inspection process including cross-references for common European standards and criteria for quality management systems of blood establishments.

The EuBIS training guide is complementary to the EuBIS manual and covers requirements applicable to blood establishments in the inspection process [18]. *Chapter 3* of the Inspection training guide is structured in the same order as the requirements set out in the Annex to Directive 2005/62/EC *(Section 3.2 – 3.9)*. In addition, it includes requirements in *section 3.10* on Traceability and notification of serious adverse reactions and events (following Directive 2005/61/EC) and on Information technology (IT) in *section 3.11*.

Each section contains a description of the inspection criterion and example evidence that should be obtained during the inspection to demonstrate compliance. Each inspection criterion is identified by an individual number (criterion No.), a reference to the applicable standard(s) and identifies the sub-process or control point.

The EuBIS training guide is complemented by documents (Annex I and Annex II) that are commonly used during the self-inspections, a template for a self-inspection audit trail and a self-inspection report. These documents facilitate the harmonisation of inspection processes and should assist in the documentation of observed deviations.

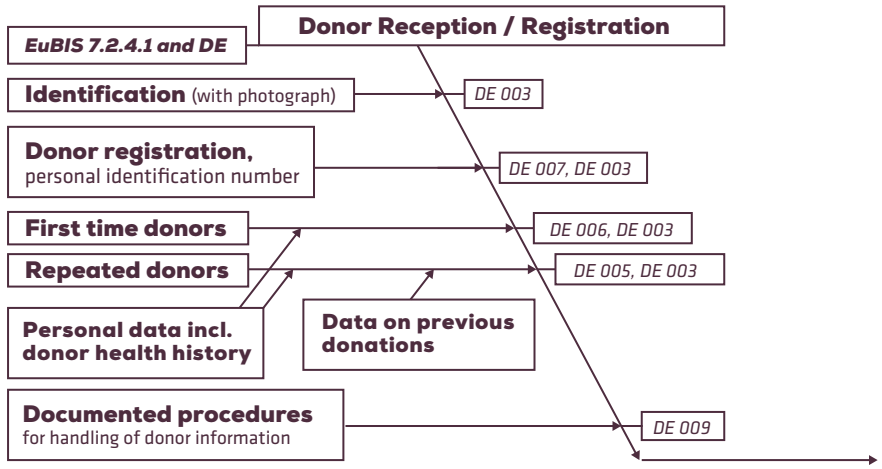


Figure 5: Simplified example of a risk based 'fish-bone' diagram for the process of 'donor reception / registration'. The diagram contains references to the criterion numbers (DE = donor eligibility) as defined by the EuBIS training guide and the chapter 7.2.4.1 of the EuBIS manual.

The structure of the EuBIS training guide follows critical aspects of quality management to be addressed in order to achieve good / best practice. For each of the quality related critical points, a criterion description, examples, evidence and references to relevant international standards (GMP, PIC/S, CoE / EDQM CD-P-TS) and legislative requirements based on the European blood directives are given.

Using 'fishbone' diagrams, quality indicators for risk assessment can be easily developed in a systematic fashion covering all relevant activities of a blood establishment. The fishbone diagram is an analysis tool that provides a systematic way of looking at effects and the causes that create or contribute to those effects. Because of the function of the fishbone diagram, it may be referred to as a cause-and-effect diagram and can be used to set quality indicators. Quality indicators are set to monitor the specifications of blood products. They should be easy to sample and effective to stimulate actions for improvement resulting in a 'parametric release' of blood components. An example of a EuBIS training guide based risk analysis using a fish-bone diagram is given in *Figure 5*.

REFERENCES

1. Robinson EAE: The European Union Blood Safety Directive and its implications for blood services. Vox Sanguinis 2007; 93, 122-130. http://dx.doi.org/10.1111/j.1423-0410.2007.00942.x
2. European Blood and Tissue Directives are available in English or translations covering the European languages under the European Commission Portal, www.europa.eu or directly to the section of Public Health, Area of blood tissue and organs at http://ec.europa.eu/health/blood_tissues_organs/policy/index_en.htm
3. Seitz R, Heiden M, Nübling CM, Unger G, Löwer J: The harmonization of the regulation of blood components: a European perspective. Vox Sanguinis 2008; 1-10. http://dx.doi.org/10.1111/j.1423-0410.2007.01026.x
4. C Seidl, M O'Connell, F Delayney, P van Krimpen, A McMillan Douglas, M Gorham, M Letowska, L Sobaga, J de Wit, E Seifried on behalf of the Project's participant. European best practice in blood transfusion: improvement of quality-related processes in blood establishments. Vox Sanguinis, ISBT Science Series 2007, Volume 2 (1), p143-9. http://dx.doi.org/10.1111/j.1751-2824.2007.00096.x
5. Slopecki A, Smith K, Moore S: The value of good manufacturing practice to a blood service in managing the delivery of quality. Vox Sanguinis 2007; 92, 187-196. http://dx.doi.org/10.1111/j.1423-0410.2006.00878.x
6. European Goood Manufacturing Practice (GMP) standard. Eudralex – The rules Governing Medicinal Products in the European Union. European Medicines Agency (EMEA). Available at http://ec.europa.eu/health/documents/eudralex/vol-4/index_en.htm
7. Council of Europe: Guide to the Preparation, Use and Quality Assurance of Blood Components, 16th edn. Strasbourg, France, Council of Europe Publishing, 2010. http://www.centronazionalesangue.it/sites/default/files/guida_edqm_16_edizione.pdf
8. International Standard Organisation (ISO) and European Committee for Standardisation (CEN) documents: ISO EN 9000; ISO EN 9001; ISO EN 9004:2000; ISO En 17025; ISO EN 13485; ISO EN 15189:2003. ISO EN Documents are available from the National Members of CEN. A list of these members is available through the homepage of CEN (www.cen.eu). http://www.cen.eu/boss/Documents/Guidelines2004finalversion.pdf
9. Pharmaceutical Inspection Convention/ Pharmaceutical Inspection Co-operation Scheme (PIC/PICS) PIC/S GMP Guide for blood establishments, PE-005-3, 25. September 2007
10. The European Blood Inspection Project (EuBIS) has been co-funded under the Public Health Programme of the European Commission, EuBIS homepage www.eubis-europe.eu.
11. Community action in the field of public health (2003-2008) (http://ec.europa.eu/health/index_en.htm). Work plan 2005 and work plan 2006 following the Decision No 1786/2002/EC of the European Parliament and of the Council of 23 September 2002 adopting a programme of Community action in the field of public health (2003-2008), Official Journal of the European Union, L 271, 9/10/2002. http://eur-lex.europa.eu/LexUriServ/LexUriServ.do?uri=OJ:L:2002:271:0001:0011:EN:PDF
12. EQUAL Blood quality. EU-Blood SOP manual assisting blood services to implement or expand their standard operating procedures (SOPs). http://www.equal-blood.de/objectives.php
13. Seitz R. The European Blood Directive. Its role in blood safty. Dev. Biol. (Basel), 2007, 127: 147-52. http://www.ncbi.nlm.nih.gov/pubmed/17486887
14. Seidl C, Brixner V, Müller-Kuller T, Sireis W, Costello P, Cermakova Z, Delanay F, Douglas AM, Nightingale M, van Galen JP, O'Conell M, Siegel W, Sobaga L, de Wit J, Seifried E. Levels of quality management of blood transfusion services in Europe. Vox Sanguinis, ISBT Science Series 2008, Vol 3(1): 54-62. http://dx.doi.org/10.1111/j.1751-2824.2008.00182.x
15. C. Seidl, HM Huber, T. Müller-Kuller, W. Sireis, A. Aquilina, K. Barotine-Toth, J.M. Cardenas, J. Ceulemans, Z. Cermakova, JP Jansen van Galen, G. Grazzini, B. Hinloopen, M. Heiden, M. Nightingale, S. Pupella, L. Sobaga, F. Teskrat, J. deWit, E. Seifried. Blood collection and processing. Quality guidelines and standards reflecting common best practice standards referring

to the EuBIS manual and guide. Vox Sanguinis, ISBT Science Series 2012. Vol. 7(1): 16-23. http://dx.doi.org/10.1111/j.1751-2824.2012.01612.x

16. The Eu-Q-Blood-SOP manual is available as e-book through the EuBIS homepage at http://www.eubis-europe.eu/eu-q-blood_manual_details.php) or can be ordered as PDF (http://www.eubis-europe.eu/blood_manual_ordering.php)
17. The EuBIS manual is available as e-book through the EuBIS homepage at http://www.eubis-europe.eu/eubis_manual_details.php) or can be ordered as PDF (http://www.eubis-europe.eu/blood_manual_ordering.php)
18. The EuBIS inspection/audit training guide is available as e-book through the EuBIS homepage (http://www.eubis-europe.eu/eubis_training_material.php) or can be ordered as PDF (http://www.eubis-europe.eu/blood_manual_ordering.php)

ACKNOWLEDGEMENTS

The authors would like to thank the contributions made by the EuBIS Academy partners Alex Aquilina, National Blood Transfusion Service, Valetta, (Malta), Klara Baroti-Toth, National Blood Transfusion Service, Budapest, (Hungary), Jose Manuel Cardenas, Blood Transfusion Center Bilbao and Elena Moro Ministry of Health - MSSSI, Madrid, (Spain); Jan Ceulemans and Philippe Vandekerckhove, Red Cross Flanders, Mechelen, (Belgium), Jan Peter Jansen van Galen, Boudewijn Hinloopen and Jeroen de Wit, Sanquin Blood Supply Foundation, Amsterdam, (The Netherlands), Giuliano Grazzini and Simonetta Pupella, Centro Nazionale Sangue, Ministry of Health, Rome, (Italy), Margarethe Heiden, Helga Marie Huber and Rainer Seitz, Paul-Ehrlich Institute Ministry of Health, Langen, (Germany); Fewzi Teskrat, Agence Nationale de Sécurité du Médicament, Paris St. Denis, (France), Mark Nightingale, National Health Service Blood and Transplant, Southhampton, (United Kingdom) to this chapter of the EBA book.

EuBIS has been co-funded under the grant agreement 2006202 by DG Sanco, European Commission (www.eubis-europe.eu); the EuBIS academy is supported by the European Blood Alliance (EBA) and co-operates with the Pharmaceutical Inspection Co-operation Scheme (PIC/S).

We would like to acknowledge the valuable contribution of participating and collaborating experts to EuBIS as follows: Stefaan Van der Spiegel, Isabel Holmquist, Silvia Villanueva, Hana Prerovska (EC, European Commission, DG SANCO, Brussels, Belgium); Dirk Meusel (European Executive Agency for Health and Consumers (EAHC), Luxembourg); Harald Schennach, TILAK; Gerhard Lanzer, UBT, Johann Kurz, MoH (Austria); Philippe Vandekerckhove and Jan Ceulemans, Red Cross Flanders (Belgium); Svetla Bakalova and Andrey Andreev, NBT (Bulgaria); Zoe Sideras MoH (Cyprus); Christina Palvad, DMA (Denmark); Tatjana Plahhova, NEBS (Estonia); Alain Beauplet and Leslie Sobaga, EFS; Fewzi Teskrat, ANSM (France); Walid Sireis, GRCBWH; Margarethe Heiden, Helga Marie Huber and Rainer Seitz, PEI (Germany); Klara Baroti-Toth and Eszter Miskovits, HNBT (Hungary); Ina Hjalmarsdottir and Sveinn Gudmundsson BTS (Iceland); Mary O'Connell, IBTS; Patrick Costello, IMB (Ireland); Giuliano Grazzini and Simonetta Pupella, CNS (Italy); Anita Daugavvanaga, MoH (Latvia) Brigitte Batliner, MoH (Liechtenstein); Frances Delaney (Luxembourg), Miriam Vela and Richard Zammit MoH (Malta); Alex Aquilina, MBTS (Malta), Jan Peter Jansen van Galen, Boudewijn Hinloopen and Jeroen de Wit, Sanquin (The Netherlands); Magdalena Letowska, Jolanta, Antoniewicz-Papis and Elżbieta Lachert IHBT (Poland); Margarida Amil, formerly ASST (Portugal); Carmen Tatu, FMP and Simona Parvu, MoH (Romania); Irena Razborsek, SBTS; Matej Breznik and Andrijana Tivadar, JAZMP (Slovenia); Jose Manuel Cardenas, CVTB and Elena Moro, MoH – MSSSI (Spain); Monica Axelsson and Torsten Mossberg, NBHW (Sweden); Ian Rees, MHRA; Mark Nightingale and Alan Slopecki NHSBT, Angus MacMillan Douglas (United Kingdom); The Council of Europe – European Directorate for the Quality of Medicines and HealthCare (EDQM), Jean-Marc Spiesser and Marie-Emmanuelle Behr-Gross (France); The EUSTITE Project, Deirdre Fehily (Italy); The European Blood Alliance (EBA), Gilles Folléa (The Netherlands); The EU Optimal Use of Blood Project, Ian Franklin and Brian McClelland, Scotland (United Kingdom); The DOMAINE Project, Wim de Kort, (The Netherlands); JACIE, Eoin McGrath (Spain).

Markus Müller
Claudio Velati
Veřa Novotný
Alex Aquilina
Erhard Seifried

12. MEDICAL EDUCATION AND TRAINING FOR BLOOD TRANSFUSION IN EUROPE

12.1 SUMMARY

Basic training in transfusion medicine during medical school and continuous medical education afterwards are the cornerstones of a safe, sufficient and sustainable supply of blood components, cells and tissues, as well as for the achievement of excellence in haemotherapy.

Transfusion medicine is a clinical discipline comprising pharmaceutical, medical, technical, scientific, organisational and quality management skills. This multifaceted speciality is closely related to, and requires, good laboratory practice, manufacturing and cell processing knowledge and practice, as well as thorough clinical training.

Supportive haemotherapy is crucial to the following disciplines: haematology, pediatrics, heart, vascular and visceral surgery, traumatology and orthopedics, anesthesiology and emergency medicine, urology, gastroenterology as well as gynecology and obstetrics. Between a third and a half of all interventions in these fields would not be possible without a steady supply of blood components and human plasma derived products. In addition, the following components are harvested, processed, tested and distributed by modern transfusion medicine institutions: haematopoietic stem cells (HSC) either from bone marrow aspiration or via apheresis from the peripheral blood of a granulocyte-colony stimulating factor (G-CSF) stimulated donor, as well as cells and tissues.

Diagnostics comprise not only immunohaematology and blood group serology, but also pathogen testing and immunogenetics in donors and patients. Solid organ transplant organisation relies on HLA diagnostics, crossmatching, blood group serology, and testing for viral or bacterial infections of the donor. These services are provided mostly by transfusion medicine departments.

This backbone of modern medicine is becoming more and more essential in a highly regulated European Union. Education and training in the field of transfusion medicine comprises three different aspects.

First of all, both medical students and residents in their first clinical years must learn the basics of immunohaematology, transplantation immunology and haemotherapy. Transfusion medicine and haemotherapy should form a part of continuous medical education (CME) for experienced practitioners as well.

Second, a qualification in transfusion medicine for medical doctors, who have received their degrees, including a fellowship programme in the field, is needed to provide specialists capable of covering all aspects of modern transfusion medicine and haemotherapy mentioned above.

Third, nurses and laboratory scientists involved in daily diagnostics and haemotherapy must have thorough knowledge of both theory and practice in the field.

While teaching the basics of immunohaematology, immunogenetics and haemotherapy is becoming an integral part of the medical curricula in an increasing number of European countries, transfusion medicine is still not a distinct medical speciality in most member states of the European Union. In addition, a clear-cut qualification programme for nurses and laboratory scientists in the field is still insufficient in most European countries.

The European Network of Transfusion Medicine Societies (Euronet-TMS) and the European Blood Alliance (EBA) have jointly initiated an update on the current situation in transfusion medicine regarding specialisation and training. Following the work of Norbert Müller, Philippe Rouger, Claudio Velati and others, the authors will discuss the current status for a medical specialisation in Europe and propose a step-by-step approach towards a curriculum for graduate advanced medical training. Such a fellowship is closely related to existing advanced medical training programmes in those countries which already offer a specialisation in transfusion medicine. Moreover, such an approach must be flexible enough to accommodate existing as well as planned curricula in different European countries.

This proposal should be discussed on a European level, become accepted by EBA and Euronet-TMS, and put into action in those countries where the national scientific societies for transfusion medicine and the responsible authorities accept such an approach. Finally, acceptance by the European Commission should be sought.

Training courses and curricula for both nurses and laboratory scientists in transfusion medicine are a second issue currently pioneered by colleagues in the United Kingdom and a few other countries. In the medium term, a pan-European approach is deemed necessary here as well.

A long-term aim of the joint Euronet-TMS / EBA initiative is to establish transfusion medicine as a specialisation in the EU, possibly also in close cooperation with the ongoing efforts of the International Society of Blood Transfusion (ISBT), the World Health Organisation (WHO), and several national societies for transfusion medicine.

Transfusion medicine and haemotherapy have evolved into complex medical disciplines comprising a broad field of subspecialties such as immunohaematology, blood component production, haemapheresis and haemostaseology. Transfusion medicine is thus an important stand-alone qualification with interfaces to analytical laboratory medicine, pharmaceutical production and clinical disciplines such as internal medicine, anaesthesiology and surgery. Physicians specialising in transfusion medicine are valuable and competent partners for these related disciplines when it comes to safe, effective and tailored haemotherapy. In addition, teaching medical students, as well as offering continuous medical education and training to colleagues, nurses and laboratory scientists in all aspects of modern transfusion medicine, helps also to achieve excellence in clinical haemotherapy.

12.2 BACKGROUND

Over the past few decades, the fields of activity and knowledge in transfusion medicine have evolved into an array of diverse areas and sub-specialities including immunohaematology, blood component production, haemapheresis, pathogen detection, methods of cell and tissue collection and manipulation, cell conservation and banking, transplant immunology and haemostaseology. Physicians in most clinical disciplines require at least basic, but more often advanced knowledge in these fields to meet the requirements of modern medicine. In addition, specialist physicians in transfusion medicine are valuable and competent partners for these related disciplines when it comes to safe, effective and tailored haemotherapy. Transfusion medicine is thus an important qualification with interfaces towards analytical laboratory medicine, pharmaceutical production, and clinical disciplines such as internal medicine, anaesthesiology or surgery.

Specifications on the educational and training requirements for persons working in transfusion medicine are not well defined. The only recommendations found in the publications of the European Union are that staff involved in donor recruitment, blood collection and component preparation and laboratory testing should be trained according to their tasks, including good manufacturing practice. They should have successfully finished an educational programme specific to their tasks, with regular refresher courses. Attended courses should be recorded in the personal files of the workers involved.

There are no specific recommendations for staff working in hospitals. Education and training may vary between countries and even within countries. As the knowledge required in the whole sequence leading to blood transfusion as a therapeutic measure is complex, transfusion medicine must be recognised as a speciality.

In addition, all hospital workers involved in blood transfusion should be educated and trained accordingly. This includes all transfusing physicians, nurses, students and laboratory scientists.

In European countries, the organisation of the blood transfusion service may differ along with the qualifications of workers in the field of blood transfusion. A way to develop an educational programme is to specify the different tasks of the workers and staff members and, according to the tasks, define the educational background and training required to perform their tasks according to good manufacturing practices (GMP) and good control practices (GCP).

STAFF IN TRANSFUSION MEDICINE IN DIFFERENT EUROPEAN COUNTRIES

- There is quite a heterogeneous picture regarding employees in transfusion medicine facilities in different European countries as well as within specific countries. The qualifications of staff working in blood transfusion services and in transfusion medicine may vary significantly from country to country.
- In blood establishments, some staff are trained on the job according to their specific tasks.
- Physicians in blood establishments involved with donation have a medical degree often followed by on-the-job training focusing on donor safety and the potential risks to the recipient. Staff involved in blood sampling, blood collection or apheresis can be nurses, or are otherwise trained on the job.
- Laboratory testing is performed by laboratory scientists often under supervision by a senior scientist, chemist or a medical specialist.
- Processing of blood components is often performed by staff trained on the job.
- The indication for transfusion of blood components in the treatment of patients is in the hand of physicians and medical specialists from various disciplines. A combined knowledge of blood components, their specifications, effects and side effect in relation to the need of the individual patient is required for physicians working in transfusion medicine.

ANALYSIS OF THE CURRENT STATUS REGARDING QUALIFICATION AND SPECIALIST MEDICAL TRAINING IN EUROPE

As depicted in annex 1, a detailed questionnaire regarding qualification and special medical training in transfusion medicine was sent out using the Euronet-TMS and EBA platform.

Fourteen countries in Europe returned the questionnaire. In four countries, transfusion medicine is a full specialisation including a specific curriculum and a formal advanced medical training programme. After a successful curriculum and a final exam, a diploma is issued. This medical speciality is accepted by the respective national medical association. Transfusion medicine is a sub-speciality within internal medicine, haematology or clinical immunology in another four European countries.
When former analyses are taken into account [1,2], a somewhat similar picture is seen.

Norbert Müller [1] in his analysis published in 2005 reported that transfusion medicine was recognised in seven out of seventeen European countries as an official medical speciality. We also found seven out of fifteen European countries in our 2006 analysis having a national qualification in transfusion medicine [2]. Our 2006 analysis combined countries with a speciality either from medicine or from biology as well as countries offering a sub-speciality in transfusion medicine *(see also table 1)*.

All three analyses do not include entirely the same group of countries, which accounts for the small differences in the absolute numbers mentioned above. However, out of about half of the member countries of the EU answering the different questionnaires, about 50 percent already have an established and at least minimally structured post-graduate medical training leading to either a full specialisation in transfusion medicine or a sub-specialisation within other medical disciplines. The question remains, as to whether professional bodies in the other half of the EU member states are either not interested in a common European qualification in transfusion medicine, or whether the wrong contact persons in those countries have been approached.

ONGOING NATIONAL EFFORTS TO ESTABLISH A SPECIALITY IN TRANSFUSION MEDICINE

In our analysis of the 14 European countries answering the questionnaire *(annex 1)*, we asked respondents from countries, where transfusion medicine currently is not established as a medical specialisation, whether there are ongoing national efforts to establish such a speciality.

In countries having established a sub-speciality within other disciplines, there is no ongoing activity in this field, as expected. Only two out of six countries, which have neither established a speciality nor a sub-speciality, report ongoing activities here.

In contrast, two countries expressed a more or less pessimistic view regarding the opportunities, a joint European initiative for the establishment of a European specialisation in transfusion medicine might offer to national activities, or regarding support of such an approach by their national societies for transfusion medicine.

STRUCTURED CURRICULUM, EXAMINATION AND DIPLOMA IN TRANSFUSION MEDICINE

In the majority of those countries which have established transfusion medicine as either a stand-alone speciality or sub-speciality, there exists a detailed curriculum and a formal advanced medical training programme for physicians specialising in transfusion medicine. However, content and duration of specific parts in these curricula differ significantly between those countries.

Again, in the majority of these countries, a medical degree is required to start an advanced medical training. In some countries, such qualifications are also open to pharmacists, biologists or experts in laboratory medicine, not always being physicians. Still, in some countries, the final qualification and acceptance by both the competent authorities (accreditation bodies) and the national medical association differ somewhat depending on the basic qualification. Sub-specialisations in other countries often start from internal medicine, clinical immunology or haematology.

Specialisations and sub-specialisations in transfusion medicine are regularly completed by one or more final exams and a diploma or a similar document is issued by the university, medical association or competent authority. Such medical diplomas are fully accepted by the respective national medical associations, either as sub-specialisation or full specialisation according to the national regulations.

CONCLUSION 1

Upon analysis, the authors concluded that there is a certain interest in the majority of European countries for establishing a common European curriculum for advanced medical training in transfusion medicine, driven by a group of highly motivated and dedicated Europeans. In addition, several European projects like the EuBIS, EU-Q-SOP, EU-OBUP (optimal use) and the DOMAINE (donor management) all include a training module as a backbone in their strategic plans.

On the other hand, there are different tasks to be accomplished. First, a common curriculum for physicians regarding an advanced medical training in transfusion medicine should be proposed and discussed in different associations like EBA and Euronet-TMS. The highest possible number of national societies for transfusion medicine in Europe should agree on this common curriculum after the European discussion has taken place. These national societies should sign such a common European curriculum and approach their national competent authority to ask for approval. If possible, international scientific support by ISBT, as well as national consultation, might add to this European project. In a second step, such a project might even be adopted by ISBT.

In the opinion of the authors, a second task to be accomplished must be a curriculum for nurses and laboratory scientists in transfusion medicine. At the moment, however, this task must be postponed due to lack of support and workforce available.

For the moment, therefore, the authors try to focus on a curriculum for advanced medical training in transfusion medicine suitable for European physicians after having completed their medical degree. We are well aware that different national structures, history, and legislation might make it difficult to implement this training programme immediately. Therefore, the proposed curriculum will consist of different modules which will enable a more flexible initial adoption of this European curriculum. The full curriculum might then be gradually translated into action in such countries.

CONSTITUENT PARTS OF A EUROPEAN CURRICULUM FOR ADVANCED MEDICAL TRAINING IN TRANSFUSION MEDICINE

The consultation of 14 different national experts in transfusion medicine in Europe delivered a relatively homogenous picture of the requirements which should be covered by a curriculum for advanced medical training in transfusion medicine.

In the questionnaire shown in annex 1, we asked for constituent parts of the clinical and advanced medical training in transfusion medicine.

CLINICAL TRAINING

Since transfusion medicine is a clinical speciality including scientific, laboratory, technical, quality management, organisation and pharmaceutical skills, all 14 respondents deemed a clinical foundation to be necessary. In addition, this programme is only suitable for physicians who have already obtained their medical degree. The required duration of such a clinical training ranges from six to twelve months up to more than three years. Most of the respondents, however, considered two years of medical training to be the optimal clinical training period.

The content of this clinical training should comprise all aspects of haemotherapy in addition to physicians´ standard clinical tasks. Therefore, disciplines covering transfusion of blood and plasma products seem to be suitable specialities for this clinical training. Internal medicine, including all sub-specialities, anaesthesiology including intensive care, gynecology/obstetrics, pediatrics and surgical disciplines like visceral surgery, heart and vascular surgery and possibly neurosurgery and urology, might be suitable disciplines for this clinical training.

SPECIFIC ADVANCED MEDICAL TRAINING IN TRANSFUSION MEDICINE

The following integral parts were considered necessary by all or most of the 14 respondents. This list shows the number of respondents (out of all answers; in brackets) who considered the named part an indispensable constituent of this advanced medical training in transfusion medicine.

- Immunohaematology and blood group serology, also including molecular diagnostics for blood group typing (14/14)
- Good manufacturing practice (GMP): Production of standard blood components (14/14)
- Good manufacturing practice (GMP): Production of apheresis products including haematopoietic stem cells (13/14)
- Clinical counselling in haemotherapy and optimal use of blood and plasma components (14/14)
- Clinical counselling in prenatal care and perinatal haemotherapy (13/14)
- Haemostaseology and clinical counselling in the usage of coagulation factor and inhibitor concentrates (13/14)
- Quality systems and quality management (13/14)
- Production safety, management of adverse events and complaints, product recall and look back procedures (14/14)
- Autologous haemotherapy and counselling in blood saving procedures (14/14)
- Donor management, donor information and counselling, communication management (13/14)
- Basics in emergency medicine and disaster management (12/14)
- Laboratory skills: Serology and nucleic acid testing (NAT; PCR) for viral and bacterial pathogens (12/14)
- Transplantation immunology, immunogenetics and human leukocyte antigen (HLA) diagnostics (11/14): In some countries, this is a (sub-)specialisation of its own.
- Basics in licensing of blood products, registration, production and marketing authorisations (11/14)

In addition, some single respondents considered the following topics to be constituent parts of this advanced medical training:

- Forensic haemogenetics and paternity testing
- Basics in cellular therapies, tissue handling and molecular biology
- Basics in epidemiology and transmissible diseases
- Basics in pediatric and adult haematology/oncology
- Therapeutic haemapheresis and photopheresis
- Haemovigilance

Since the last-mentioned topics were only mentioned by single or small groups of respondents, and most topics can be or already are included in topics mentioned above, the authors decided to include the remaining valuable additions into existing topics, or alternatively, add them to a list of optional tasks to be fulfilled.

PROPOSAL FOR A EUROPEAN CURRICULUM FOR ADVANCED MEDICAL TRAINING IN TRANSFUSION MEDICINE

General principles

This novel European curriculum for advanced medical training in transfusion medicine will consist of different modules. These modules, which might be independently mastered by individual physicians in their respective countries, will, nevertheless, have a common structure and organisation and will build up on each other. Each module is defined by its theoretical content and scientific background and the requirements for practical training. In addition, the minimal required time to fully master each module is defined. Supervision by the national society of transfusion medicine, or alternatively, a university based blood establishment should be guaranteed in close cooperation with the respective national competent authority.

After successful finalisation of each module, a final exam should be completed, and a certificate issued by the organisations mentioned above. In the long run, these certificates should even be accepted by other European countries as well, thus enabling physicians in their advanced medical training in transfusion medicine to freely gain insights from different European approaches towards transfusion medicine during their training and education course.

The final exam should then be performed by the national medical association or the respective authority in each country, and a final diploma issued. This diploma might be the cornerstone toward the long-term aim of establishing a European specialisation in transfusion medicine according to the European directive 2005/36/EC on the mutual recognition of professional qualifications.

Mutual recognition

The general system of mutual recognition of diplomas and qualifications in the European Union takes the form of an individual recognition system. Competent authorities in the host country, in which the individual wishes to have his diploma being recognised, perform an individual examination on a case-by-case basis. This is quite complicated and time consuming.

For certain professions including medical doctors, however, the general system provides for an automatic recognition system for diplomas.

The most recent European directive on the mutual recognition of professional qualifications throughout the European member states is directive 2005/36/EC currently in force. This directive contains a list of specialisations that are automatically recognised after advanced medical training by all Members States or by only some members. However, transfusion medicine, blood transfusion or immunohaematology are not mentioned in the directive annexes. Therefore, automatic recognition cannot take place.

Directive 2005/36/EC on the recognition of professional qualifications, however, offers the possibility of including new medical qualifications into the said annex: Article 26/2 of directive 2005/36/EC reads as follows: "The inclusion in Annex V, point 5.1.3 of new medical specialities common to at least two fifths of the Member States may be decided on in accordance with the procedure referred to in Article 58/2 with a view to updating this Directive in the light of changes in national legislation."

PROPOSED TRAINING PROGRAMME

Module 1: Clinical training

A two year clinical training following the medical diploma should be the foundation for registered physicians. It must comprise all aspects of haemotherapy, in addition to physicians´ standard clinical tasks. Cellular blood components as well as plasma products must be ordered, transfused and potential adverse events treated.

The indications for blood components and transfusion triggers must be applied in daily routine. Pre-transfusion protocols must be followed and the whole documentation and quality control must be done. Therefore, disciplines covering transfusion of blood and plasma products on a regular, i.e. daily or almost daily basis, are deemed suitable for such clinical training. Internal medicine including all sub-specialities, anaesthesiology including intensive care, gynecology/obstetrics, pediatrics and surgical disciplines like visceral surgery, heart and vascular surgery and possibly neurosurgery and urology as well might be accepted disciplines for this clinical training.

Small parts of the clinical training might be covered by outpatient care. Laboratory medicine including microbiology, virology or infection epidemiology can be part of the clinical training as well. However, at least half of the two years of clinical training must be devoted to direct clinical care of patients.

A certificate should be issued by the head of the clinical department and focus on haemotherapy for the purpose followed by this curriculum.

Module 2: Donor Medical doctor

The third year of the curriculum should be devoted to the management of whole blood and apheresis donors. Blood donation in all its aspects should be the focus of physicians taking part in module two.

Planning, organisation and implementation of blood drives and blood collections, including whole blood donations, single product and multi-product apheresis procedures, stem cell apheresis and bone marrow harvesting, if possible, should be the major topics of this year in advanced medical training.

This module must be performed in a suitable blood establishment, where sufficient numbers of the above mentioned procedures are performed, and where continuous supervision of the trainee by a senior physician with good expertise in transfusion medicine is guaranteed.

The trainee should perform the following tasks on a regular basis: donor selection; donor interview and examination; medical care of the donor before, during and after the donation process; both whole blood and autologous donation; as well as allogeneic apheresis procedures.

Basics in infection epidemiology and a sound knowledge of transfusion-transmitted diseases are key elements for donor counselling.

By the end of module two, the trainee should have mastered the following skills: diagnostics, emergency and long-term treatment, as well as correct documentation and reporting of any adverse event occurring during or after donation procedures.

Basics in blood supply management and organisation of blood supply in emergency situations should be part of this training, insofar as the donation departments are involved. Further parts of these skills are covered in module four.

In addition, preparative and therapeutic haemapheresis procedures including therapeutic leukapheresis and photopheresis, if performed in the blood establishment, should be part of the training. Diagnostic procedures to be performed before stimulation of haematopoietic stem cell (HSC) donors should be part of this curriculum, as well as good knowledge of adverse events of G-CSF mobilisation and apheresis procedures.

Interventions, emergency treatment and donor counselling in such cases must also be an integral part of this training. Basics in cellular therapies, tissue handling and molecular biology, as well as knowledge of adult and pediatric haematopoietic stem cell (HSC) transplantation strategies (including basics in haematology/oncology) are also required to enable a specialist in transfusion medicine to answer questions arising from these disciplines.

In vitro preparation and possible expansion of autologous and allogeneic HSC and mesenchymal stem cell (MSC) products should be understood by the trainee if performed in the blood establishment. Storage, freezing protocols, and release of the final (apheresis) products must be part of the training.

Donation related laboratory analysis, hygiene protocols and quality management related to donation procedures are also essential for this module.

Module 3: Laboratory

Module three will comprise at least three different laboratory entities important for transfusion medicine. This module should not be completed within less than 12 months of full time employment in the respective laboratories. From our experience, the time devoted for this important module should be at least one year. A more thorough training is provided, if this period is considerably longer.

Immunohaematology: serological crossmatching and serological as well as molecular blood group typing of patients are cornerstones in transfusion medicine.

Clinical counselling in haemotherapy, both in adult and pediatric patient groups, including perinatal haemotherapy, is essential for the optimal utilisation of blood components in contemporary medicine. In addition, clinical counselling in haemostaseology and the optimal use of coagulation factors and inhibitor concentrates has to be part of the curriculum.

Training and education should be performed in a laboratory, where all relevant laboratory tests in the field are regularly used and clinical counselling in the fields mentioned above is performed. Trainees must be supervised by a senior physician experienced in the field and in teaching advanced medical training. Preferably, this should be the head of the laboratory or his or her deputy.

The second important part in module three is **blood donor screening**. Blood group typing and serological as well as molecular testing for pathogens like viruses, bacteria and protozoa are standard procedures in present-day blood establishments.

Modern laboratory tests like nucleic acid testing (NAT) and molecular blood group typing, as well as quality control of a laboratory should also be part of the curriculum.

Laboratory management and implementation of novel test procedures like testing for antibodies against human leukocyte antigens (HLA) in blood donors, in order to prevent transfusion associated acute lung injury (TRALI), should also be part of the training.

Immunogenetics: HLA diagnostics, transplantation immunology and forensic haemogenetics are the third part of the laboratory module. While immunogenetics seems to be a sub-specialisation in some European countries, the authors believe that HLA diagnostics is an important element in transfusion medicine and, therefore, should be integrated into the curriculum.

Solid organ and HSC transplantation management, but also clinical counselling in and management of adverse events like TRALI, require a profound knowledge in transplantation immunology. Forensic haemogenetics and paternity testing might also be included here, but could be seen as optional elements of the curriculum.

After completion of this module, the trainee should be capable of clinical counselling in adverse events, clinical management of bleeding patients, perioperative management of haemotherapy and laboratory support in HSC and solid organ transplantation. Optimal use of blood components, autologous haemotherapy and blood saving procedures should be managed by the trainee as well. Further, a thorough knowledge of immunohaematology and blood donor screening should enable a physician to take over responsible positions in these fields after completion of this advanced training.

Module 4: Good manufacturing practice, quality management, basics in licensing as well as research and development

Production and distribution of standard blood components from whole blood donations according to good manufacturing practice (GMP) are the backbone of a blood establishment. The Council of Europe (CoE) defined specifications and quality control parameters for packed red cell concentrates (PRC), platelet concentrates (PC) and therapeutic plasma, which were adopted at least in parts by most European countries.

In addition, GMP compliant production of apheresis products including PRC, PC, granulocyte concentrates (GC) and therapeutic plasma is also key for blood establishments. Haematopoietic stem cell (HSC) concentrates and donor lymphocytes (DL) are standard products also provided by most blood transfusion services.

Therapeutic leukapheresis and photopheresis procedures are frequently requested apheresis procedures in clinics dealing with haematopoietic malignancies. Most frequently, specialists in transfusion medicine are either performing such procedures or are at least involved. Basic knowledge in adult and pediatric haematology and emergency management seems to be necessary as well in order to perform these tasks properly.

Modern cellular therapies recently introduced in standard clinical care require knowledge in cell and tissue handling and storage as well as modern laboratory skills in transfusion medicine.

Therefore, a solid knowledge of all aspects of GMP compliant production, management, safety, quality control, adverse event management and look back procedures, complaint and recall management in homologous as well as autologous blood component provision to the clinical colleagues is deemed necessary.

Stock management of blood components in emergency and disaster situations as well as optimal provision and reduction of waste rates should be part of module four.

Modern blood establishments cannot exist without professional quality management. The main goal of every blood establishment is to supply patients in need and their treating physicians with the best possible blood components regarding content and function, safety and availability. Quality management with all its facets serves this goal. Quality assurance, drug registration and safety, as well as quality control must be part of a modern curriculum in advanced medical training in transfusion medicine. Haemovigilance and blood donor vigilance management should also be part of this training.

In such European countries, where blood components are considered medical drugs, basic knowledge in blood component licensing, registration of blood products, as well as production and marketing authorisations for blood components must be part of the curriculum.

Research and development are not only key to a pharmaceutical producer, but are most important in a quickly developing field of modern medicine. Clinical study management and a scientific approach to haemotherapy and transfusion medicine should, therefore, also be part of the curriculum.

CONCLUSION 2

Modern medical therapies like stem cell transplantation, cellular therapy, transplantation of solid organs, regenerative medicine and surgery cannot be performed without a safe supply of blood products, high quality standards, special blood products, and laboratory services provided by blood banks and transfusion medicine specialists.

Good laboratory practice (GLP), good manufacturing practice (GMP), quality management systems and quality control on the pharmaceutical manufacturer´s level are only a few examples of the standards in today´s blood banking.

The curriculum in transfusion medicine as described above is not confined to Europe. U.S. colleagues have also proposed a " curriculum content in transfusion medicine and blood banking education in pathology residency programs" in 2007 [4].

Shaz and Hillyer [3] in their 2010 U.S. review of transfusion medicine as a profession state that "transfusion medicine physicians need to be leaders on local, national and international levels; participate in research and education; and provide competent medical consultation."

The two authors conclude their article with the following statement. "As transfusion medicine is a discipline without borders and infinite possibilities, the field will continue to expand clinically, academically, and scientifically as long as transfusion medicine specialists continue to engage passionately as an advocate for patients and donors and approach each day with questions to be answered and energy and dedication to find the answers." [3].

Modern technology like e-learning tools [5] might help to facilitate the success of such a curriculum in transfusion medicine.

We are well aware, that the implementation of the whole curriculum in all European countries might take its time. However, some countries might easily adopt the whole programme at once. Others might begin with the implementation of single modules. This approach might help the scientific societies for transfusion medicine in such countries, which do not currently have a specialisation and qualification in transfusion medicine, to establish this, in line with other qualifications in advanced medicine in their respective countries.

Our scientific field of knowledge and clinical skills is currently growing and gaining more and more importance with the advent of cellular therapies and molecular diagnostics in daily clinical routine. Training and education in all aspects of modern haemotherapy, as well as a specialisation in transfusion medicine on a European level, therefore, seem to be indispensable for optimal European medical care.

REFERENCES

1. Müller N. Training and education. In: Rouger P, Hossenlopp C (eds.) Blood Transfusion in Europe. The White Book 2005. Elsevier SAS Paris 2005; chapter 8, pp. 129-140. http://www.amazon.co.uk/Blood-Transfusion-Europe-White-Book/dp/2842995880
2. Mueller MM, Seifried E. Blood transfusion in Europe: basic principles for initial and continuous training in transfusion medicine: an approach to an European harmonisation. Transfus Clin Biol 2006;13:282-289. http://dx.doi.org/10.1016/j.tracli.2006.11.004
3. Shaz BH, Hillyer CD. Transfusion medicine as a profession: evolution over the past 50 years. Transfusion 2010;50:2536-2541. http://dx.doi.org/10.1111/j.1537-2995.2010.02849.x
4. Fung MK, Crookston KP, Wehrli G, Domen R, Lopez-Plaza I, Davenport R, Gottschall J, Spitalnik S. A proposal for curriculum content in transfusion medicine and blood banking education in pathology residency programs. Transfusion 2007;47:1930-1936. http://onlinelibrary.wiley.com/doi/10.1111/j.1537-2995.2007.01417.x/abstract;jsessionid=408352F6EE0B066E059D0315BF0BC632.d02t01
5. Peterson D, Robinson K, Verrall T, Quested B, Saxon B. e-Learning and transfusion medicine. ISBT Science Series 2007;2:27-32. http://dx.doi.org/10.1111/j.1751-2824.2007.00107.x

ACKNOWLEDGEMENT

The authors wish to acknowledge the valuable feedback from colleagues from Austria, the Czech Republic, Denmark, Estonia, France, Germany, Greece, Italy, the Netherlands, Poland, Romania, Slovenia, Spain, Switzerland and the United Kingdom. The ongoing editorial support of Mrs. Martina Pfahl is highly appreciated as well.

Table 1: Answers from a preliminary EBA questionnaire by some European countries regarding the qualification in transfusion medicine in 2005

Country	Qualification?	Remarks
Austria	YES!	
Belgium	No	Francophone since 2001: post-graduate degree in immuno-haematology / transfusion
Denmark	(Yes)	Since 1966: since 1983: "Clinical Immunology" (part?)
UK: England, Wales, Scotland, N. Ireland	(Yes)	But only sub-speciality within haematology
Finland	NO!	
France	(Yes)	Academic/university: "hématologie-transfusion" (nominated professors); hospital level: "hémobiologie"
Germany	YES!	Since 1992
Ireland	No	"Specialist recognition" in transfusion medicine by specializing in haematology; take MCRPath in transfusion medicine
The Netherlands	(Yes)	Sub-speciality of internal medicine "internist-transfusion specialist"
Norway	(Yes)	"Immunology and transfusion medicine"
Portugal	Yes	Since 1982
Slovenia	YES!	
Sweden	Yes	Since 1967: "Blood group serology & transfusion" à since 1992: Transfusion medicine
Switzerland	No	Transfusion medicine optional part of haematology

YES!: full specialisation in transfusion medicine; **Yes:** specialisation in transfusion medicine including limitations for a European mutual recognition; **(Yes):** sub-speciality or open to other fields and professions; **No:** optional parts of other specialisations but no single clear-cut curriculum; **NO!:** no advanced medical training in transfusion medicine leading to a specialisation, which might enable a European mutual recognition

Annex 1: This questionnaire was answered by 14 different European countries taking part in the White Book 2011 activities.

QUESTIONNAIRE: BLOOD TRANSFUSION IN EUROPE

Specialisation & qualification in transfusion medicine (specialist medical training) throughout Europe

Thank you in advance for completing this questionnaire! Please add comments in the appropriate field attached to every question or at the end of this questionnaire and in such case refer to the number of the question, for which this comment is added!

1.) For which **country** do you provide these answers?

_____

2.) Would you please identify yourself?

Name: _____

Address: _____

_____

Phone: _____

Mail: _____

3.) Is there a formal qualification and an officially recognised specialisation in transfusion medicine in your country? (Separate speciality or sub-speciality within e.g. haematology or internal medicine?)

Yes ☐ → if your answer is **YES**: Please underline the appropriate in your country: separate speciality? Sub-speciality? Within haematology? Within internal medicine? Within other specialities? and continue with question # 6.)!

No ☐ → if your answer is **NO**, please read the following questions!

Comments? _____

4.) Are there ongoing efforts to establish a speciality in transfusion medicine in your country?

Yes ☐

No ☐

Comments? _____

5.) Do you believe that it is worthwhile to set up an European initiative aiming for the establishment of an European specialisation in transfusion medicine? Would this probably help you in establishing a national specialisation? Would such an European initiative probably be supported by your national transfusion medicine society? (Please underline where applicable!)

Yes ☐

No ☐

Comments? _____
Please continue now with question # 10!

6.) Since there is a formal qualification in transfusion medicine in your country: Is there a specific curriculum and a formal advanced medical training programme for physicians specialising in transfusion medicine?

Yes ☐

No ☐

Comments? _____

7.) What are the required qualifications (e.g. in basic medical training) to achieve admission to specialist medical training in transfusion medicine? Is a medical degree required? Is basic clinical training required to join such a programme? Do other qualifications apart from medicine (e.g. degree in pharmaceutics or biology, etc) also allow you to join such training programmes?

_____
_____
_____
_____

8.) This question relates to the organisation of this specialisation in your country: How is this qualification programme in transfusion medicine organised? This includes: Minimal requirements regarding time in clinical training, time at an institute for transfusion medicine in advanced medical training; Is there a final exam and a diploma issued? By whom are curriculum, final exam, diploma, etc. regulated, organised and issued?

_____
_____
_____
_____
_____
_____
_____

9.) Does your national medical association fully accept this speciality?

_____
_____
_____
_____

10.) The final part of this questionnaire deals with the European harmonisation in the field of transfusion medicine specialist training: Which constituent parts of this training do you deem necessary and indispensable for a harmonisad training course?

- **Basic medical training:**
  Necessary ☐ dispensable ("nice to have") ☐
  If necessary: How long? _____ years

  Which specialities (e.g. internal medicine, paediatrics, gynaecology/obstetrics surgery, neurosurgery, urology, anaesthesiology, others? – please underline applic..)

  Comments?
  _____

- **Immunohaematology/ blood group serology**
  Necessary ☐ dispensable (“nice to have”) ☐

- **Production (GMP) of standard blood products**
  Necessary ☐ dispensable (“nice to have”) ☐

- **Production (GMP) of apheresis products (including stem cells)**
  Necessary ☐ dispensable (“nice to have”) ☐

- **Clinical counselling in haemotherapy/optimal use of blood products**
  Necessary ☐ dispensable (“nice to have”) ☐

- **Counselling in prenatal care/perinatal haemotherapy**
  Necessary ☐ dispensable (“nice to have”) ☐

- **Haemostaseology/clinical use of factor concentrates**
  Necessary ☐ dispensable (“nice to have”) ☐

- **Transplant immunology/HLA diagnostics**
  Necessary ☐ dispensable (“nice to have”) ☐

- **Quality management**
  Necessary ☐ dispensable (“nice to have”) ☐

- **Production safety/adverse event management/look back**
  Necessary ☐ dispensable (“nice to have”) ☐

- **Autologous haemotherapy**
  Necessary ☐ dispensable (“nice to have”) ☐

- **Donor management/information&communication management**
  Necessary ☐ dispensable (“nice to have”) ☐

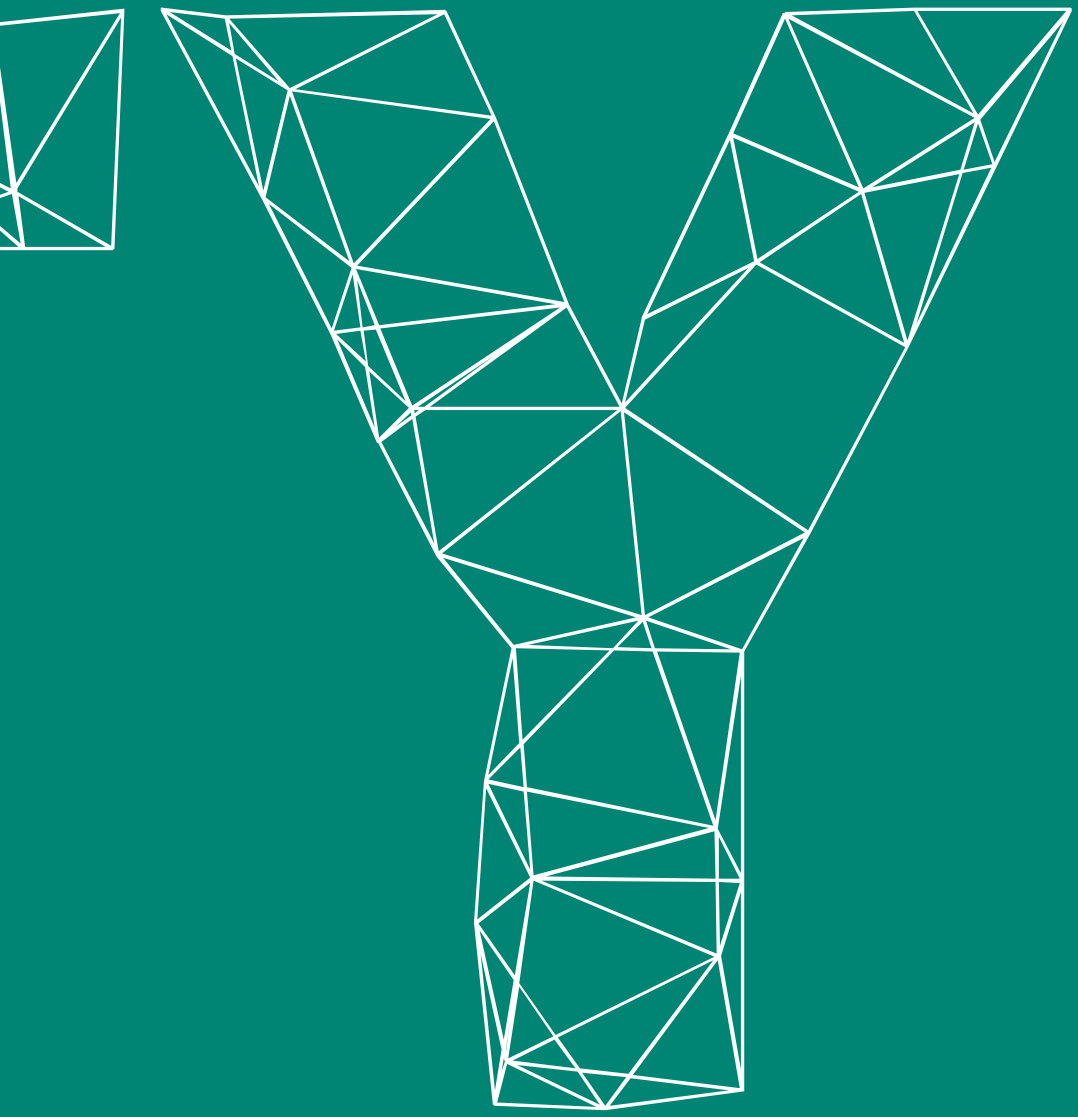
- **Basics in emergency medicine & disaster management**
  Necessary ☐ dispensable (“nice to have”) ☐

- **Lab: serology & NAT (PCR) in viral & bacterial testing**
  Necessary ☐ dispensable (“nice to have”) ☐

- **Basics in licensing of blood products/marketing authorisation**
  Necessary ☐ dispensable (“nice to have”) ☐

- **Others?**
  Please specify: _____
  Necessary ☐ dispensable (“nice to have”) ☐

Thank you very much for completing this questionnaire!
Please send back to:
Professor Dr. Erhard Seifried, MD, PhD
Dr. Markus M. Mueller, MD
GRC Blood Donor Service
Sandhofstrasse 1
60528 Frankfurt/Main, GERMANY
phone: +49 69 6782 233 **fax: +49 69 6782 231**
email: m.mueller@blutspende.de



BY MANAGEMENT

Tissues and Cells of Human Origin

Blood, tissues and cells from human origin: the European Blood Alliance Perspective

SAFETY BY MANAGEMENT

Tissues and Cells of Human origin

George Galea

13. THE ROLE OF BLOOD ESTABLISHMENTS IN CELLULAR THERAPIES:

INTRODUCTION

13.1 CONTEXT AND ENVIRONMENT: SCIENCE DEVELOPS, SO SHOULD THE STRATEGY

As indicated in the Directive 2004/23/EC, "The transplantation of human tissues and cells is a strongly expanding field of medicine offering great opportunities for the treatment of as yet incurable diseases." Cellular therapy (CT), consisting of therapeutic use of human cells, is not a single paradigm. There are various platforms as starting materials, e.g. autologous, allogeneic xenogeneic, gene therapy based or a combination of several of these.

Diverse regulatory systems: In many countries, different starting materials have different regulatory oversights. These range from approval of what is considered routine practice, for example, a routine stem cell transplant for a variety of malignant conditions e.g. lymphoma; approval of the processing device; or the more complex approvals such as market authorisations, and approval of Advanced Therapeutic Medicinal Products (ATMPs). Such complex regulatory processes are very often country specific. In addition, CT shares common characteristics and interactions with tissue engineering, gene therapy, bio-engineering and regenerative medicine *(Fig 1)*. All these fields are evolving rapidly.

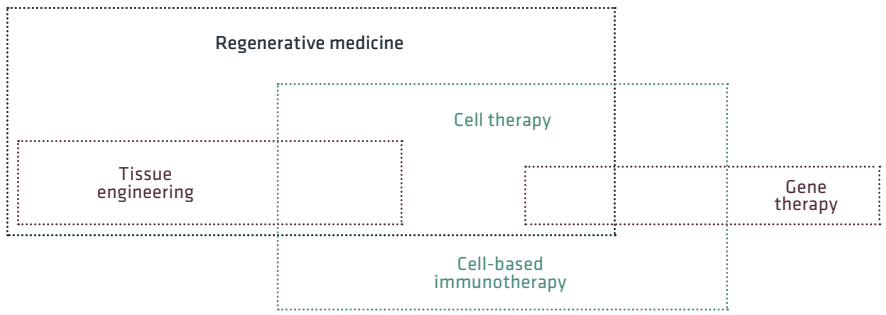


Figure 1: Interactions of cellular therapy with tissue engineering, gene therapy, bioengineering and regenerative medicine

Clinical status: There are currently around 300 companies involved with over 250 cell based therapy products in the market or in some stage of clinical development. Approximately half are still in phase one, another half in phase two and three clinical trials, and approximately 30-40 CT productsare commercially available in at least one country (L. Buckler, personal communication, 2012).

Only a third of these (around 10-13 products) have received regulatory approval and are currently marketed. Therefore, approximately 90% of the therapies are still in development and still require pre-market approval. The majority of these products are based on allogeneic cell platforms. It is also important to note that the estimated revenue of these products in 2011 was over €880 million.

Role for BEs? Many industry and other stakeholders are making strategic decisions about their involvement in cellular therapy and, in fact, the majority of big pharmaceutical companies and life science companies have cell strategies in place or in development. Clearly blood establishments are asking the same questions, and there is a need for a reflection on policy and strategy for CT from all stakeholders, including BEs. However, the environment for BEs is somewhat different, as discussed below.

Financial considerations: In some countries BEs are under severe financial constraints, with pressures to consolidate and to focus on delivering core services. The level of investment required to get involved in CT is significant and the demand for CT products is currently uncertain. Long term prospects for CT products imply that it is a relatively nascent industry with many early phase products, but few approved ones. The CT product cycle, from proof of concept to phase three clinical trials and effective clinical use is very long, often around ten years *(Fig. 2)*.

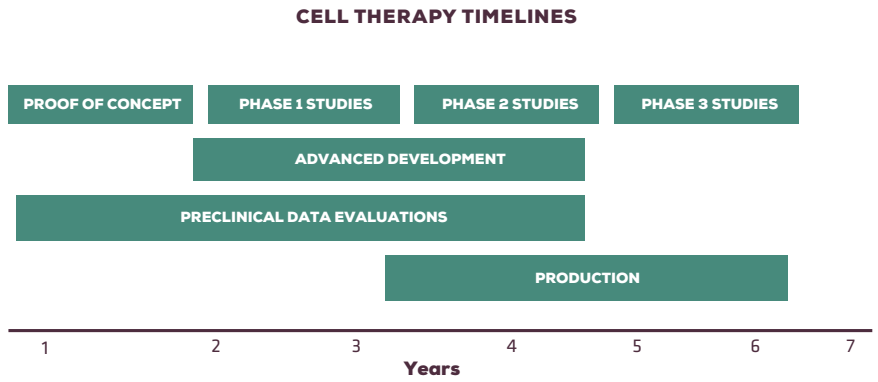


Figure 2: Cell Therapy product timelines, from research to effective clinical use.

It is, therefore, a real challenge to initiate such costly activities, even when efficacy for patients has been established. Added value comes from using existing infrastructure; expertise in activities in the whole chain, from collection to vigilance; the ability to retain top medical and technical staff; and experience in cost effectiveness and efficiency. Therefore,BE senior management need to understand the environment and the risks in investing in such therapies.

International picture: From discussions in the non-profit BEs (EBA and Alliance of Blood Operators - ABO –an association of BEs from Australia, Canada, USA, UK and EBA members) it became clear that BEs in different parts of the world are at different stages in relation to CTs. However, there are some issues, common to all.

Synergies between BEs and CT: In all BEs where haematopoietic stem cell collections and processing takes place (even minimal manipulation) significant growth in activity has been observed over the past few years. This did not happen by chance, but developed due to the synergies that exist within BEs between their blood manufacturing processes and those required for CT work. In 2012 it has been estimated that current CT work within BEs in the USA alone is worth over €4.8 million.

CT has the potential of becoming an important sector of activity. There has been significant progress in the past 10 years in this field and changes have been incremental but pretty fundamental. CT is now very much part of corporate and academic policy and financial consciousness. It is felt that the lines between blood and cellular work and even synthetics (e.g. tissue engineering) are blurring.

Moreover core activities for BEs are relatively static. Therefore, if BEs wish to be forward looking, they need to capitalise on their significant strengths and assess what synergies exist between blood component and CT activities. This is a way BEs can get involved in this very exciting area of work, while minimising the financial and economic risks.

13.2 OBJECTIVE AND WORKING METHOD

Experts in the European Blood Alliance Tissue and Cells Working Group (EBA T&C WG) and ABO experts in CT identified the need for a more in-depth reflectionon the role of BEs in CT. The method chosen to conduct this reflection on policy and strategy for BEs consisted of an analysis of strengths, weaknesses, opportunities and threats (SWOT) for BEs in this field. An initial reflection identified five major domains of CT related activities for such an analysis.

1. Scope: The Scope of CT activities *(chapter 14)* aimed at first providing an overview of the current status of CT. An attempt was made to grade the CT types according to their complexity, infrastructure and level of synergy with current BE activities. Human Embryonic stem cells, gene therapy and tissue engineering have been considered outside the scope of this work.

2. Regulatory aspects: The regulatory aspects were tackled next *(chapter 14)*. BEs work in a very tightly regulated environment and have significant expertise in inspections and in dealing with Competent Authorities and regulators. If BEs wish to engage in CTs, such activities will comprise a definite strength. A very detailed overview of the regulatory conditions in different countries has been undertaken. This is a valuable comparison and illustrates that, although all regulators have a common aim of safety and efficacy of new products, the way such issues are dealt with are very varied indeed. This is particularly so in the EU where every Member State has regulated according to its own requirements. A serious attempt at harmonising regulatory requirements would add very significant value to streamlining the entire process and increasing efficiency, at equal or even higher levels of quality and safety for donors and patients. There is no doubt that current regulations could certainly be improved in this regard.

3. Research: Research issues were then considered *(chapter 16)*, focussing on the skills and expertise of BE staff and the BEs working infrastructure, which can be immensely beneficial and, therefore, advantageous. However, pitfalls are recognised and explained. This chapter details some specific roles and routes BEs could take to increase their profile and visibility.

4. Intellectual property: Sharing expertise on intellectual property (IP) issues was considered next *(chapter 17)*. CT is a relatively new area for BEs to get involved in and, therefore, it is important that BEs understand the potential commercial implications of getting involved. Many companies involved in CT have got much experience in IP protection. BEs need to understand this to ensure that their efforts are properly rewarded.

5. Ethical issues: Finally the ethical issues linked to involvement in CT were addressed *(chapter 18)*. It was felt that this was a very important aspect of this work. Built over many years, BEs have got the trust of the public, and this needs to be protected. When venturing into a new area of activity, it is important that BEs do not inadvertently get caught into ethical controversies, that may be detrimental to their core activities, and risk losing the public (donor) trust.

Each author of these chapters was given a free hand to write their section but had to include a SWOT analysis on the area they covered. Inescapably, this has meant, there is some degree of duplication. This is no bad thing, because consistently very similar conclusions were reached independently by the different contributors. This fact alone makes the SWOT analyses more robust and meaningful. At the end, each of the chapters on CT was discussed with the full authors' group and amended from the comments and discussion. This allowed for clarification and interpretation of differences of the SWOT analyses according to their specific circumstances and environments (e.g. Europe, North America, Australia).

These chapters covered the main principles. No attempt was made to delve into detailed financial aspects or risk assessments. It is clear that the time lines for return on investment are long and, being such new products, risks are not small. Much also depends on the particular environment where a specific BE is operating.

However, BEs bring with them very significant advantages that can be used to maximize opportunities for the future and puts BEs at the heart of this exciting field of medicine. I hope that these points have been well covered. A possible stepwise progression of CT activities in a given BE is proposed in the fig.3.

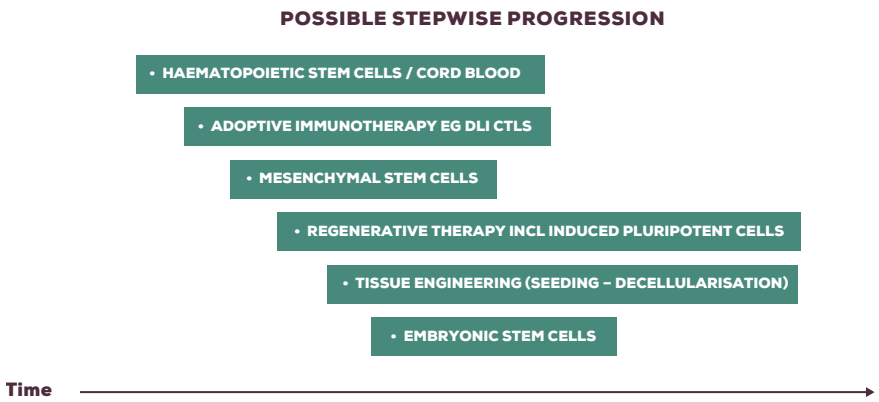


Figure 3: A possible stepwise progression of CT activities in a given BE.

Finally, this collaborative work gathering BE experts from Europe, North America and Australia led to elaborate conclusions and recommendations *(chapter 19)*. Editorially I tried wherever I could to make the sections part of a single narrative, but I felt that too much editing would interfere too much with the writings of the contributors. I hope I got the balance right.

All together these chapters on CT should be considered as a top level strategic report, and has now enough detail for members of ABO to assist them in their decisions on whether they wish to get involved in CT. I also think that these chapters on CT could form a basis for all policy and decision making in the field of CT.

I am very grateful to all members who have given so freely of their knowledge, expertise, time and engagement. If ever there was an example of the synergies of collaboration, this one would be prime.

Halvard Bönig
Rich Feliciano
George Galea
Keld Homburg
Primož Rožman
Lee Ann Weitekamp
Erhard Seifried

14. THE ROLE OF BLOOD ESTABLISH-MENTS IN CELLULAR THERAPIES: SCOPE OF ACTIVITIES

To various extents, and beyond their traditional roles of providing erythrocytes and platelets for transfusion, many blood establishments (BEs) are getting involved in cellular therapy activities. Those that are not are currently assessing the role for BEs in general and their own organisation, in particular, in cellular therapy work.

Donors, patients and the community as a whole rightfully expect safety and ethical standards applied to cellular therapeutics not to fall short of standards applicable to normal blood products. Therefore, many experts believe that cellular therapeutic generation should be in the domain of BEs. We have here attempted to provide some background to promote internal and external discussions, and to assist decision making with respect to these expanded services provided by BEs. The work was commissioned by Alliance of Blood Alliance (ABO) Board and, therefore, this document attempted to address cellular therapies (CTs) and related activities from Australian, European and North-American points of view. Basic concepts seem to be consistent, but nomenclature slightly differs in these three continents.

In this chapter we have aimed to provide some suggestions as to the potential scope of cellular therapy activities by BEs. The depth of any blood establishment's involvement in the field will be dictated by numerous factors, including local infrastructure, experience of blood establishment staff, and local need. CTs are heavily regulated and it is reasonable to expect that no BE will aim to offer the entire range of activities in this field. However, established quality systems, extensive validations of processes, and activity specific licence requirements make BEs good candidates for being involved in numerous aspects of cellular therapeutics, provided the safety and efficacy of the products can be demonstrated to obtain licensing or marketing authorisation.

Haematopoietic stem/progenitor cells have been used for more than 40 years for autologous and allogeneic transplantation [1]. They can, therefore, be considered "classic" cellular therapeutics: they are also among the easiest to generate. At roughly 60,000 haematopoietic stem cell transplantations world-wide (for all three sources of haematopoietic stem cells combined - Bone marrow, Peripheral Blood stem cells and cord blood), these are probably also the most common "cellular therapy" products.

Comparing those numbers to red cell concentrate requirements, it immediately should become clear that quantitatively (and also economically) cellular therapy will likely not be able to compete with "standard" blood products in terms of numbers, while at the same time adding a significant layer of complexity to BEs' operations. Is it worth the effort? Opposing forces of humanitarian and economic factors will play into the response to this question. The answer will thus likely not be the same in all countries. It will vary between places where access to health care is a commodity versus a human right.

14.1 DONOR EVALUATION AND DONOR REGISTRIES

Different countries have taken different approaches to address the need for matched-unrelated stem cell donor recruitment, registry and search unit management, etc. This discussion is beyond the scope of this chapter; suffice to say that in those countries where there is an unmet need for professional stem cell donor management, BEs with their large pools of blood donors may have an edge over organisations starting from scratch, both in terms of donor relationships and registry infrastructure.

The need for extensive donor evaluation, whether autologous, allogeneic-related or matched-unrelated, applies essentially to all cellular therapies, except when embryonic or cadaveric donors are involved. Adequate donor evaluation requires physicians with considerable clinical experience and, in the case of stem cell mobilisation, specific knowledge about mobilizing agents/regimens [2].

Many BEs are able to care successfully for stem cell donors. More so than clinicians, transfusion medicine specialists have a track record in donor care and attention to donor safety; they also have the infrastructure in place for the required vigilance systems. Considerable public trust in BEs makes them prime contenders particularly also for allogeneic donor care issues.

Hospital clinicians on the other hand may – knowingly or inadvertently – undervalue donor safety, or may at least be perceived to do so. Moreover, for haematopoietic stem cell transplantation, international standards such as World Marrow Donor Association (WMDA) guidelines (and in some cases, local laws) require that donor assessment and informed consent be performed by an individual totally independent of the patient's physician, to avoid any impression of coercion. By extension, similar standards could be applied to donors for any other type of cellular therapy.

Therefore BEs are a natural place to maintain donor registries, specifically including unrelated marrow and cord blood donors. In the latter example, they are also very suited to process and store cord blood (see below).

14.2 FOUR TIERS OF CT PRODUCTS

CT products have been categorised to reflect both the state of complexity and the requirements necessary for BEs to operate in the field. Some are well established products; others are newer and more experimental. A SWOT analysis is presented after each tier to help BEs evaluate their potential role. This is also summarised at the end.

TIER 1: Established, simple and needing little specific infrastructure
TIER 2: Simple, established cell products requiring a GMP facility with class A in B work environment
TIER 3: Simple cell products requiring a GMP facility with class A in B work environment which are less well established
TIER 4: Complex experimental cellular therapeutics

14.2.1 TIER 1: ESTABLISHED, SIMPLE AND NEEDING LITTLE SPECIFIC INFRASTRUCTURE

1. HAEMATOPOIETIC STEM CELL TRANSPLANT AND DONOR LYMPHOCYTE PRODUCT GENERATION

Mobilised peripheral blood stem cells and bone marrow stem cells, which are the two most common stem cell sources used for transplantation today [3], as well as granulocytes, can be collected within the normal blood donor centre or hospital infrastructure, i.e. their generation ideally lends itself to blood centres which are only entering the field of cellular therapies.

In response to legislation, haematopoietic stem cells for haematopoietic reconstitution require specific license for operators: some countries even consider them to be drugs for which a pharmaceutical license is required. Hospitals may shun the considerable effort associated with licensing, and some BEs may, therefore, be able to use their experience with biological drug licensing and other regulatory issues as an entry into Cellular Therapy generation. The technology required for stem cell collection is commercially available and fairly simple to use, and transfusion medicine specialists are acquainted with similar technology.

Common manipulations of stem cell products not requiring a Gmp facility or specific equipment

ABO major or minor mismatch between donor and recipient may occasionally require erythrocyte or plasma reduction. Erythrocyte removal from bone marrow is achieved by apheresis technology (with machines such as COBE Spectra or COBE2991), using closed systems. For plasma removal, sterile tube welding devices such as SCD from Terumo and standard centrifuges are required standard equipment in any blood establishment. Moreover, all testing, cross matching (ABO and HLA) and (stem) cell enumerations are current practices within BEs.

Mobilised peripheral blood stem cells, allogenenic or autologous, for haematopoietic reconstitution

For mobilised stem cell apheresis, leukapheresis technology [4], automatic haemacytometry and flow cytometric capacity for CD34+ and CD3+ cell enumeration are required.

Because of significant electrolyte shift during stem cell apheresis, immediate access to a biochemical laboratory is also critical. A facility clean enough for whole blood or component collection is generally sufficient for peripheral blood stem cell collection. Importantly, the significantly longer run time for "stem cell" apheresis compared to other types of donations, as well as published semi-mandatory guidelines by Foundation for the Accreditation off cellular theraphy (FACT) / Joint Accreditation Committee of the International Society for Cellular Therapy and the European Group for Blood and Marrow Transplantation (JACIE) demand that stem cell apheresis activities be physically separate from other activities (clinical, whole blood or component collection). Designated and specifically trained personnel, both nursing and medical staff, are required, because of the longer duration, the risk for complications (specifically with respect to electrolyte imbalance) which is considerably higher than with normal donors.

In a surprising lack of consequentiality by regulators and accrediting bodies, hand-written labels/product information or manual, uncontrolled data entry currently remain acceptable. To ensure product safety (standards should be at least equal to standard blood products), IT solutions similar to those for standard blood products have already been established for product generation, testing, labelling, document preparation and release. BEs in many countries already use them and have gained considerable expertise in this area.

The considerable expense and the duration of adequate IT validation considering product frequency should be borne in mind and that also opens opportunities for collaboration among BEs. This aspect of product safety clearly plays to the strengths of BEs. Benchmarking should include, at the very least, regular calculation of apheresis outcomes and comparison against published data, as well as transplantation outcomes. Donor follow-up is still required, although it is often delegated to transplant units for autologous and family donors, and to donor registries for unrelated donors.

Bone marrow collection, allogenenic or autologous, for haematopoietic reconstitution

For bone marrow collection, access to an aseptic operating theatre, and anaesthesia support are both required. The technique for marrow harvesting is not dissimilar to a diagnostic tap [5]; benchmarking requires, at a minimum, average marrow cellularity and donor and recipient outcome.

Ample data for benchmarking have been published. The technology required in addition to operating rooms is similar to peripheral blood stem cells, i.e. flow cytometry and haemacytometry. The same considerations for product safety and IT support apply to bone marrow as to peripheral blood stem cells. Since in Europe, marrow aspiration may only be performed by physicians, two of which are required for a marrow harvest, labour cost is considerable. In the US, a physician may be assisted by a mid-level practitioner during marrow harvest.

Any autologous product will require cryopreservation. Many regulators demand use of a clean room facility for the manipulations preceding cryopreservation; this will be discussed below *(Tier 2)*. It may be reasonable to assume that if clinicians agree to yield

allogeneic stem cell collection to BEs, that they will also expect them to take over the more laborious and investment-intensive task of autologous stem cell product generation and cryopreservation *(see Tier 2)*.

Lymphocyte preparations

Approximately 10% of stem cell transplant recipients (with numbers increasing because of current transplant protocols) will go on to require an unstimulated lymphocyte transfusion from their stem cell donor, also referred to as "donor lymphocyte infusion" (DLI). In the absence of stimulation, DLI is minimally-invasive (similar to a platelet apheresis or multi-component donation), and donor evaluation can accordingly be scaled down relative to stem cell donor preparation. Apheresis technology and quality control techniques are the same as for mobilised-donor apheresis [6]. Cryopreservation capacity is generally required; since most of the product is cryopreserved in incremental doses, only a small aliquot is administered freshly.

Granulocyte concentrates

Patients with transient neutropenia or qualitative neutrophil defects and severe infections may require granulocyte transfusions to control infection [7]. Even though controlled trials do not exist and it may be ethically difficult achieve them, the same logic that is applied to severely anemic or thrombocytopenic patients indicates that indeed replacement of a short-lived mature cell type with such cells from an allogeneic donor should be beneficial. Before the advent of Imatinib, patients with chronic myeloblastic leukemia often served as granulocyte donors. Nowadays, suitable healthy donors are recruited. They receive an injection of granulocyte-colony stimulating factor the evening prior to granulocyte apheresis. These donors can be drawn from the patient's circle of friends and relatives, or recruited from a healthy donor pool. The shelf life of granulocytes is short (24 h); a therapeutic dose for an adult is $>10^{10}$ granulocytes.

In order for granulocytes to separate from red cells during apheresis, sedimentation enhancers, generally high molecular-weight hydroxyethyl starch (HES), are co-infused with the anticoagulant. Because of the extremely long half-life of HES, some countries allow only one cycle of granulocyte donation per year. The technology of granulocyte apheresis is commercially available. Granulocytes are irradiated prior to infusion, thus the risk of graft vs host (GvH) is minimal and extensive tissue compatibility testing is not required. Quality control is simple; it only requires the same Infectious Disease Markers (IDMs) as for normal blood products and haemacytometry with machine differential for neutrophil enumeration and estimation of red cell contamination. Red and white cross-match are required (patient plasma incubated with donor erythrocytes and lymphocytes).

Cord blood collection

Since the first description of an allogeneic umbilical cord blood stem cell transplantation more than 20 years ago [8], residual post-natal placental blood-derived stem cells, or "cord blood" stem cells, have become an important source of transplantable cells for allogeneic stem cell transplantation.

Cord blood stem cell grafts differ from adult-donor stem cell transplants in their relatively greater immunological immaturity, which allows for transplantation of less-than-optimally matched cord blood units. Cord blood has become a preferred transplant in countries with little public support of volunteer stem cell donation, as well as in places with particularly great ethnic diversity, such as in the USA.

The role of allogeneic cord blood transplantation is viewed differently in different countries, for reasons that may not be entirely scientifically justified. The small size of the grafts makes them less than optimally suited for larger recipients (although double-cord transplants can offer a useful approach), a second donation in the case of poor or non-engraftment is not possible, nor are DLIs available in case of impending relapse or graft rejection. For complex reasons, likely including the greater immunological immaturity of cord blood cells, immune reconstitution is markedly delayed after cord blood transplantation, and late losses due to virus infections are not uncommon.

Compared to adult stem cell donors, medical history of donors of cord blood is less well known and the frequency of donor-derived leukemia, according to data communicated by the National Marrow Donor Programme (USA), may be higher than with the use of adult-donor stem cell products. Nevertheless, for recipients lacking a matched-related or –unrelated living donor, using cord blood is a potentially life-saving opportunity.

The cost of cord blood banking is considerable. Cord blood products are generated prospectively, before their HLA type is known, and thus, before their potential value can be estimated. Many cord bloods are collected and shipped, only to find that critical volumes or cell numbers meriting cryopreservation have not been met, and significantly fewer than 1% of all banked cord blood units will ever be clinically applied.

It follows that in order for allogeneic cord blood banking to be cost-effective, one distributed cord blood has to offset the cost of 100 processed and HLA-typed cord blood units. It should be obvious that this expectation is unrealistic, as confirmed by systematic analyses [9]. Philanthropy, government funding or cord blood banks jointly funded by parents and others have been successful, but those considering entering the allogeneic cord blood banking arena should be aware that cord blood is not a blockbuster drug.

Allogeneic cord blood banking requires trained and licensed collection units (obstetric hospitals), validated shipping to processing units, and trained and licensed processing and storage units. Technical requirements include technology for erythrocyte removal and volume contraction, generally density centrifugation-based, serology/NAT, haemacytometry and flow cytometry as well as low-resolution HLA typing for quality assessment, cryopreservation and storage technology.

Even though cord blood processing is largely a closed process, some regulatory bodies have seen a need for a class A in B environment for cord blood processing. Accreditation by FACT /Netcord or equivalent organisations is required before cord blood processing units are allowed to deposit their product information in publicly searchable databases. Administrative staff are needed for database management and handling of requests for cord blood products. These are all areas where BEs should make themselves indispensible, and many of them already do.

As for the therapeutic role of autologous cord blood, the potential benefit is less clear than for allogeneic cord blood. For treatment of the donor's own leukemia, the cells are unsuited because, as was shown, informative oncogenic mutations are generally observed at birth. Also, stem cell transplantation for leukemia hinges on immunological anti-leukemia activity which is only achieved with allogeneic transplants.

Use in the setting of sibling transplantation is often quoted as a potential benefit by commercial autologous cord blood banks, but this is neither autologous use, which causes significant regulatory issues (transformation of an autologous into an allogeneic product, even though manufacturing processes are exactly the same), nor is it clear how this product is advantageous over collection of stem cells directly from the living sibling.

Generation of regenerative medicine products from autologous cord blood has been another promise by autologous cord blood banks, a promise with which medical progress has failed so far to catch up. The question as to whether adult autologous cells from marrow or from IPS (Induced pluripotent stem) cells generated from, e.g., skin fibroblasts will be less suitable for regenerative medicine purposes than cryopreserved autologous cord blood cells will need to be asked and tested once such therapies become available. For lack of compelling arguments in favour of autologous cord blood, many professional groups have issued statements discouraging autologous cord blood banking. At the very least, future parents and grand-parents should be clearly advised about the current lack of data supporting the usefulness of banked autologous cord blood.

Manufacture of autologous cord blood is performed in very similar ways as allogeneic cord blood. Requirements for microbiological testing, specifically NAT testing, are often less stringent for autologous cell products. As directed cell products, storage of autologous cord blood will have to be separate from off-the-shelf undirected allogeneic cord blood.

Cell product collection as starting material for commercial cellular therapeutics generation

Some pharmaceutical companies generate advanced cellular therapeutics from autologous, i.e. patient-derived cells. Since they generally lack the infrastructure for region-spanning cell collection, collaboration with BEs may prove mutually beneficial. Examples of starting materials for such products include lymphocyte apheresis for targeted immune therapies (i.e. Provenge for prostatic cancer) or bone marrow for regenerative medicine (i.e. NurOwn for ALS, ChondroCelect for cartilage repair, t2c001 for myocardial infarction).

The techniques for collection are described above, i.e. their complexity is manageable. Quality controls will be minimal, as these will be performed in the centralised cell factory. Generally, the commercial partner will bear the responsibility for regulatory matters. BEs should realise that their involvement may be interpreted by patients as a "seal of approval", i.e. care must be taken not to taint the currently excellent relationship, BEs enjoy in the public mind if industrial partners or cellular products are carelessly selected. For cell products and commercial partners that have received the approval of BEs, such partnerships can facilitate patient access to novel therapeutic approaches.

2. SWOT ANALYSIS OF TIER 1 CT PRODUCTS (SEE ANNEX 1)

The list of strengths of BEs with respect to "classic" cellular therapeutics is long. They include the following: demonstrable reputation for donor care; over decades-long experience with pharmaceutical manufacturing under GMP (regulatory/licensing, pharmacovigilance, quality testing, quality management, IT, ...); experience with apheresis technology. They also have de-centralised structures which provide easy donor and customer access, issues with which BEs favourably distinguish themselves in relation to hospitals and commercial entities.

Weaknesses may pertain to infrastructures which are more geared to the healthy donors than to patients, but partnerships with hospitals can alleviate that problem. The Tier 1 cellular therapeutics are a good entry point for BEs wishing to enter the arena of cellular therapeutics generation. Stem cell products for haematopoietic reconstitution have left the kind of unregulated realm where each hospital would have its apheresis machine in the corner, to become highly controlled, licensed products.

Given the generally good working relationships between BEs with health care providers in the field of non nucleated cellular therapeutics, it should not come as a surprise that many hospitals in Europe have yielded the provision of stem cell services to BEs. Little specific infrastructure beyond what is available in any blood establishment and limited new technology (flow cytometry) is required for these products. The complexity of the products is so modest that the risk of not being able to deliver them is minimal, although rigorous training requires some start-up time and funding. Financial risks are modest, since market size is fairly well established and largely stable; also, products are medically established and thus covered by health insurances.

The relative high frequency of the Tier 1 products among all cellular therapy products implies a comparatively favourable balance between set-up investments and routine production. The fact that there is no "market price" for stem cell products will require BEs to carefully calculate their costs. What will be new for BEs is that more complex products are required for numerically much rarer patients than what has been the case up to now.

14.2.2 TIER 2: SIMPLE, ESTABLISHED CELL PRODUCTS REQUIRING A GMP FACILITY WITH CLASS A IN B WORK ENVIRONMENT

1. CRYOPRESERVATION OF CELL-RICH PRODUCTS

All autologous haematopoietic stem cell products need to be cryopreserved, to maintain their viability while the patient is undergoing high-dose therapy. Similarly, DLI products are usually cryopreserved except for one aliquot that is given freshly. Cryopreservant, typically Demethyl Sulfoxyde (DMSO), is added to cell suspensions which are then rapidly cooled down in controlled-rate freezers [10].

Required materials include an sterile connection device (SCD) tube welding device, centrifuge, class A cabinet (some regulators require a B environment, others may be satisfied with C or even D), controlled-rate freezer and cryo-tank. Tank filling status and temperature must be continuously monitored and alarm-fitted, to guarantee product integrity. Environmental requirements for aliquoting of cellular therapy products will vary depending on local custom, from A in B to A in D.

2. IMMUNOMAGNETICALLY MANIPULATED STEM CELL PRODUCTS

For patients for whom no matched stem cell donor can be identified, transplantation of a haplo-identical immune cell-depleted graft can be life-saving. Immune cell-depleted grafts are also used for recipients of matched allogeneic transplants who cannot tolerate the nephro- or hepatotoxic immunosuppressants required after T-cell replete transplantation.

The specific expertise required for haplo-identical stem cell transplantation is not available in all transplant centres. Reagents for immunomagnetic enrichment of CD34+ cells or for immunomagnetic depletion of CD3 and CD19 or for alpha/beta T-cells and CD19

cells are commercially available, as are automatic immunomagnetic separation devices like Miltenyi's CliniMACS [11].

An A in B environment, or equivalent, is required, but established protocols are available, so that the generation of these products is straight forward. Quality controls are the same as for standard stem cell products. In terms of regulatory requirements, immunomagnetic manipulation is considered minimal, i.e. the products are non-ATMP cell products.

Sometimes, autologous grafts are similarly enriched for "stem cells", either for depletion of potential contaminating tumour cells in the graft or for depletion of immune cells, when autografts are used to treat aggressive forms of autoimmune disease. The same technology is used as for allogeneic stem cell products.

3. ISLET CELLS

The concept of pancreatic islet cell transplantation was proposed more than 50 years ago as a treatment for diabetes. The technique is established at approximately 25 centres world-wide, yet the number of annual islet cell transplants does not currently exceed 100.

Autologous pancreatic islet cells are generated from patients requiring gastrointestinal surgery which necessitates pancreas resection (e.g., chronic pancreatitis with cysts). Allogeneic pancreatic islet cells are derived from cadaveric (multi-organ) donors [12].

Autodigestion limits storage and transport time, which poses significant logistic challenges. Islet cells are prepared from fresh pancreas by repetitive collagenase digestion steps and separation from exocrine pancreatic tissue, using a Ricordi chamber and differential centrifugation in an A in B environment. Islet cells are generally injected via the portal vein into the liver; other sites have also been successful.

Quality control, in addition to the usual microbiological safety tests, includes yield and purity of the islet fractions as well as viability scores. The process is currently very labour intensive and long - (approx. 10 hours). Moreover, the processing steps do not lend themselves to automation and a number of variables can only be controlled to a limited extent. Post purification, the islets have only a shelf life of 48 hours prior to transplantation. The short survival time of pancreatic islet cells outside the body limits transportation of pancreas or of isolated islet cells to distant sites, i.e. only patients close to the isolation process are normally considered, although this may change as experience with islet viability increases. The large network of BEs may be very advantageous in this regard.

4. AUTOLOGOUS/ALLOGENEIC CELLS FOR REGENERATIVE MEDICINE

Autologous bone marrow cells have been used with considerable success for regenerative medicine purposes with a wide array of indications, from critical size bone defects, to peripheral vascular disease, myocardial infarction and heart failure. In all cases, a therapeutic benefit was apparent, but satisfactory cellular and molecular mechanisms could not be delineated.

For myocardial infarction (MI), the benefit of mononuclear bone marrow cell therapy has been unequivocally demonstrated [13]. Because of the high frequency of coronary heart disease / MI, market size may appear considerable larger than for haematopoietic stem cell transplantation, but the realistic market is probably smaller:

All medical establishments that want to perform cell aspiration for regenerative treatment are "production sites" and require inspections by regulators and by the manufacturer of the drug. They have to establish SOPs and training manuals, document compliance and ongoing training, report outcome parameters, etc., an effort which many medical establishments have shunned.

The heterotopic use of cells for these and other regenerative medicine indications classify the cell products as advanced therapy medicinal products (ATMPs). If a facility should decide to use bone marrow mononuclear cells for several indications, even if the same cell preparation protocol is applied, for each of the clinical applications separate marketing applications will need to be filed with the regulatory bodies.

Some cellular preparations may be complex to generate but, in the case of autologous progenitor cells, generation of the products is extremely simple. Bone marrow cells are collected by aspiration under local anaesthesia, then buffy coats are prepared using one of several available techniques. Manual density centrifugation, density centrifugation with semiautomatic devices or fully automatic filter-based methods work equally well. The former requires an A in B environment, the other two are closed systems.

Whether cells isolated with the different techniques have different therapeutic value remains unanswered. Quality controls include the usual virus safety parameters, as well as viability and some haemacytometry and flow cytometry. Quality control is complicated by the lack of suitable "potency" assays. Since the cell or cells responsible for the therapeutic benefit remains elusive, no minimal or maximal effective doses have been identified. What useful measure for product quality assessment can be applied, therefore, remains to be determined.

5. SWOT ANALYSIS FOR TIER 2 CT PRODUCTS *(SEE ANNEX 1)*

Those BEs capable of generating Tier 1 products will also be able to produce Tier 2 products, although with the exception of cryopreservation capacity, demand for Tier 2 products may be not be required in the area served by that blood establishment. The strengths of BEs which enable them to support these products are the same as mentioned above. Specifically in the field of therapies for more frequent illnesses BEs may find themselves in competition with money-making entities such as start-ups and big pharma.

Even if none of the cellular products described here are patentable, the threat alone to pursue legal action against BEs on the part of industry lawyers may suffice for them not to pursue these preparations further *(see Chapter 17)*. Novel therapeutics, specifically also for some more common illnesses, may strengthen the political clout of transfusion medicine within the medical community and may also offer economic opportunity. The significant financial commitment required for development, clinical testing and licensing of these cellular therapeutics, as well as the formidable expense of operating a GMP facility and a cryopreservation laboratory and storage device must be considered.

14.2.3 TIER 3: SIMPLE CELL PRODUCTS REQUIRING A GMP FACILITY WITH CLASS A IN B WORK ENVIRONMENT WHICH ARE LESS WELL ESTABLISHED

1. ANTIGEN-SPECIFIC LYMPHOCYTES FOR ADOPTIVE TRANSFER OF IMMUNITY

In allogeneic transplantation, the number of T-cells which can be safely administered without causing severe GvHD ranges from between 5×10^4 and 1×10^6 per kg body weight for haplo-identical and fully matched donor-recipient constellations respectively. Therefore, separation of the rare T-cells directed against specific desired antigens from those allo-reactive T-cells is desirable.

Adoptive transfer of antigen-specific donor lymphocytes is well established for refractory viral disease after stem cell transplantation [14]. Promising results for fungal illness as well as for tumor-antigen specific T-cell transfer have also been demonstrated, but these latter indications currently remain at the research stage.

Very small numbers (a few thousand per kg of the recipient) of antigen specific T-cells have been shown to be of clinical benefit, since the cells will, under the influence of the virus in the recipient, proliferate dramatically. A variety of expansion or isolation techniques have been applied successfully. As starting material, donor buffy coats or unstimulated apheresis products have been used. If the original stem cell donor does not have T-cells which respond to the antigen in question, the patient's haplo-identical relatives (parents, children) can be considered as donors; their close contact to the patient reasonably predicts responsiveness to the same virus that their relative is shedding.

Antigen-specific T-cells can be enriched by pulsing with relevant antigens in vitro, which causes specific T-cells to proliferate. The technology has got certain disadvantages, such as a considerable delay between harvest and application, which almost demands prospective generation of these cells. Since the cells are cultured for prolonged periods of time ex vivo, cells generated with this technology are classified as advanced therapy medicinal products; the requirements for quality control for expanded cells will be considerable and will reasonably include assays of ploidy, senescence and transformation.

Alternatively, antigen-specific T-cells have been generated by capturing antigen-specific cells by virtue of antigen-mediated cell activation (commercial cytokine capture assay) or with artificially folded HLA-molecules displaying recombinant viral antigens (e.g. streptamer technology). Generation of such cell products takes less than one day, i.e. they are readily available, and because these cells are only minimally manipulated, the cell products are not regulated as ATMPs.

A disadvantage may be that relatively high frequencies of antigen-specific T-cells in the starting population are needed, in the order of magnitude of 1:1000-1:2000 T-cells. At these frequencies, 100 and morefold enrichment is feasible, but products will not homogeneously consist of virus-specific T-cells. Contamination with potentially allo-reactive T-cells may be considerable if the frequency of specific T-cells in the starting population was low. Immunomagnetic methods with the same devices as for immunomagnetically manipulated stem cell products are applied for cell isolation. Quality control involves, in addition to the usual viral/bacterial safety assays, flow cytometry, generally of the frequency of Interferon-gamma (IFNγ) producing cells in response to antigen stimulation. Cells are generally dosed according to the remaining non-antigen specific, potentially allo-reactive T-cell contamination, at doses considered safe by the transplant physician (see above).

Autologous antigen-specific T-cells, generated with the same technology, have also been used with some success in the scenario of allogeneic transplantation, for instance, for prevention of virus re-activation in patients with EBV-induced malignancies.

2. MESENCHYMAL STROMA CELLS

Cells with fibroblast-like morphology and capacity for differentiation into various mesenchymal lineages can be prospectively isolated from a variety of tissues, including bone marrow and adipose tissue, and expanded in vitro without the need for specific growth factors. Collectively termed mesenchymal stroma cells (MSC), it is clear that these cells are highly heterogeneous populations. This is the case, not only between sources and between donors, but also within the "MSC" population. For instance, from one donor, the "MSC" population may contain cells with very different capacities.

Morphological or immunological markers which would allow prediction of expansion or lineage capacity or of potency remain to be determined. Use of MSC for immunomodulation and for regenerative medicine purposes has been proposed (see below) [15].

All previously presented cell products, which are minimally manipulated, despite significant intra-donor variability, are relatively homogeneous, irrespective of minor protocol differences. MSCs on the other hand are cultured over longer periods of time and protocols vary markedly. It is likely that even small permutations of culture conditions will affect MSC properties and substantial effort continues to be invested into this question.

Unfortunately, most of the generated MSC products are only described phenotypically or characterised in vitro. Whether the reported changes in selection or culture methods benefit or harm their clinical usefulness is rarely addressed. It may be reasonable to assume that MSCs which are, for instance, relatively skewed for chondrocytic differentiation may be more useful for cartilage regeneration. However, whether greater in vitro plasticity also portends stronger immunomodulatory effects is less clear. In other words, even though more than 5000 doses of MSCs have been dispensed to GvHD patients alone, the MSC field remains in its early days and the weight of the evidence in favour of their clinical usefulness remains a matter of debate.

Many different protocols for MSC generation have been proposed. MSCs can be enriched from their tissue of origin either by plastic adherence or by immunomagnetic enrichment of cells expressing certain markers which are more or less specific for MSCs, such as CD73, CD105 or CD271, or by depletion of non-MSCs by virtue of CD45, CD31 and GlyA antibodies. MSCs are exceedingly rare cells, so that prior to clinical use, considerable in vitro expansion is required.

Expansion can be achieved in a variety of media. Specific growth factors are not required. Currently platelet lysate is the preferred additive for MSC expansion, mostly because of the relatively well defined safety profile of the starting material it is derived from, i.e. platelet concentrates, and because of its abundance and low cost. Expansion can be done in biogenerators (bioreactors), although their cost remains prohibitive at this time. Alternatively, labour and space intensive expansion in large tissue culture flasks has been successful.

It is likely that different selection methods and culture conditions will yield very distinct products. Whether these differences will be systematic or random, and in how far they are

donor and tissue of origin dependent, etc. remains unclear. Questions such as these should be addressed before conclusions about their clinical role can be drawn. If the products are not similar, how far can clinical outcomes in different studies be compared?

MSCs are a typical example of an ATMP. Because of their prolonged ex vivo culture, quality control requirements are considerable and will be responsible for much of the cost of these cells, although testing requirements vary significantly between countries and even regions. In addition to the usual serological tests on donor blood, the absence of infectious agents in the cell pellets will have to be demonstrated.

Identity can be demonstrated by flow cytometric analyses with a consensus panel of surface markers as well as by demonstrating in vitro differentiation into one or more mesenchymal lineages. Chromosomal stability, senescence and non-transformation may have to be shown. The extent of these analyses will depend on the clinical indication.

The less critical the indication, the more stringent the quality controls will need to be, in order to balance risks and potential benefits in the best interest of the recipient. Thus for a severe GvH disease with its dismal clinical prognosis, regulators may be swayed to forego in vivo tumorigenicity assays in nude mice, but for cartilage repair, such controls should reasonably be performed. Similarly, application in immune competent hosts may be viewed differently than in immune incompetent hosts, because rejection of MSCs will be faster and more efficient, i.e. they will likely be safer, in the former. With respect to tumorigenicity, autologous MSCs must also be considered less safe than allogeneic MSCs, because they cannot be rejected based on HLA disparity.

As for all cultured cells, negativity for endotoxin and mycoplasma as well as sterility must be ascertained. Given the great differences between individual MSC donors and given the current practice for stem cell products, where each product (even two products from the same donor, collected on consecutive days) is considered an individual batch, regulators could ask that all tests are performed on each batch. The bulk of the product would thus be utilised for quality controls, and the ensuing cost would be prohibitive.

Thorough analyses of 2-3 individual MSC batches generated according to defined criteria and extrapolation for future, similarly generated MSC batches has been accepted by regulators. Alternatively, MSC pools from large marrow aspirates from several donors have been generated, to maximise similarity between individual doses and to be able to generate a large number thereof: such a pool was qualified as a “master cell bank”.

Immunomodulatory effects of MSCs are one of two fields in which these cells may be used. A significant body of data has accumulated for their efficacy in the treatment of acute GvHD, although benefits of the magnitude reported initially were never reproduced. Other inflammatory entities may also benefit.

Research activity surrounding MSCs is considerable. Comparability of published data suffers from poor definition and low level of homogeneity of the therapeutic cells, variable dosing, variable timing for additional doses, if any, etc. Therefore, the clinical benefit is still not unequivocally established. After intravenous infusion, MSCs may or may not go to sites of inflammation – evidence for both has been provided – and in response to systemic or local inflammatory mediators they secrete incompletely defined anti-inflammatory mediators. Some of these mediators have been characterised, yet their systemic application does not faithfully reproduce the effect of MSCs, indicating that there is more to the effect.

The view held by some, that the secret of MSC therapy is LOCAL production of relevant mediators, is tainted by the observation that although MSCs are quantitatively retained in lung they can still exert therapeutic benefit, at least in mice. Evidence has been provided that the transplanted cells themselves do not prevail for long, but some tolerogenic skewing of T-cells is maintained for more extended periods of time. It is fair to say, though, that the therapeutic mechanism, if any, is not well understood and that more research is needed.

As quality controls for MSCs for this indication, as well as for other indications where the cells are used with the intention of modulating immune functions (rheumatic illness, solid organ rejection, haematopoietic graft facilitation, etc.), some in vitro assay of immune modulation, e.g. suppression of MLR, will need to be added.

An alternative use of MSCs is in regenerative medicine, specifically regeneration of hard tissues (cartilage, bone). Autologous BM-MSCs are usually used. MSCs can be injected topically in their immature form, with the expectation to see differentiation in vivo, or they can be induced to the desired lineage ex vivo. Some therapeutic effect for MSC-derived cartilage has been demonstrated, and commercial products have been licensed in some countries. Academic and commercial entities are also pursuing MSC-derived neuron-like cells for treatment of amyotrophic lateral sclerosis (ALS), among other regenerative medicine targets.

3. SWOT ANALYSIS FOR THE TIER 3 CT PRODUCTS (SEE ANNEX 1)

BEs which have been able to generate Tier 1 and 2 products have all infrastructure in place to take cellular therapy further. The expertise for the significantly more complex technology required both for production and testing may not be found in all BEs, and experienced cellular therapy personnel are currently heavily in demand.

The opportunity of participating in and shaping cutting-edge medical progress, which is politically certainly desirable, must be balanced against considerable financial risks: each of the described products will be extremely expensive, because of the cost of GMP-grade reagents and the extensive testing that is required. Moreover, the number of products of each kind for which expertise, technology, licenses, SOPs, reagents, etc. must be maintained is relatively small; a reasonable estimate is that in all of Europe, 50 CMV-T-cell transfers are performed annually. As a result of its significant cost, under-prescribing should not come as a surprise. Moreover, with respect to MSCs and some other more novel products, commercial manufacturers of MSCs may attempt to convince BEs to relinquish their development efforts in this area.

14.2.4 TIER 4: COMPLEX EXPERIMENTAL CELLULAR THERAPEUTICS

1. TIER 4 ACTIVITIES AND PRODUCTS

Academic cellular therapy approaches encompass a much wider array of cellular therapeutics, from simple to complex. It should be clear that if BEs decide to venture into the field of cellular therapeutics, their academic partners will expect them to take over translation, or clinical development (up-scaling, regulatory affairs, quality control, pharmacovigilance) of novel cell-based medicines for which they have identified a need. Any cellular therapeutic will be developed with patients in mind, in close collaboration with clinicians. Some of the more complex cellular therapeutics, however, will require collaborations also with basic scientists and engineers. It is beyond the scope of this chapter to provide an all-inclusive list of cellular therapeutics which are currently under various stages of development and to speculate about their future roles.

As examples for such more complex cellular therapies, we should mention virally transduced cell based gene therapy products. They require specific logistics (including GMP facilities and personnel exclusively designated for virus production) which only very few GMP facilities will be able to offer. Also the potential market is limited, so that not very many such factories will be needed. There is no reason why BEs should not claim this expertise, although it may be fair to say that generation of such vectors is not a deeply rooted skill in transfusion medicine. Viral gene transfer likewise requires special GMP facilities.

Targeted immune therapies for cancer treatment are likewise a busily researched field which will require collaborations with clinical and basic immunologists, as well as with engineers in collaboration with whom devices for cell separation and for cell culture will need to be developed. Engineers will also be critical partners for development of biogenerators. Additional fields may include cell-based wound-care products (possibly MSC-based), cell-based drug delivery systems and tissue engineering from autologous cells.

Another large field of active research are therapies generated from embryonic stem cells (allogeneic) and from induced pluripotent stem cells (likely autologous). This area remains purely in the academic field at this point, but some BEs might certainly want to get involved even at this early time.

2. SWOT ANALYSIS FOR TIER 4 CT PRODUCTS (SEE ANNEX 1)

The decision for getting involved in early translational and pre-clinical experimental cellular therapeutics development will be predominantly driven by academic ambition. If economic reasons prevail, then it will be more cost effective to scout for good ideas and then partner up with the inventors.

Expertise with cellular therapeutics generation, importantly including all regulatory matters, will exist in BEs venturing into Tier 4 cellular therapeutics research and development. Previous experience in up-scaling to clinical scale and GMP will be indispensible. Existing pharmacovigilance programmes enable BEs to perform or support clinical trials.

Weaknesses relative to clinical/academic and commercial competitors are worth mentioning: Lack of patient access may inhibit BEs from identifying areas of need. This can be overcome by close academic ties to clinical and basic science partners.

The considerable expense of cellular therapeutic development “from scratch” cannot be absorbed by the BEs, nor will they be eligible for venture capital. Whether Tier 4 cellular therapeutics R&D will be an economic opportunity is questionable, and if this is the driving force it might be prudent to stay away. Because most of these products are targeting orphan diseases/diagnoses, even if they turned out to become miracle drugs, the revenue will not allow patenting, will not refinance development costs, and may not even cover the sheer cost of the product.

Thus the only way to be able to afford front-row cellular therapeutics R&D will be through rigorously funded research programs. The occasional blockbuster cellular therapeutic will likely not remain with the BEs, because the significant capital required for building from scratch sizeable GMP production sites for thousands of cellular therapy products per year requires funding from sources inaccessible to BEs.

REFERENCES

1. Ferrebee JW, Thomas ED. Transplantation of marrow in man. Arch Intern Med. 1960;106:523-31. http://dx.doi.org/10.1001/archinte.1960.03820040061007
2. Pulsipher MA, Nagler A, Iannone R, Nelson RM. Weighing the risks of G-CSF administration, leukopheresis, and standard marrow harvest: ethical and safety considerations for normal pediatric hematopoietic cell donors. Pediatr Blood Cancer. 2006;46:422-33. http://dx.doi.org/10.1002/pbc.20708
3. Bensinger WI. Allogeneic transplantation: peripheral blood vs. bone marrow. Curr Opin Oncol. 2012;24:191-6. http://dx.doi.org/10.1097/CCO.0b013e32834f5c27
4. Brauninger S, Bialleck H, Thorausch K, Felt T, Seifried E, Bonig H. Allogeneic donor peripheral blood "stem cell" apheresis: prospective comparison of two apheresis systems. Transfusion. 2012;52:1137-45. http://dx.doi.org/10.1111/j.1537-2995.2011.03414.x
5. Thomas ED, Storb R: Technique for human marrow grafting. Blood 1970; 36:507. http://blood-journal.hematologylibrary.org/content/36/4/507.long
6. Klein HG. Adoptive immunotherapy: novel applications of blood cell separators. J Clin Apher. 1988;4:198-202. http://dx.doi.org/10.1002/jca.2920040412
7. Pammi M, Brocklehurst P. Granulocyte transfusions for neonates with confirmed or suspected sepsis and neutropenia. Cochrane Database Syst Rev. 2011;(10):CD003956. http://dx.doi.org/10.1002/14651858.CD003956.pub2
8. Gluckman E, Broxmeyer HA, Auerbach AD, Friedman HS, Douglas GW, Devergie A, Esperou H, Thierry D, Socie G, Lehn P, et al. Hematopoietic reconstitution in a patient with Fanconi's anemia by means of umbilical-cord blood from an HLA-identical sibling. N Engl J Med. 1989;321:1174-8. http://www.ncbi.nlm.nih.gov/pubmed/2571931
9. Bart T. Cost effectiveness of cord blood versus bone marrow and peripheral blood stem cells. Clinicoecon Outcomes Res. 2010;2:141-7. http://dx.doi.org/10.2147/CEOR.S11210
10. Watt SM, Austin E, Armitage S. Cryopreservation of hematopoietic stem/ progenitor cells for therapeutic use. Methods Mol Biol. 2007;368:237-59. http://dx.doi.org/10.1007/978-1-59745-362-2_17
11. Hohaus S, Murea S, Voso MT, Haas R. Mobilization and selection of CD34+ cells. Recent Results Cancer Res. 1998;144:1-7. http://www.ncbi.nlm.nih.gov/pubmed/9304701
12. Soggia A, Hoarau E, Bechetoille C, Simon MT, Heinis M, Duvillié B. Cell-based therapy of diabetes: what are the new sources of beta cells? Diabetes Metab. 2011;37(5):371-5. http://dx.doi.org/10.1016/j.diabet.2011.05.007
13. Schächinger V, Erbs S, Elsässer A, Haberbosch W, Hambrecht R, Hölschermann H, Yu J, Corti R, Mathey DG, Hamm CW, Süselbeck T, Assmus B, Tonn T, Dimmeler S, Zeiher AM; Intracoronary bone marrow-derived progenitor cells in acute myocardial infarction. REPAIR-AMI Investigators. N Engl J Med. 2006;355:1210-21. http://www.nejm.org/doi/full/10.1056/NEJMoa060186
14. Feuchtinger T, Opherk K, Bethge WA, Topp MS, Schuster FR, Weissinger EM, Mohty M, Or R, Maschan M, Schumm M, Hamprecht K, Handgretinger R, Lang P, Einsele H. Adoptive transfer of pp65-specific T cells for the treatment of chemorefractory cytomegalovirus disease or reactivation after haploidentical and matched unrelated stem cell transplantation. Blood. 2010;116:4360-7. http://bloodjournal.hematologylibrary.org/content/116/20/4360.long
15. English K, French A, Wood KJ. Mesenchymal stromal cells: facilitators of successful transplantation? Cell Stem Cell. 2010;7:431-42. http://www.sciencedirect.com/science/article/pii/S1934590910004522

ANNEX 1: SWOT analysis applied to the four tiers of cellular therapy activities for blood establishments

Goal: From the point of view of the BE, analyse why is it beneficial / detrimental (risky) for BE's to be involved in CT activities (categorised in 4 tiers to reflect both the state of c omplexity and the requirements necessary for BEs to enter the field, or stay in it).

CT product category	Strengths	Weaknesses	Opportunities	Threats
	What strengths do BEs have for involvement in CT activities?	**What weaknesses do BEs have for involvement in CT activities?**	**What opportunities are there for BEs for involvement in CT activities?**	**What threats are there for BEs for involvement in CT activities?**
TIER 1: ESTABLISHED, SIMPLE AND NEEDING LITTLE SPECIFIC INFRASTRUCTURE	- Demonstrable reputation for donor care - Over decades-long experience with manufacturing under GMP - Greater experience of highly controlled environment for BE as compared to hospitals. - Experience with apheresis technology - De-centralised structures which provide easy donor and customer (hospital) access	- Infrastructures more geared to the healthy than to patients	- Partnerships with hospitals can mitigate against the weaknesses - Limited specific infrastructure beyond what is available in any BE and limited new technology are required for these activities - The relative high frequency of Tier 1 products among all CT products implies a comparatively favourable balance between set-up investments and routine production. - Tier 1 CT activities may be a good entry point for BE wishing to enter the arena of CT	- The complexity of the products is so modest that the risk of not being able to deliver them is minimal (rigorous training required) - Financial risks are modest: market size is well established and stable; and products are medically established and thus covered by health insurances. - The fact that there is no "market price" for stem cell products will require BE to carefully calculate their costs
TIER 2: SIMPLE, ESTABLISHED CELL PRODUCTS REQUIRING A GMP FACILITY WITH CLASS A IN B WORK ENVIRONMENT	- Same as for Tier 1 products	- Same as for Tier 1 products	- Those BEs capable of generating Tier 1 products will also be able to produce Tier 2 products - Novel therapeutics, specifically for some more common illnesses, may strengthen the political clout of transfusion medicine and improve reputation of BE - This could offer opportunity for developing partnership with hospitals and academic institutions - It may also offer economic opportunity	- The significant financial commitment required for development, clinical testing and licensing of these CT products, as well as the formidable expense of operating a GMP, a cryopreservation and storage facilities must be considered. - The threat of IPR litigation against BE must be considered *(see IPR Chapter)* - In the field of therapies for more frequent illnesses, BEs may find themselves in competition with money-making entities such as start-ups and big pharma.
TIER 3: SIMPLE CELL PRODUCTS REQUIRING A GMP FACILITY WITH CLASS A IN B WORK ENVIRONMENT WHICH ARE LESS WELL ESTABLISHED	- BEs which have been able to generate Tier 1 and 2 products have all infrastructure in place to take CT further	- The expertise for the significantly more complex technology required both for production and testing may not be found in all BEs - Experienced CT personnel is currently heavily sought.	- BEs which have been able to generate Tier 1 and 2 products should have opportunity to further develop and leverage partnerships with hospitals, academic institutions, and industry	- Considerable financial risks: each of the described products are likely to be extremely expensive - As a consequence of their expected high price, underprescribing of these CT products is possible - The threat of IPR litigation against BE must be considered *(see IPR Chapter)* - Competition in this area is likely to be significant
TIER 4: COMPLEX EXPERIMENTAL CELLULAR THERAPEUTICS	- All as in Tiers 1 - 3 - Previous experience in up-scaling to clinical scale and GMP (indispensible) - Existing vigilance programs enable BEs to support clinical trials.	- Lack of awareness of this specific field and related economical uncertainties - Lack of direct clinical access may shield BEs from identifying areas of need.	- To secure partnerships with academic institutions - Promote rigorously funded CT R&D programs	- The considerable expense of CT development "from scratch" cannot be absorbed by the BEs alone - Because some of these products are targeting orphan diseases /diagnoses, development costs may not be covered

Gilles Folléa
Dana Devine
Joanne Pink
Ruth Sylvester

15. THE ROLE OF BLOOD ESTABLISHMENTS IN CELLULAR THERAPIES: REGULATORY ASPECTS

15.1 OVERVIEW OF REGULATORY FRAMEWORK OF BLOOD ESTABLISHMENTS

To ensure the safety, purity and potency of the products, the protection of the donors and the patients who receive them, the collection and preparation of blood and blood products for transfusion in most developed countries is regulated by a competent authority. Blood and blood products are biologics that are considered the same as pharmaceuticals and, therefore, must comply with the same manufacturing rules.

Mandatory quality programmes and the implementation of current Good Manufacturing Practices (cGMPs) are the mainstay of this approach. The main difference between a true pharmaceutical and a blood product is that the originating material is a human donor and each individual unit is a lot. Blood establishments (BEs) operate within these confines having developed standardised processes and procedures concerning the following: the recruitment and screening of donors; collection, testing and labeling of products; deferral of unsuitable donors; destruction of unsafe products; and the tracking and tracing of all products from "cradle to grave" most effectively accomplished with computerised systems.

BEs undergo rigorous audits performed both internally and by external agencies. The external audits are performed by multiple agencies including competent authority and professional accrediting bodies. The frequency of these audits is usually at least annually and often, in the case of internal audits, the frequency is multiple times per annum.

The staffing and training requirements are well established, ensuring that sufficient qualified, competent individuals are available. Change control is a vital programme ensuring that implementation of new/modified procedures, testing requirements, instrumentation, etc. occurs in an organised, coordinated process. All of this is underpinned by a comprehensive quality programme to monitor and continuously improve processes across the continuum of operations.

15.2 INTERNATIONAL CT REGULATORY LANDSCAPE

To facilitate their comparison, the main regulatory requirements for CT activities and products as established in regulations for the European Union [1,2], Australia [3-5], Canada [6,7], and USA [8-12] have been summarised in two tables.

Table one summarises regulatory requirements for all CT products: *(Tiers 1-4)* for Australia, Canada and USA and those for CT products of levels 1-3 for EU *(annex 1)*.

Table two summarises, in a separate table *(annex 2)*, the corresponding regulatory requirements [13,14] for the EU, as the EU has a specific regulation for advanced therapeutic medicinal products (ATMP).

Thus, this analysis encompasses the CT activities and products of the four tiers described in the previous chapter.

Some CT products are relatively new on the regulatory landscape and some issues are still emerging. Though overall, the general aspects of regulation are similar to those of blood, there are some important differences. Some are primarily related to the uniqueness and limited quantity of some CT products, with use limited to small numbers of patients, rendering them equivalent to orphan drugs. On the other hand, some CT products (e.g. those derived from cell banks) may be given to many people, with the risk of exposure to possibly thousands of patients.

In some respects, these products are more akin to vaccines. Additionally, these products have different processing/storage requirements, including prolonged culture and passages. The primary uniqueness of CT products is that many of these products are new and still undergoing research and development. Despite these differences, the environments within which they are manufactured are, and need to be, very similar to those required for blood products.

The competent authority and agencies overseeing and ensuring the safety and effectiveness of these products are, in some cases, the same and, in others, different from those regulating blood. Likewise, the approach to the regulation of CTs is very similar among participating countries, despite the fact that each country has specific unique characteristics.

Each country has a competent authority primarily responsible for specific CTs. In some cases it is a single agency; in others, more than one. The specific agency/department responsible often depends on the function/modification/intended use of the CT. All require either registration or licensure of the establishment and/or product. All also require periodic external inspection by a regulatory authority.

Donor eligibility requirements vary from non-specific to detailed criteria. All mandate informed consent, strict confidentiality/privacy of donors and recipients, and the tracking and tracing of products from origin to recipient. Importation is approved by the responsible competent authority. Each of the regulatory agencies mandates reporting of adverse reactions/events, the variability being the timeframe and specifics. The primary difference between the countries relates primarily to the specific product included in the definition of CT *(Annexes 1 and 2)*.

To help identify the different considerations involved in the regulatory aspects of CT products and activities in BEs, a SWOT analysis is presented below and summarised in Annex 3.

15.2.1 WEAKNESSES AND THREATS FOR BEs

Competent authorities and authorization regimes: regarding the CAs / regulators, the status of CT products and the requirements for authorisation of establishments manufacturing CT products and licensing of CT products, the situation appears to be different in EU as compared to the other countries.

In Australia, Canada and the USA, for CT products of tiers 1–3, there is one national regulator for CT. In EU countries, there could be several regulators involved and this varies from country to country. Therefore, in EU countries, knowing the right regulator(s) for each CT product could be a real difficulty. This does not hold true for ATMPs in EU, as the marketing authorisation procedure is centralised and carried out by the European Medicines Agency (EMA).

CT Product status: although the status of CT products is pretty clear in Australia, Canada and the USA (either drug or biological class 3 or 4), this could vary in EU countries for CT products of tiers 1–3. Depending on the regulator(s) involved this status could vary from medicinal product (drug) to status close to blood products (different from medicinal product). This situation has arisen because each EU country adapted its national transposition of the EU Directive (common rule), as the EU rules allow each country to adopt more stringent rules as compared to the Directive. This explains the lack of harmonization of CT regulatory requirements. This does not hold true for ATMPs in EU, as their status is clearly a medicinal product one.

Fear of change: regulators' fear of changes / innovation and lengthy and complex processes for licensing CT products are perceived as threats to BEs.

Technical requirements: (and their adaptation to scientific and technical progress) also impact the regulatory environment. While in Australia, Canada and the USA, BEs have established quality systems, with extensive validations of processes and activity specific license requirements, most BEs in those countries have limited involvement in specific CT technologies. For this reason, most are not sufficiently experienced in complex CT technologies (these activities are more developed in academic centres).

There appears to be a greater involvement and experience in some EU BEs than anywhere else, particularly in the more complex technical requirements of some products. As a consequence, direct regulatory expertise and experience in BEs is relatively limited, potentially increasing the difficulty for such BEs to enter the CT field. On the other hand, this should also be considered an opportunity for these BEs to learn from the ones who have had greater involvement.

Within this context, potential barriers to market entry include the following:
- Capability of the BEs to execute: the timely establishment of a new CT process, including the regulatory process (eg licensing), is considerably more challenging for BEs with limited experience in complex CT technologies.
- Acceptance of the higher risk profile by Boards: for such BEs contemplating implementation of a complex CT process, the change in risk profile may lead to difficulty to have new CT developments accepted by their Boards.
- Liability issues about risk for patients / issues with insurance companies (seems to be higher in the USA).
- Availability of funding: this could result in non-acceptance by the funder to fund a new set of activities.

Import/export of human cells: Canada and the USA have extensive experience and consider the high regulatory constraints in their countries as a threat.

Clinical trials: the regulatory activities related to the use of Biologics in Clinical Trials, are currently not fully developed in BEs as they are mostly carried out in academic centres, particularly in North America. This has resulted in limited expertise in the regulatory aspects of related products. Some EU BEs do have some experience in this area, and it will be fruitful to exchange information with others.

Timelines: finally, it is important to stress that the timelines, (i.e. how long it takes to put a product through clinical trials and then as part of the therapeutic armamentarium.) are long and there will be many failures. The governance expectations and funding arrangements for BEs may not be able to accommodate or tolerate long delays in achieving product licensing. This could lead BEs to abandon (some) CT activities, particularly when this is factored in with the heavy burden of regulatory requirements.

15.2.2 STRENGTHS AND OPPORTUNITIES FOR BEs

Authorisation and licensing: the requirements for authorisation of establishments manufacturing CT products and licensing of CT products, are complex. In Australia, Canada and the US, where it is felt that CT involvement is relatively less mature than in the EU, the depth of GMP experience within BEs provides an opportunity for leveraging and sharing experience on regulatory issues with the regulators.

Expertise and experience in Quality assurance (QA): all ABO members recognise that the in-depth experience in GMP and particularly in QA/Quality Control, audits and inspections are strength for BEs. Guidelines and training for inspection in the area of tissues and cells, developed by the EU funded EUSTITE programme (completed in 2010), should be disseminated to all BEs.

Expertise and experience in donor management: everyone agrees that the experience of BEs in donor selection, evaluation and consent, through working with blood and haematopoietic stem cell (HSC) donors is a considerable strength and opportunity for BEs. This, along with the regulatory knowledge in this area, positions them favorably to facilitate management of donors for CT products. This has been already been capitalised

upon by some BEs working in partnership with companies manufacturing commercial CT products (e.g. Provenge, Dendreon) by carrying out the collections of source material.

Experience in simple *(tier 1)* CT technologies: most BEs have gained significant experience in technical and scientific aspects of simple *(tier 1)* CT technologies. And an appreciable number of BEs are also experienced in more complex CT technologies (particularly in the EU *(tiers 2 & 3)*. Their expertise in the regulatory issues is also a significant strength for these BEs and gives them an opportunity to further develop CT activities and progress to higher levels of complexity *(e.g. from tier 2 to 3)*, since regulations tend to become more complex as the complexity of the cellular products increases.

Networking opportunities: an opportunity for BEs would be to develop a network with other BEs (at continental level, e.g. Europe for EBA members) to share the technical and regulatory burden of complex CT activities.

Opportunities partnerships: another opportunity for BEs would be to develop partnerships with pharmaceutical / biological companies, to share the technical and regulatory burden of more complex CT activities. Where such collaborations already exist, they should be fostered and developed further. BEs have both technical and regulatory expertise in this area. This should be mutually beneficial and should cover the whole process from collection of the source material, to further manufacturing (as BEs have GMP infrastructures).

Data management and vigilance: all BEs have an extensive body of expertise in data protection, confidentiality management, traceability and vigilance. This could be an opportunity for BEs to implement and/or further develop CT related vigilance (biovigilance for CT products, donor vigilance, medical device vigilance and, when appropriate, reagent vigilance, e.g. for the reagents used in QC of CT products).

The same applies to notification of serious adverse reactions and events (SARE) in which all BEs have extensive experience. An opportunity for BEs would be to benefit from the experience acquired in blood products to improve / develop effective systems of notification for CT activities and products in / from BEs (in partnership with CAs). In this perspective, the tools provided by the EUSTITE programme for SARE grading, impact assessment and reporting should be disseminated to all relevant BEs. The experience of multi-national cooperation in vigilance in the area of tissues and cells, gained by the EUSTITE programme should be extended further, even beyond the EU, creating a real ABO BE networking for CTs.

Reporting obligations: all BEs have extensive experience in reporting obligations, which should be considered as an opportunity to comply with the same obligations applied to CT activities and products.

Import/export of human cells: some BEs in some EU countries have gained experience, which could be an opportunity to share with other members where appropriate.

Clinical trials: the regulatory activities related to the use of biological products in clinical trials, are currently actively developed in several BEs in EU. This experience could be used to further develop high level CT activities in the relevant BEs. If appropriate, it could also be shared with other members to help them in such development. This could lead to the establishment of a network of BEs (at a continental level, e.g. EBA for EU).

Timelines: finally, some BEs, particularly in EU, have considerable experience in licensing complex CT products. An opportunity exists for all members to share and leverage this experience, particularly within the context of the growing experience in managed convergence. They may also consider influencing through (lobbying / advocacy) the CAs to set up "acceptable" rules for licensing rare CT products intended for limited number of patients. This could help reducing constraints and time required to make such products available for patients.

15.3 CONCLUSIONS AND RECOMMENDATIONS

In order to better understand the potential added value and risks for BEs to implement and/or further develop CT activities and products, focusing on regulatory aspects, we compared the main regulatory requirements for CT activities and products *(tiers 1 – 4, see Chapter 14)*, in EU, Australia, Canada and the USA. Based on this comparison, a SWOT analysis led to the following main conclusions and recommendations for ABO members.

Regulatory experience: for BEs having no experience in CT product manufacturing, given the fact that the technical and regulatory requirements are growing with the complexity of CT processes and products *(tiers 1, 2, 3, 4)*, it will be more difficult to directly enter the field of CT. Regulatory experience acquired with blood products (GMP, licensing, traceability, vigilances) could mitigate this somewhat. However BEs are well positioned to leverage their GMP competence through a consulting agreement or partnership approach.

Conversely, for BEs having already acquired experience in CT processes and products, including the regulatory requirements and processes, this experience will facilitate the development of CT products of growing complexity.

BE networking: the creation of a network of BEs could facilitate sharing the experience and burden of the regulatory constraints. This could be done at a continental level (e.g. EBA BEs for EU), but there would also be benefits in a more global approach.

Constructive collaboration with competent authorities: the development of constructive collaboration with CAs, according to the managed convergence principles, could help in setting up "acceptable" rules for licensing rare CT products intended for limited number of patients and begin the process of harmonisation of regulatory rules for CT products. This could be done at a global level, to reduce time and costs for the clinical benefit of patients and all involved stakeholders (including BEs and health care providers).

REFERENCES

1. Directive 2004/23/EC of the European Parliament and of the CounciN on setting standards of quality and safety for the donation, procurement, testing, processing, preservation, storage and distribution of human tissues and cells. http://europa.eu/legislation_summaries/public_health/threats_to_health/c11573_en.htk
2. Commission Directive 2006/86/EC implementing Directive 2004/23/EC of the European Parliament and of the Council as regards traceability requirements, notification of serious adverse reactions and events and certain technical requirements for the coding, processing, preservation, storage and distribution of human tissues and cells. http://eur-lex.europa.eu/LexUriServ/LexUriServ.do?uri=CELEX:32006D0086:en:NOk
3. Australian Regulatory Guidelines for Biologicals, version 1.0, June 2011. http://www.tga.gov.au/industry/biologicals-argb.htm
4. Australian Regulatory framework for biologicals. http://www.tga.gov.au/industry/biologicals-framework.htm
5. Australian Therapeutic Goods Order No. 75 - Standard for Haematopoietic Progenitor Cells Derived from Cord Blood (01/08/2007). http://www.comlaw.gov.au/Details/F2007L03598 Publication of the Safety of Human Cells, Tissues and Organs for Transplantation Regulations in Canada Gazette Part II: Safety of human cells, tissues and organs for transplantation regulations. JUS-604762: a? S.. 2004, c. 23, s. 2.
6. http://www.hc-sc.gc.ca/dhp-mps/brgtherap/reg-init/cell/cto_regs_rias-reir-eng.php
7. Canadian Standards Association. *CSA Standard Z900.1-03: Cells, Tissues, and Organs for Transplantation and Assisted Reproduction: General Requirements.2003. Accesssible at www.csa.ca,* list ID 2013667
8. 21 CFR 211: Code of Federal Regulations Title 21, Part 211: Current Good Manufacturing Practice for finished pharmaceuticals. http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfcfr/CFRSearch.cfm?CFRPart=211
9. 21 CFR 820: Code of Federal Regulations Title 21, Part 820: Quality system regulation http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfcfr/CFRSearch.cfm?CFRPart=820
10. 21 CFR 2171: Code of Federal Regulations Title 21, Part 2171: Human cells, tissues and cellular and tissue-based products. http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfcfr/CFRSearch.cfm?CFRPart=1271
11. FDA Webpage, Cellular & Gene Therapy Products: http://www.fda.gov/BiologicsBloodVaccines/CellularGeneTherapyProducts/default.htm
12. FDA cellular therapy guidances: http://www.fda.gov/BiologicsBloodVaccines/GuidanceComplianceRegulatoryInformation/Guidances/CellularandGeneTherapy/default.htm
13. Regulation (EC) No 1394/2007 of the European Parliament and of the Council on advanced therapy medicinal products and amending Directive 2001/83/EC and Regulation (EC) No 726/2004. http://ec.europa.eu/health/files/eudralex/vol-1/reg_2007_1394/reg_2007_1394_en.pdf
14. Commission Directive 2009/120/EC amending Directive 2001/83/EC of the European Parliament and of the Council on the Community code relating to medicinal products for human use as regards advanced therapy medicinal products. http://ec.europa.eu/health/human-use/advanced-therapies/developments/index_en.htm

Annex 1: Main regulatory requirements for CT products and activities (ATMP not included for EU, all levels CT products included for others)

Item	Australia	Canada		EU	USA
Regulatory ref	Australian Regulatory Guidelines for Biologicals, version 1.0, June 2011 ***Note**: The Biologicals Regulatory Framework came into effect on 31 May 2011 with the amendment of the Therapeutic Goods Act 1989 (Cwlth) (TG Act). Transition arrangements apply for up to three years to allow all biologicals to meet the new arrangements, which are administered by the Therapeutic Goods Administration (TGA). Cellular Therapies typically classified as Class 3 or 4 Biologicals – beyond minimal manipulation.*	· Safety of Human Cells, Tissues and Organs for Transplantation Regulations · National standard CAN/CSA Z900.1, *Cells, Tissues and Organs for Transplantation and Assisted Reproduction: General Requirements* as well as the subset standards *The regulations directly reference the national standard.* *Applies to minimally manipulated cells and tissues for transplantation in another individual*		Directive 2004/23/EC: standards of quality and safety for the donation, procurement, testing, processing, preservation, storage and distribution of human tissues and cells Directive 2006/86/EC: traceability requirements, notification of serious adverse reactions and events and certain technical requirements	21 US Code of Federal Regulation Part 211 – GMP of Finished Pharmaceutical, Part 1271 – Good Tissue Practices – HCT/Ps Part 820 – Medical Device products
Definitions	Therapeutic goods, biological (Class 1, 2, 3 & 4), minimal manipulation, complex methods of modification, homologous, ARTG (Australian Register of Therapeutic Goods), Medicines, Medical Devices, Exceptional Release, Dossier, manufacture	Accident, adverse reaction, banked, cell, distribute, donor, donor assessment record, donor identification code, donor screening, donor suitability assessment, donor testing, error, establishment, exceptional distribution, exterior label, exterior package, interior label, interior package, medical director, minimally manipulated, package insert, processing, quality assurance system, scientific director, serious adverse reaction, source establishment, tissue, transplant		Cells, donor, donation, procurement, processing, storage, distribution, serious adverse event, serious adverse reaction, "tissue establishment"	HCT/P - Human Cells Tissues & Cellular & Tissue-Based Product – 361 HCT/P must meet all 4: · Minimally manipulated AND · Homologous Use AND · Not combined with any other article AND · Doesn't have systemic affect & not dependent on metabolic activity of living cells for its primary function OR if so is for use only in: autologous, in 1° or 2° relative, or reproductive use – 351 – HCT/Ps that don't meet all 361 criteria, are manipulated, cultured or expanded cell products are considered medical devices
Competent authority	Therapeutic Goods Administration (TGA) – for biologicals Gene Technology Regulator – for genetically modified biological	Health Canada		Designated by member state Responsible for implementing the requirements	US Food and Drug Administration (FDA) – Centres for Biologics Evaluation and Research (CBER) – 361 HCT/Ps – Centres for Devices and Radiological Health (CDRH) – medical devices
Accreditation, designation, authorisation or licensing of establishments and cell preparation processes	Mandatory compliance with the Biologicals Framework (TGA) incorporating: - Therapeutic Goods Act and - Therapeutic Goods Regulations, - Therapeutic Goods Orders, - Product standards, and other technical product requirements - Labeling standards - Default standards (BP, EP or USP) - Manufacturing Principles & cGMP - Listing on ARTG for supply 2 types of "license": a) A manufacturing license (GMP compliance) is required for manufacture of Class 2, 3 & 4 Biologicals, and b) supply of these biologicals requires approval of Product Dossier (compliance with relevant product standards) and listing on ARTG.	Establishments that import, process, distribute and transplant must be registered with Health Canada		Mandatory for establishments where activities of testing, processing, preservation, storage or distribution of human cells intended for human applications. Responsibility of CA.	All HCT/P manufacturers must register & list products with FDA/CBER 351 HCT/P Devices may require submission for Premarket Approval (PMA) or 510(k) demonstration of substantial equivalence to another product already approved. Cord Bloods now (as of 1 Oct 11) required to be licensed or used under IND. Other professional accrediting (not licensing) organisations: AABB College of American Pathologist FACT/Netcord Joint Commission National Marrow Donor Program

▼ P.288

▼ P.289

Item	Australia	Canada		EU	USA
Inspections and control measures	Audit frequency by CA determined on basis of risk (higher risk products & processes audited more frequently, typically 12-18 months for Classes 2, 3 & 4). After biologicals have been approved for supply, ongoing (post-market) controls include manufacturing surveillance, targeted review and laboratory testing, reporting adverse events, investigations and recalls.	Carried out by Health Canada. The inspection strategy is in development. The majority of registered establishments have been inspected once.		Carried out by CA Interval < 2 years Includes facilities of any third parties	Subject to inspection by FDA as necessary in FDA's judgment, usually bi-annually.
Donor selection and evaluation: Principles	Minimal eligibility criteria used to determine donor risk of exposure to infectious disease and ineligibility periods. Private Medical and Social History interview must be conducted by a trained interviewer and should be at a face-to-face interview with the donor or guardian/next-of-kin.	Not specifically mentioned in the Regulations. The national standard states no monetary inducement, goods or services shall be offered to donors, next of kin, donor's estate or third party.		MS shall endeavor to ensure - **voluntary and unpaid** donations of (tissues and) cells - procurement of (tissues and) cells carried out on a **non-profit** basis.	Title 21 CFR Part 1270, 1271 Subpart C requires donor screening and testing for communicable diseases. Guidance Document on Eligibility Determination for Donors of HCT/Ps (Feb 07)
Donor selection and evaluation: Consent	Mandatory informed consent.	Consent procedures shall conform to applicable laws, regulations and medical standard of practice. Record of consent maintained in donor record.		Mandatory consent requirements met	Mandatory consent.
Donor selection and evaluation : Data protection and confidentiality	Unrelated donor and recipient information kept confidential. The interview must occur no more than 30 days prior to or 30 days after collection, and must occur prior to release of product from quarantine, unless otherwise specified in product-specific Orders under section 10 of the Act.	Donor Identification codes are used for labeling products and to link back to donor information so donors remain anonymous.		All data rendered anonymous so that neither donors nor recipients remain identifiable	Donor confidentiality maintained. Patient confidentiality governed by HIPPA Act (privacy law).
Technical requirements (and their adaptation to scientific and technical progress)	A product dossier submission is evaluated to ensure compliance with any default standards (such as pharmacopoeia monographs), product-specific standards and Labeling standards. The level of detail in the dossier should correspond to the potential risk that the product poses to the recipient. For Class 4 biologicals, additional supporting data is required, including sections on non-clinical and clinical development.	Regulatory framework is based on the National standard which a Technical Committee prepares. Requirements cover: donor suitability assessment, infectious disease testing, storage, distribution, exceptional distribution (when cells not processed under the regulations), quality assurance system, packaging and labeling		Requirements (decided and adapted by the EC, assisted by a committee) for: quality system, selection criteria for the donor of cells, laboratory tests for donors, cell procurement procedures and reception at the establishment, cell processing, storage and distribution, direct distribution to recipient of specific cells, written agreements with third parties	Guidance for Current Good Tissue Practices published Dec 11 details requirements.
Traceability	Donors, Products and Constituents are uniquely identified and form part of batch record to ensure traceability. Records are retained for a minimum of 20 years.	A donor identification code (DIC) is assigned to each donor of a cell, tissue. DIC must be component of records system. Records retained minimum of 10 years after transplantation, distribution, final disposition or expiry of the cell or tissue.		All cells procured, processed, stored or distributed and products and materials coming into contact with these cells, for mininimum 30 yrs. Unique code to each donation	Traceability and trackability maintained back to donor. Each product has unique number. ISBT not mandatory.

▼ P.290

▼ P.291

Item	Australia	Canada		EU	USA
Import/export of human cells	Before biologicals can be legally imported, exported, manufactured or supplied in Australia, they must be: · included on the Australian Register of Therapeutic Goods (ARTG) or · otherwise exempted, approved or authorised as per the Biologicals Regulatory Framework e.g. for clinical trials, exceptional release, emergency use etc (see below). · Australian Quarantine Inspection Service (AQIS) Import Permit application & approval required for biological goods.	Establishments that import (other than transplant establishments that don't further distribute) must be registered except lymphohaematopoietic cells may be imported from an establishment that is not registered. If foreign establishment is only involved in storage and distribution of CTO to Canadian establishments it is not required to register. No requirements for export.		Undertaken by accredited establishments, with equivalent standards of quality and safety	All imports must be registered and approved by FDA/CBER and CDRH.
Register of establishments and reporting obligations	Establishments required to keep a detailed record of activities and quality data which are the subject of regular management review. Annual update of dossier and re-submission to TGA. Mandatory reporting of adverse events and recalls. Mandatory reporting of any change to license conditions.	Establishments shall keep records of their activities. There is no requirement to submit annual reports. Health Canada maintains a listing of registered establishments that is available to the public		Establishments shall keep a record of their activities Annual report (publicly accessible.) to submit to CA	Registration with FDA of manufacturers and their products. Records maintained at least 10 years after expiration of products.
Notification of serious adverse events and reactions	Manufacturers required to monitor and keep records of all adverse events, including mandatory reporting of serious adverse events within statutory timeframes: · 48 hours if the event represents a serious threat to public health; · 10 days if the event led to the death or serious deterioration in the state of health of a patient, a user of the biological or another person; · 30 days if the event, if it occurred again, might lead to the death or serious deterioration in the state of health of a patient, a user of the biological or another person. Medical practitioners, patients, and others are encouraged to report any incidents/ adverse events to the TGA. The TGA investigates and responds to adverse events as appropriate. In addition to the mandatory adverse event reporting requirements the TGA will also have a voluntary incident reporting scheme for biologicals where any incidents involving a biological can be reported.	Health Canada must be notified of suspected error or accident identified after distribution of cells that could lead to a serious adverse reaction involving the transmission of an infectious disease or disease agent or an unexpected serious adverse reaction that is thought to involve the transmission of an infectious disease or disease agent. Report should include steps to mitigate further risk, root cause analysis and corrective actions taken.		CA is notified by Responsible Person of any serious adverse events and reactions, with a report analyzing cause and ensuing outcome Procedure enabling recalls	Mandatory reporting of adverse events and deviations from Title 21 to FDA.

▼ P.292

▼ P.293

Item	Australia	Canada	EU	USA
Inclusions (Regulated as biologicals)	– Human tissue therapy products, such as: · skin · musculoskeletal–bone, collagen · cardiovascular–heart valves · ocular–whole eye, cornea – Human cellular therapy products, such as: · stem cells and progenitor cells; e.g. – mesenchymal stem cells (MSCs) – haematopoietic progenitor cells for uses other than haematopoietic reconstitution – other stem cells (e.g. neural, epithelial) – other progenitor cells (e.g. nasal cells) · other human cell-based products, such as fibroblasts, epithelial cells, chondrocytes · immunotherapy products, such as – cell-based tumour vaccines – human cellular vaccines · genetically modified cells – Combination products i.e. biologicals presented as a combination product with a medical device (e.g. metal stent coated with a matrix and endothelial cells) – Kits, systems or procedure packs where a biological is packaged together with other biological products – No biological medicines are regulated as biologicals (see below)	Organs and minimally manipulated cells and tissues.		361 HCT/Ps – minimally manipulated, intended for homologous use only and not combined with another article. – Amniotic membrane with used alone & w/o added cells – Bone – Cartilage – Cornea – Fascia – Ligament – Pericardium – Peripheral or umbilical cord blood stem cells (for auto or 1/2° relative) – Sclera – Skin – Tendon – Vascular graft – Heart Valves – Dura Mater – Reproductive cells & tissues 351 Products – not 361s. – Demineralised bone + carrier – Decellularised Pulmonary Artery Patch Allograft – Cryopreserved amniotic membrane clipped into thermoplastic ring set – Interactive wound healing device – bovine collagen and allogeneic fibroblasts/keratinocytes – Somatic Cellular Therapy products – Gene Therapy products – Manipulated Autologous Cells for Structural Use (MAS)

▼ P.294

▼ P.295

Item	Australia	Canada		EU	USA
Exclusions (Biologicals that are excluded from regulation as therapeutic goods)	- Fresh viable human organs, or parts of human organs, for direct donor-to-host transplantation and used in accordance with applicable laws and standards - Fresh viable human haematopoietic progenitor cells (HPSCs) for direct donor-to-host transplantation for the purpose of haematopoietic reconstitution (e.g. bone marrow cells and cord blood) - human tissue and cells that are: · collected from a patient who is under the clinical care and treatment of a medical practitioner registered under a law of a State or an internal Territory; and · manufactured by that medical practitioner, or by a person or persons under the professional supervision of that medical practitioner, for therapeutic application in the treatment of a single indication and in a single course of treatment of that patient by the same medical practitioner, or by a person or persons under the professional supervision of the same medical practitioner - reproductive tissue (e.g. sperm, eggs, embryos for in vitro fertilisation and other assisted reproductive technologies) that are 'unmanipulated' (i.e. they have not been processed in any way apart from freezing).	- Cells, tissues and organs that are for non-homologous or, autologous use; - heart valves and dura mater; - tissues and cells – except for islet cells, and except for lymphohaematopoietic cells that are derived from bone marrow,- that have a systemic effect and depend on their metabolic activity for their primary function; - medical devices that contain cells or tissues and that are the subject of investigational testing involving human subjects under Part 3 of the Medical Devices Regulations; - cells, tissues and organs that are the subject of clinical trials under Division 5 of Part C of the Food and Drug Regulations; - Class IV medical devices that are regulated under the Medical Devices Regulations; - blood components, blood products and whole blood, except for cord blood and peripheral blood for use in lymphohaematopoietic cell transplantation; - cells and tissues that are regulated under the Assisted Human Reproduction Act or any of its regulations; and semen that is regulated under the Processing and Distribution of Semen for Assisted Conception Regulations.		Organs	Organs
Exclusions (Products that are regulated as therapeutic goods but not as biologicals)	- blood, blood components - haematopoietic progenitor cells (used for haematopoietic reconstitution), other than those which are excluded from regulation (see above); - samples of human cells or tissues that are solely for diagnostic purposes in the same individual - in-vitro diagnostic devices (IVDs) - biological medicines including · vaccines (that do not contain viable human cells) · recombinant products · plasma-derived products (or that contain plasma-derived products)				

▼ P.296

▼ P.297

Item	Australia	Canada		EU	USA
Exceptional Release	The TG Regulations allow exceptional release of a biological when the following conditions are all met: - The patient is seriously ill and has been clinically assessed by the treating medical practitioner to require the biological urgently to treat a serious condition. - A biological that is included on the ARTG and conforms with the applicable manufacturing requirements and standards is not available or not available within the time necessary for treatment to occur, OR A biological is available that is included on the ARTG but it does not conform with the relevant standards specified under section 10 of the TG Act and/or the relevant manufacturing principles as specified under section 36 of the TG Act. - No other approved therapeutic good would be suitable. - In light of the above and given the clinical situation, the biological is assessed by the treating medical practitioner as the most suitable treatment for the patient. Therapeutic Goods Administration Australian Regulatory Guidelines for Biologicals Part 2 Section 2.2 Approval for inclusion on the ARTG V1.0 June 2011 Page 26 of 30 - The biological is to be used only for the treatment of one patient.	A source establishment may distribute cells or tissues that have not been determined safe for transplantation if all of the following conditions are met: - a cell or tissue that has been determined safe for transplantation is not immediately available; - the transplant physician or dentist, based on their clinical judgment, authorises the exceptional distribution; and - the transplant establishment obtains the informed consent of the recipient.			
Use of Biologics in Clinical Trials	The use of biologicals in clinical trials is regulated by TGA under similar arrangements to those for medicines and medical devices i.e. Clinical Trial Notification and Clinical Trial Exemption Schemes.	Health Canada Food and Drug Regulations Part C, Division 5			Governed by FDA/CBER or CDRH under IND.
Timelines? i.e. how long it takes to put a product "on the market"	TGA must respond to application within 40 days of submission (incl fee) – acceptance for evaluation or rejection. Evaluation must be completed within 365 days of notice of acceptance and evaluation process.	Depends The Special Access Program (SAP) is followed to access a drug (e.g. biologics) that cannot otherwise be sold or distributed in Canada.			Depends

Annex 2: Main regulatory requirements for Cellular Therapy Advanced Therapy Medicinal Products (EU only: separate specific regulation for these products)

Item	EU
Regulatory ref	-Regulation EC/1394/2007 on advanced therapy medicinal products -Directive 2009/120/EC relating to medicinal products for human use as regards advanced therapy medicinal products
Definitions	- ATMP: gene TMP, somatic cell TMP, tissue engineered TMP. - Cells considered 'engineered' if subject to substantial manipulation and/or not intended to be used for the same essential function(s) in the recipient as in the donor. - Combined ATMP: incorporate medical device(s)
Marketing authorisation procedure	- Centralised authorisation procedure, with a single scientific evaluation of the quality, safety and efficacy of product, carried out to the highest possible standard by the European Medicines Agency (EMA). - A Committee for Advanced Therapies should prepare a draft opinion on the quality, safety and efficacy of each ATMP for final approval by the EMA's Committee for Medicinal Products for Human Use. - Combined ATMP must comply also with the related requirements (e.g. medical devices)
Clinical trials	Current rules for MPs (Directive 2001/20/EC) + detailed guidelines on good clinical practice specific to ATMPs.
Donation, procurement and testing of human cells	- Human cells contained in ATMPs should be procured from voluntary and unpaid donation. - Donation, procurement and testing made in accordance with Directive 2004/23/EC.
Technical requirements	- Guidelines in line with the principles of GMP and specific to ATMPs. - Specific requirements for ATMPs containing devices
Summary of product characteristics, labeling and package leaflet	- Rules specific to ATMPs. - Unique donation (patient if Autologous) and product codes on special immediate packaging
Post-authorisation follow-up of efficacy and adverse reactions, and risk management	- Specific guidelines for ATMPs - Traceability: data to be kept for a minimum of 30 years after the expiry date of the product, or longer if required by EC. - In case of bankruptcy or liquidation of the marketing authorisation holder, data shall be transferred to EMA.
Scientific recommendation on advanced therapy classification	- Any applicant developing a product based on ATMP cells may request a scientific recommendation of the EMA with a view to determining whether the referred product falls, on scientific grounds, within the definition of ATMP. - The Agency shall publish summaries of the recommendations delivered.
Report and review	By 30/12/2012, the EC shall publish a report on the application of this Regulation, including information on different types of ATMPs authorised.

Annex 3: SWOT analysis: regulatory requirements for Cellular Therapy (all levels included: 1 - 4)

GOAL: From the point of view of the BE, why is it beneficial / detrimental (risky) for BEs to be involved in CTs regarding the regulatory requirements?

Item	Strengths	Weaknesses	Opportunities	Threats
	What strengths are there for BEs involvement in CTs from a regulatory perspective?	**What weaknesses are there for BEs involvement in CTs from a regulatory perspective?**	**What opportunities are there for BEs involvement in CTs from a regulatory Perspective?**	**What threats are there for BEs involvement in CTs from a regulatory Perspective?**
Regulatory ref	Knowledge / experience of BE	No	No	No
Competent authority	AU, CA,US: same regulators for BEs / BPs and CT products EU: one common set of rules for the 27 countries (Directive)	EU: different regulators for BEs and CT products (high diversity between countries)	AU, CA, US: similar way to envisage regulatory harmonisation from one field (BE / BP) to another (CT); sharing experience between domains.	EU: transposition of EU Directive led to different rules in different countries (more stringent than original Directive); difficulty to identify the right regulators
Accreditation, designation, authorisation or licensing of establishments / processes / CT products	AU: evidence based approach in reasonable period of time EU: some BEs have good experience of licensing process even for high complexity level CT products.		CA, US: experience in evolution of BPs under Drug Act could be useful EU: the acquired experience could be used to share management of regulatory constraints within ABO members and develop a specific managed convergence for this field.	- CA, US complexity of licensing complex products - All: regulators' fear of changes / innovation? - All: lengthy and complex process
Inspections and control measures	All: extensive experience for BE/BP	No	GMP experience	No
Donor selection and evaluation : principles, consent	All: extensive experience with blood donors and haematopoietic stem cell (HSC) donors	No	Experience in blood donors could facilitate management of CT donors	Potential risk of competition between blood and CT donors (e.g. apheresis donors)? Low.

▼ P.300

Item	Strengths	Weaknesses	Opportunities	Threats
Technical requirements (and their adaptation to scientific and technical progress)	All: extensive experience in GMP and simple processes involving blood cells. EU: extensive experience in GMP; many BEs experienced in simple (level 1) CT technologies and appreciable number of BEs experienced in complex CT technologies (level 2 & 3) (more developed than in AU, the USA and CA). AU BEs provides GMP CT consultancy services, but no direct CT technology experience.	AU, CA, USA: most BEs not very involved in specific CT technologies not sufficiently experienced in complex CT technologies (more developed in academic centres). EU: a few countries with BEs not involved in CT	All: collections for CT in BEs are growing and could be further developed; BEs have both technical and regulatory expertise. EU: current experience could be used to develop CT activities of higher levels (2, 3, ATMP), including the regulatory aspects. All: develop partnerships with Pharmaceutical / Biological companies to share the technical and regulatory burden of higher levels CT activities	High level of regulatory constraints could lead to reinforce the following threats: - BE not sufficiently experienced in complex CT technologies, and difficulty to set up this in as short time? - Change in risk profile may lead to difficulty to have new CT developments accepted by Boards? - Non acceptance by funder to fund a new set of activities?
Data protection and confidentiality	All: extensive experience in constraints of data protection for blood donors	No	No	No
Traceability	Very extensive experience in traceability, lookback, vigilances and related IT systems	No	All: use the current experience to develop/ set up required vigilances (biovigilance, MD vigilance…)	No
Notification of serious adverse events and reactions	All: extensive experience in this reporting, mandatory for BPs, (although a national vigilance system is not developed in all countries)	No	All: take benefit from the experience acquired in BE/BP to improve / develop effective system of notification for CT activities and products in / from BEs (in partnership with CAs when feasible)	No

▶ P.301

Item	Strengths	Weaknesses	Opportunities	Threats
Register of establishments and reporting obligations	Extensive experience	No	All: use the experience acquired in BE/BP for CT activities in BEs	No
Import/export of human cells	All: some experience in import / export of CT products (e.g. HSC) but in some cases as 3rd parties EU: good experience in some EU BEs	US: very limited experience in import / export apart rare type RBC	AU: some experience but still limited, could be developed further. EU: the current experience could be shared with ABO members	CA & USA: FDA constraints very high.
Use of Biologics in Clinical Trials	EU: several BEs involved in manufacturing CT products for clinical trials, including regulatory aspects	AU, CA, USA: these activities are currently more carried out in Academic centres (not BEs)	EU: the current experience could be used to further develop high level CT activities in concerned BE (and if appropriate shared with other members to help them in such development). Set up a network of ABO BEs for these activities, regarding the regulatory aspects?	For BEs not involved yet, risk to never enter the field?
Timelines? i.e. how long it takes to put a product on the market	Experience in licensing rare blood products (e.g. plasma derived)	Need of a solid structure to sustain long delays of licensing	Influence (lobbying / advocacy) the CA to set up "acceptable" rules for licensing rare CT products for limited number of patients.	Obligation to abandon some CT activities, given the too heavy burden of regulatory constraints?

René van Lier
David Allan

16. THE ROLE OF BLOOD ESTABLISHMENTS IN CELLULAR THERAPIES: RESEARCH ISSUES

With increasing activity in the area of cellular therapy to treat human disease, blood establishments are faced with decisions regarding their level of engagement and leadership. Cellular Therapy is a broad term that may encompass many types of cellular products that require varying degrees of cell manipulation and preparation prior to use in humans. Much research is still required in the development of cellular therapeutics before their full potential can be realised. The topic of this chapter is the opportunities for blood establishments in the developmental and research work required for the translation of promising concepts into clinical practice.

1. **Experience of blood establishments**
   Blood establishments are uniquely positioned within the field of cellular therapy due to ready access and familiarity with donors, and access to originating material for the production of many cellular therapy products. The collective expertise and knowledge of blood establishments related to standardised preparation and delivery of blood components for routine patient care brings an infrastructure that is ideally suited to facilitate translational studies. Issues such as quality assurance of products, microbiological qualification, patient-specific component delivery, biovigilance and traceability areas, these are all particular areas of expertise that blood establishments could bring to research collaborations or partnerships in the area of cellular therapy.

   Moreover, blood establishments routinely develop cooperative and collaborative relationships with hospitals, research institutes and academic laboratories and would be familiar with processes that allow for the integration of complementary knowledge from different sites.

2. **Potential limits for blood establishments**
   Some areas that may be less well developed in blood establishments include the current lack of practical or real hands-on experience with the production of some cellular therapeutics. In addition, the mandate of blood establishments to maintain a safe and reliable blood supply has not typically included cellular therapy products aside from peripheral blood progenitor cell processing and umbilical cord blood collection and storage. Thus, funding may not be available, especially during climates of fiscal restraint, to expand their operations into cellular therapeutics. Further, blood establishments in some jurisdictions may not have previous experience partnering with academic institutions in externally funded research competitions.

   Current research activity within most blood establishments does not typically encompass research on novel cellular therapeutics. Furthermore, some blood establishments may harbor internal reluctance to embrace research activities in new areas of interest. Blood establishments that partner with other academic institutions may be viewed as facilitators and not leaders in cellular therapy research, which may limit external visibility and de-emphasize credit for any related successes. Traditionally, blood operators have been reluctant to embrace early phases of exploratory basic or clinical research and there may be internal resistance to participating in cellular therapy research that is deemed overly "pre-clinical".

3. **Potential threats for blood establishments**
   It is also worth discussing potential threats to blood establishments associated with increased activity in the area of cellular therapy. Many novel cellular therapies will not work at first or will be seen as competing with alternative therapies, thus bringing potential negative attention to the research efforts of scientists affiliated with blood establishments.

   The involvement of private companies in the development and manufacturing of cellular therapies may create challenges in the regulation and safety of these specialised cell products. The length of time related to completing and communicating "proof of concept" studies may limit (I) the generation of high impact communications and (II) could stall the acquisition of competitive external funding. Moreover, the potential for adverse outcomes associated with novel cellular therapy may be an impediment for more conservative blood establishments.

4. **Opportunities for blood establishments**
   Given the obvious expertise of blood operators, and acknowledging potential limitations associated with research in cell therapeutics, it is worth identifying particular opportunities that blood operators should consider with regards to cellular therapy. Early involvement in the field may allow blood operators to exert a level of rigor and standardisation to the development of methods that link standard practices in blood transfusion to the preparation and delivery of advanced therapeutic medicinal products (ATMPs).

   Several of today's labile blood products might become tomorrow ATMPs; for example, pathogen attenuated blood products or stem cell-derived red blood cells (RBCs). Involvement in cellular therapy may allow blood establishments to capitalize on a strategic interface between basic research and health care providers; positioning themselves on the side of product manufacturing and preparation and distinguishing their involvement from questions related to product use.

   Involvement in cellular therapy would undoubtedly require the development of teams comprising partners in academic institutes, including basic and early clinical researchers. Enhancing these partnerships may accelerate progress in the field of cellular therapy and yield benefits in other areas involving conventional blood products. In turn, these partnerships would stand to augment the academic profile of blood establishments and their ability to collaborate in multi-center/multi-national research activities.

In summary, cellular therapy is an emerging field of medical science with an increasing use of cellular products manufactured in blood establishments. Much research is still required and the optimal timing and level of engagement of blood establishments remains to be defined. There are particular strengths that blood operators can contribute, while involvement in research related to cellular therapy may also introduce new risks or threats to blood establishments. Various factors will govern decisions of blood establishments in unique ways and blood operators will need to consider carefully their degree of support and engagement in research opportunities related to cellular therapy.

To structure the different considerations that can be made concerning research on cellular therapeutics, a SWOT analysis is presented in Annex 1.

5. **Conclusions**

The scope chapter described the different tiers that can be distinguished in the field of cellular therapeutics. The spectrum runs from established therapies that have obtained a solid position in the treatment of patients, to complex innovative therapies that are still highly experimental. As a consequence, the contribution of blood establishments (BEs) to research and development in this field will, therefore, vary from applied research and collaboration in clinical studies to basic cell biological, haematological and immunological studies that aim to generate new ATMPs.

Many BEs will have the possibility of contributing to R&D where it concerns the relatively simple cellular products. It is important to engage in this type of research since BEs possess ample expertise on the good manufacturing practice (GMP) production of cells for transfusion which will increase the quality and efficacy of cellular therapeutics.

On the other hand fundamental studies on novel ATMPs will be restricted to those BEs that have a solid and proper link with academia and have the possibility of funding basic research that will only be economically profitable in the long run. Still, when successful (e.g. by acquiring intellectual property) this will strengthen the position of BEs: it will open the opportunity to supply a broader set of therapeutics in the future; generate a complementary and strong position in relation to the academic hospitals; and raise the profile of BEs as an attractive employer for top level personnel.

Research on cellular therapeutics is necessary to strengthen the position of BEs in this field, both in scientific, medical and economic terms. Since considerable differences between BEs in terms of size, academic profile, facilities and resources exist between BEs, both the direction and volume of the research efforts will vary greatly. In this respect, it is worthwhile to actively explore how complementary research activities between BEs may be coordinated and intensified. Further information on this subject could be found in some recent reviews [1,2].

SELECTED REFERENCES

1. Franks HA, Wang Q, Patel PM. New anticancer immunotherapies. Anticancer Res.2012, 32:2439-53. http://www.ncbi.nlm.nih.gov/pubmed/22753700
2. English K, French A, Wood KJ. Mesenchymal Stromal Cells: Facilitators of Successful Transplantation? http://dx.doi.org/10.1016/j.stem.2010.09.009

Annex 1: SWOT Analysis applied to research issues in cellular therapies for Blood Establishments:

Strengths
- Blood establishments (BEs) have ample access to donors and originating material.
- BEs have knowledge of standardised preparation and delivery of blood components for routine patient care, which will facilitate translational studies.
- BEs have extensive experience with crucial, although sometimes overlooked issues such as quality assurance, microbiological qualification, patient-specific component delivery, biovigilance and traceability.
- BEs can cooperate with multiple academic laboratories allowing for the integration of complementary knowledge from different sites.
- BEs maintain close ties to clinical partners and can produce low-volume pharmaceuticals which may not be attractive for big pharmaceutical companies.

Weaknesses
- Many BEs do not have hands-on experience with cellular therapies.
- BEs may not have funds (or do not have access to external funding) for doing innovative research.
- BEs do not have many researchers with high profiles in fundamental research.
- BEs are seen as mere facilitators in the process which limits external visibility.
- BEs are not natural partners in the early (exploratory) phase of clinical research.

Opportunities
- Develop methods that link standard practices in blood transfusion to the preparation and delivery of ATMP's.
- Several of today's labile blood product might become tomorrow ATMP's: pathogen attenuated blood products, stem cell-derived RBCs.
- Capitalize on a strategic position between basic research and health care; virtue of a clear distinction between product preparation and product use.
- Team-up with academic institutes/partners in basic and early clinical research.
- Increase the independent academic profile of BEs.
- Obtain funding by participating in multi-centre/multi-national collaboration.

Threats
- (Many) novel cellular therapies will not work or will face stiff competition from alternative therapies (e.g. inhibitors of Tyrosine Kinases vs allo-bone marrow transplant for chronic myeloid leukaemia).
- Cellular therapies may become a big success in the near future and private companies could enter the market.
- Proof of concepts takes long which limits ability (I) to generate high impact output and (II) to obtain external funding.
- Inherent risks of manipulated products and potential for adverse events may limit involvement of BEs.

Kari Aranko
Jukka Partanen
Laurence Le Texier
Andrew Hadley

17. THE ROLE OF BLOOD ESTABLISHMENTS IN CELLULAR THERAPIES:

INTELLECTUAL PROPERTY ISSUES

17.1 INTRODUCTION

The next generation of regenerative medicine will involve the use of blood or marrow-derived stem cells to replace or regenerate human cells, tissues or organs for disorders such as heart disease, stroke and diabetes. In parallel with these developments, a range of new cell therapies (CT) is entering clinical trials which involve the manipulation of stem cells or immune cells to modulate the immune response in patients with cancer, viral infection or post-transplant complications. It is unlikely that these innovative CTs will be developed *de novo* within blood establishment (BE) laboratories, for the following reasons:

Timeframes: New cellular therapy products are developed over a 7 to 15 year time frame.

Financial considerations: Cellular therapy development is capital intensive, frequently requiring over €100 million.

BE skill sets: BEs tend to lack the skills required to ensure successful product design, development and commercial launch.

Intellectual property rights: Competitive products already in development have claimed significant intellectual property protection in key product and therapy areas.

Options for BEs: Given this background, BEs may choose to position themselves as collaborative organisations in order to develop and/or market innovative CTs in partnership with commercial or academic organisations. This proposition may have a higher intrinsic value than manufacturing under contract, but it requires BEs to assert their own intellectual property and to consider intellectual property rights (IPR) infringement and freedom to operate issues. Failure to adequately consider IPR exposes organisations to the risk of incurring punitive infringement liabilities. This may be a significant cultural change for some BEs requiring new skills to be brought into the organisation.

This chapter therefore considers the following issues:

- The need to establish freedom to operate when bringing innovative CTs to market.
- Protecting IPR associated with the development of new CTs.

17.2 INNOVATIVE CELLULAR THERAPY CONCEPTS AND FREEDOM TO OPERATE

Patents: Many thousands of patents have been granted covering stem cells and innovative cellular therapies [1,2]. A current patent search on 'cellular therapy' in patent class a61 (medical science) gave more than 7000 patents or applications in the World Patent Index database. This constitutes a significant thicket of intellectual property claims through which any organisation would need to navigate to bring an innovative cellular therapy product to market.

BEs may choose to obviate the risks of patent infringement by restricting activities to the 'compassionate' use of new CTs (i.e. for a very few patients), or by limiting involvement to participation in clinical trials. Both of these options stop short of taking a product to the market, except as a specialist manufacturing organisation working under contract to a third party with the relevant rights to exploit the intellectual property.

IPR and freedom to operate issues become a major concern for organisations seeking to develop and market cellular therapies. Product concepts envisaged by many BEs tend to build on established CT approaches already demonstrated in the clinic because they will be relatively low risk product opportunities, close to regulatory approval and, therefore, revenue generating.

However, companies sponsoring clinical trials of their products will have asserted substantial patent portfolios, typically to the tune of over a hundred related patents. These patents or patent applications cover cell types, cell processing methods, cell storage media and the use of certain cell selection criteria. Both autologous and allogeneic applications may be covered in patent applications. Patent law provides intellectual property protection for professional and commercial use of the invention regardless of the regulatory requirements for marketing authorisation of the application.

The patent landscape for four examples of CT is described briefly below.

Cytotoxic T Lymphocytes: Cell selection and expansion technologies now exist to create virus-specific cytotoxic T lymphocytes (CTL). Such cells can be infused into patients prophylactically or as therapy for proven viral diseases such as CMV, EBV or adenovirus, or cancer. Much of this technology is in the public domain. However, several commercial organisations in Europe and the US developing these treatments are running multicentre clinical trials and currently hold numerous patents.

Mesenchymal Stroma Cells: (MSC) are a promising therapeutic class of stem cells for a range of indications including Crohn's disease and graft versus host disease (GvHD). They are implicated in both anti-inflammatory and tissue regeneration roles. There are several companies actively pursuing MSC-derived therapies including Osiris (USA), Cellerix (Spain)

and Anterogen (Korea). Osiris' Prochymal, for example, is an MSC product indicated for GvHD and Crohn's disease. Osiris has filed 180 patents covering biology, composition of matter, manufacturing process and quality assurance.

Dendritic Cells: Are a promising platform for the development of novel immunotherapies for the treatment of cancer. Each vaccine is specific to the cancer being treated. Experimental vaccines are in the clinic and include treatment for melanoma, a cancer whose incidence is growing rapidly. Dendreon Inc has developed an autologous cell product (Provenge) for the treatment of prostate cancer that has been approved by the FDA. A broad European patent for Provenge and other cellular therapies has been granted.

Regulatory T Cells: Emerging evidence suggests a therapeutic role for the use of donor regulatory T cells in the treatment of GvHD. This therapy requires access to donor stem cell populations, and this may be one reason why commercial activity in this area seems to be low. This may provide BEs with greater freedom to operate in this area. However, our patent search [Partanen, unpublished] gave about 500 patents or applications with a key word 'regulatory T cell' in the World Patent Index data base, demonstrating once again in the cellular therapy fields the patent thicket needing to be navigated.

Limitations on patent designation: There are, nevertheless, certain exemptions or limitations on the exclusive rights of a patent-holder that may be considered while assessing freedom to operate.

- An experimental use exemption may apply to the private or non-professional use of a patented invention. Generally this exemption is limited and may not be relevant to BEs.
- It is permitted to use a patented invention in order to study or to develop the invention further.
- In the context of CT, the exemption for a pharmacy to mix or prepare a drug prescribed by a doctor may be of interest. The EU patent convention (CPC 27c article) states that "patent shall not extend to [...] the extemporaneous preparation for individual cases in a pharmacy of a medicine". It is assumed that the preparation must be done only in a pharmacy for a single case, without prior preparations. It is unclear whether preparing a CT product under a hospital exemption permit (or 'compassionate' use) by a BE for a series of patients in hospital care could infringe third party IPR. Certainly, considerable prior effort and planning would be required and the activity is clearly professional.

It follows from the above considerations that BEs should be fully aware of the patents held by third parties to ensure that they have freedom to operate when developing and/or marketing their own CTs. To proceed without doing this would leave organisations exposed to the risk of substantial litigation and potential liability for punitive damages – multiples of the commercial loss incurred by the patent holder.

17.3 ASSERTING INTELLECTUAL PROPERTY RIGHTS

New product concepts are frequently developed by BEs in partnership with external organisations (academic or commercial) that provide the primary scientific observations to which BEs add the necessary cell processing and regulatory expertise. This arrangement typically leads to two types of patents: the first, on the therapeutic invention; the second, on the process by which the materials are prepared for therapeutic use.

Although unmanipulated human cells are not patentable *(Table 1)*, an isolated therapeutic cell or cell preparation can be patented if the cells in question are novel, or are modified *ex vivo* to impart a unique feature. Novel methods and production processes are also patentable as are methods for evaluating the quality or status of cell preparations and products. An interesting and largely untested issue is the extent to which organisations may have freedom to operate with cell types which are closely-related to, or derived from, cell types whose patents are held by third parties.

Table 1: What can be protected by a patent?

Three conditions are essential for an invention to be patentable:

- Novelty; the invention must not be public before the filing.
- Non-obviousness; the invention must be sufficiently different to its close relatives, and
- Industrial applicability.

Several categories are not patentable. Typically natural laws and scientific findings as such, or species of animals cannot be patented in most legislations. In the EU, the human body, its parts or any developmental stage are not patentable. However, cells and tissues can be patented once 'isolated' or technically applied outside the body. Hence, an isolated cell type, or 'product' can be patented but the naturally-occurring cell cannot. Business models can be patented in the USA, but not in the EU.

The value of patenting relates to the right of the owner of the patent to exclude others from making commercial or professional use of an invention. The use in this context refers to using, selling, offering and keeping in stock the invention. In most jurisdictions, the term 'use' encompasses any professional use by an authority such as a non-profit organisation, university or foundation.

A patent is valid only in those territories or jurisdictions in which it is granted and kept in force. It is, therefore, essential to understand that only those patents that are both granted and kept valid in the country in question should be primarily considered when estimating freedom to operate.

Advantage of partnerships: The exclusivity provided by intellectual property rights is crucial to justify the long-term and significant investment needed to bring innovative CTs to the market. One approach to protecting and commercialising intellectual property emerging from collaboration is to place responsibility on an academic partner. In this way, a BE might share in any benefit from the exploitation of joint intellectual property. This approach has the advantage of making collaborations simple to establish. However, it may not always serve the best interests of a BE if the collaborating party is insufficiently motivated to recognise and protect BE intellectual property, especially when background or process-related in nature.

Further, the attractiveness of most European countries as a market for novel CTs reflects the robust way in which intellectual property is respected. Therefore, it is in the interest of BEs to signal that they understand the significance of intellectual property in the development of novel CTs.

BEs and IPR: BEs could also assert their own IPR, including know-how, while negotiating licensing rights for cell products with commercial partners. BEs should also recognise that long-term experience and know-how could constitute valuable IPR in a form of a trade secret. It is common in many fields to exchange IPR to ensure freedom to operate for both parties.

BE collective patent portfolio: There may be an opportunity for BEs to act in concert to assert a collective patent portfolio. As the patent portfolio of an individual BE may be relatively modest in comparison with an active CT company, a common patent pool could strengthen the position of BEs. In addition, it could reduce the recurring cost of maintaining patents. Examples of costs related to filing and processing of patents are given in *Table 2*.

Table 2: How much does a patent cost?

Protecting intellectual property can be expensive and advice from a patent professional should be sought in formulating a cost-effective approach.

A rough estimate of the costs in the application phase is the following '€5.000 rule of thumb':

- Step one, 'priority' filing to get an early filing date for the invention: €5.000 per application
- Step two (within 12-month priority phase), international patent co-operation treaty (PCT) phase to gain extra time for evaluation of the invention: €5.000 per application
- Step three (within 18-month PCT phase): €5.000 per each region (+ costs of translations when needed) for the final evaluation and granting the patent.
- Step four: validation and annual fees: €5.000 per 10-year period per a region.
- In addition, legal fees to defend any patents which may be challenged.

Publication considerations: The need to assert IPR should be balanced against the need to publish the scientific results in their early phase. Scientific publication, while it adds to the corpus of knowledge and enables researchers to make discoveries, also creates 'prior art' that is taken into account when the novelty and the inventive step of the invention are evaluated. The existence of 'prior art' makes it impossible for any organisation to protect innovation by patenting. However, after filing a patent application, there are no reasons to refrain from publishing, as patent applications are in the public domain. If a BE wants to protect its inventions by patenting, it should create an internal policy and process to control what can be published before filing a patent application.

Case law vacuum: A challenge facing the CT industry is the novelty and the inventive level of the technology and the absence of relevant intellectual property case law. This creates uncertainty about the scope of patent protection and opportunities for asserting IPR. It is not clear how best to interpret the scope of third party patents or applications, making estimation of freedom-to-operate difficult. Hence, BEs seeking to develop and market innovative CT products must acquire a thorough in-house knowledge of related IPR risks and/or consult IPR professionals.

17.4 SWOT ANALYSIS

A SWOT analysis regarding IPR is presented in *table 3*.

Table 3: SWOT Analysis from the BE point of view regarding IPR in cellular therapy

Strengths	Weaknesses	Opportunities	Threats
Long-term commitment	Most BEs have limited experience recognising, protecting and exploiting IP.	A breakthrough invention could/should be largely protected in terms of territories, opening licensing opportunities in other countries for BEs.	Thousands of patents covering CTs market limit BEs' freedom-to-operate and expose them to a risk of substantial litigation and potential liability for punitive damages due to patent infringement.
Strong expertise and know-how (tacit information) in cell culturing, processing and banking constitute trade secret opportunities	Most BEs do not dedicate enough inner work force to the field of IP and licensing & business development.	BEs could use some of their patents as technology transfer incomes, especially in the fields in which they do not want to carry on developments	Threats on IPR litigation might halt the development in the field and limit patients access to new CTs
	Most BEs are not commercially oriented	BEs could share information on the intellectual property landscape.	Researchers publishing their results without consideration of patenting.
	BEs are regional or national, limiting the interest and risk-taking in managing global IPR	BEs could join forces to secure freedom to operate based on hospital exemption or compassionate use. Option to develop a common global patent portfolio and share it with national not-for-profit BEs.	

17.5 CONCLUSIONS AND RECOMMENDATIONS

IPR and freedom to operate issues have become major concerns for organisations seeking to develop and market cellular therapies. Therefore, BEs seeking to do so should do the following:

Develop policy on IPR: Develop a sustainable policy to assert intellectual property rights.

Update status of IPR and freedom to operate: Maintain a high level of awareness of the relevant intellectual property landscape and obtain the necessary assurances regarding freedom to operate before developing or marketing a novel cellular therapy.

Appropriate training: BE staff should receive training and support from a knowledgeable patent agent.

Collaborate internationally: BEs should also develop mechanisms to share information on the intellectual property landscape and jointly secure freedom to operate (at least based on hospital exemption or compassionate use).

Develop common patent portfolio: BEs should explore options to develop a common patent portfolio for not-for-profit BEs.

SELECTED REFERENCES

1. Konski, A.F. and Spielthenner D. Stem cell patents: a landscape analysis. Nature Biotechnology 2009; 27: 722-726. http://dx.doi.org/10.1038/nbt0809-722
2. Bergman K, Graff G. The global stem cell patent landscape: implications for efficient technology transfer and commercial development. Nature Biotechnology, 2007; 24: 419-424. http://dx.doi.org/10.1038/nbt0407-419
3. Harlin M and O'Connor K.A. Leveraging your biotech intellectual property. Nature Biotechnology 2008; 26: 607-609. http://dx.doi.org/10.1038/bioe.2008.5
4. Pamp C. Intellectual Property in Science. Chapter 3: Intellectual Property Rights in Research and Early Innovation. pp 107-160. 2010. Jure Förlag AB, Stockholm Sweden. http://www.goodreads.com/author/show/6263148.Caroline_Pamp
5. Pamp C. Intellectual Property in Science. Chapter 5: The Scope of the Experimental Use Exemption and its Relation to Research tools. pp 238-301. 2010. Jure Förlag AB, Stockholm Sweden. http://www.goodreads.com/author/show/6263148.Caroline_Pamp
6. Mason C. Cell therapy industry: billion dollar global business with unlimited potential. Regenerative Medicine 2011; 6; 265-272. http://dx.doi.org/10.2217/rme.11.28.
7. Powell W.W. Networks of learning in Biotechnology: Opportunities and constrains associated with relational contracting in a knowledge-intensive field. pp 251-266. In R. Dreyfuss, D Zimmerman and H Fist (eds): Expanding the boundaries of intellectual property. 2004. Oxford University Press, Oxford UK. http://faculty.haas.berkeley.edu/shapiro/standards.pdf

Lisa McLaughlin
Yves Charpak
Gilles Folléa

18. THE ROLE OF BLOOD ESTABLISHMENTS IN CELLULAR THERAPIES: ETHICAL ISSUES

As part of the Alliance of Blood Operator (ABO) committee's task – to develop a policy report on the role of blood establishments (BEs) in the field of cellular therapy – we have been asked to look at two questions:

- Which ethical principles should an ABO BE comply with, if involved in the cellular therapy field?
- Is it ethical for blood centres to engage in the business of cellular therapy?

We first established an overview of the ethical questions raised by cell therapies *per se*, irrespective of the operator of said therapies. Then we discussed the basic ethical principles for ABO BEs. We also asked whether engaging in cell therapy is a legitimate path for BEs – one key factor determining legitimacy being the ability to deal with these ethical issues.

The definitions used in this chapter are as follows:
Ethics: the principles of conduct governing a group.
Ethical: conforming to accepted professional standards of conduct.

18.1 KEY ETHICAL DEBATES IN THE FIELD OF CELLULAR THERAPIES AND BASIC PRINCIPLES FOR ABO BEs

Cellular therapies raise many ethical questions, most of which pertain to the following topics: donation, banking, patenting, stem cells, property and access. The nonprofit question is not a matter of debate for ABO BEs, as all of them are nonprofit.

18.1.1 DONATION

Regarding financial incentives/compensation for donors, the main ethical questions are: Is compensation of (living) donors compatible with ethics? How does one balance the need to increase donations with the obligation to prevent the "sale" of human bodies? The Nuffield Council "intervention ladder" *(Fig. 1)*. distinguishing altruist focused and non-altruist focused interventions to promote donations of human components, provides examples to illustrate these ethical questions. Different forms of payment are synthetized in Fig 2.

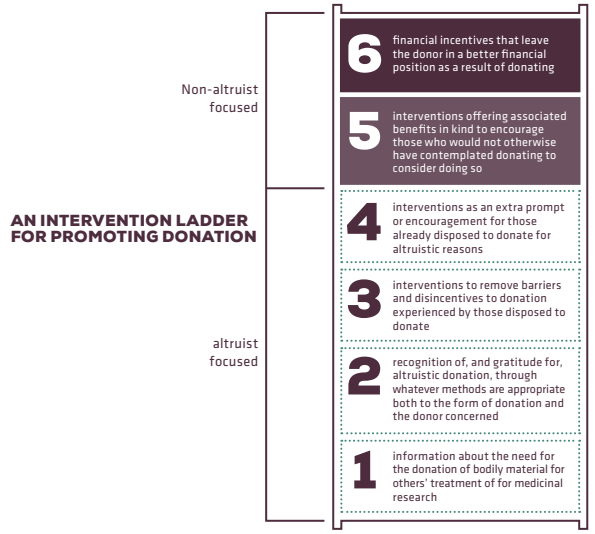


Figure 1: The Nuffield Council "intervention ladder" is an example to illustrate ethical questions linked to donations of human cells for cellular therapies [1].

According to the **EU Directive on 2004/23/EC** [2] on tissues and cells: "Donors may receive compensation, which is strictly limited to making good the expenses and inconveniences related to the donation".

As observed in the 2nd Report on Voluntary and Unpaid Donation of Tissues and Cells from the European Commission issued in June 2011 [3], this Directive has been implemented in various ways in EU countries: some received no payment whatsoever; others receive disguised "payments".

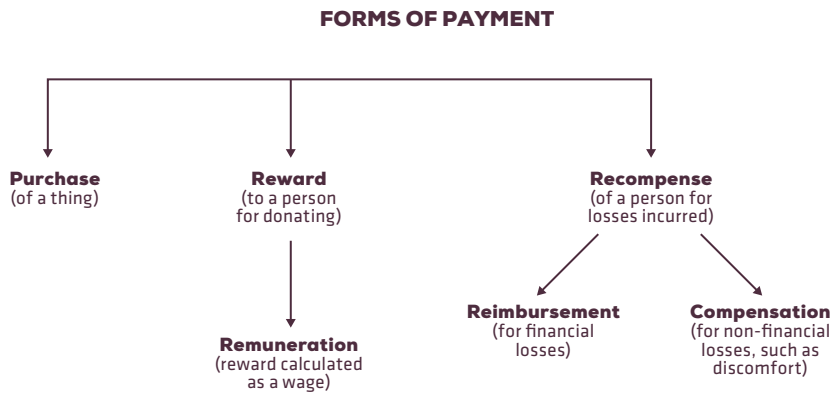


Figure 2: Different forms of payment of components from human body.

All ABO BEs operate on the principle of the unremunerated volunteer blood donor and have done so for many years. There are good ethical and practical reasons for doing this, not least of which is the safety of the products that are produced. The principle of voluntary donation has been affirmed by most professional and statutory bodies involved in the field of transfusion. Cellular therapy should also be based on similar ethical principles.

The Council of Europe's "Additional Protocol To The Convention On Human Rights And Biomedicine Concerning Transplantation Of Organs And Tissues Of Human Origin", issued in 2002 [4] clearly states prohibition of financial gain: "The human body and its parts shall not, as such, give rise to financial gain or comparable advantage.
The aforementioned provision shall not prevent payments which do not constitute a financial gain or a comparable advantage, in particular:

- compensation of living donors for loss of earnings and any other justifiable expenses caused by the removal or by the related medical examinations;
- payment of a justifiable fee for legitimate medical or related technical services rendered in connection with transplantation;
- compensation in case of undue damage resulting from the removal of organs or tissues from living persons".

The prohibition against remuneration of haematopoietic stem cells donors has recently been challenged in the United States. A recent article argued as follows:

Haematopoietic stem cell donors should not be paid because of ethical concerns raised by remuneration, potential to damage the public will to act altruistically, the potential for coercion and exploitation of donors, increased risk to patients, harm to local transplantation programmes and international stem cell exchange, and the possibility of benefiting some patients while disadvantaging others [5].

However BEs need to be aware of significant pressures that may arise by getting involved in this area. Who would have the ownership rights to a set of donated cells that become a useful master cell bank of a very useful product? What kind of collaboration agreements should be made between BEs and commercial companies involved in cell therapy? Should there be profit sharing? Such ethical questions need to be well rehearsed so that any negative impacts (true or perceived) are handled correctly. These discrepancies have an impact on **exchange/sharing** of human tissues and cells (T&Cs) between countries: is it ethical to "import" such human components from a country with a different compensation policy (even if this policy is in line with the EU Directive)?

18.1.2 BANKING

Should tissues and cells banking be provided by public, non-profit or private bodies? Whose responsibility is it to fund the costs of T&C banking? Is the emergence of a tissues and cells worldwide "market" still compatible with the ethical principle that "human bodies are not for sale"? Is T&C banking for autologous use less ethical than for homologous use?

A reflection of the Council of Europe on these issues led to the Recommendation Rec(2004)8 of the Committee of Ministers of the Council of Europe on autologous cord blood banks [6]. This recommendations states that "If cord blood banks are established, they should be based on altruistic and voluntary cord blood donation and used for allogeneic transplantation and related research". It also recommends that "Autologous cord blood banks that are being established must meet the quality and safety standards set out in the Council of Europe's Guide to safety and quality assurance for organs, tissues and cells."

A European Parliament resolution on voluntary and unpaid donation of tissues and cells has been voted in September 2012 [7]. This resolution:

- "Stresses that donation should be voluntary, unpaid and anonymous (except in the case of procurement from a living person for a relative), governed by protective legal and ethical rules which respect the integrity of the person [...]
- Expects all Member States to establish public tissue and cell banks [...]
- Calls for European standards and requirements for private tissue and cell banks [...]
- Proposes that Member States consider adopting and enforcing operational and ethical standards for public and private cord blood banks that uphold the principle of non-commercialisation of the human body and its parts,
- Expects all Member States to establish at least one public stem cell bank [...]
- Calls for European standards and requirements for private stem cell banks;
- Notes that collaboration models and opportunities between public and private sectors already exist in some Member States, and encourages public and private cord blood banks to collaborate closely in order to increase the availability and exchange of national, European and international cord blood and tissue samples; calls on Member States to appropriately regulate both public and private banks to guarantee the fullest transparency and safety of cord blood, underlining that banks need to ensure working practices which are open and robust in their information sharing, in order to provide maximum benefit for the patient [...]"

18.1.3 PATENTING

Patents in the biomedical research field: is it ethical to claim patents on living organisms (even if allowed by the law)?

Stem cells: the recent ruling of the Court of Justice of the EU (Brüstle, Oct 2011) excludes embryonic stem cells and their derivatives (i.e. cell lines derived from embryonic stem cells) from patentability:

"A process which involves removal of a stem cell from a human embryo at the blastocyst stage, entailing the destruction of that embryo, cannot be patented" [8].

18.1.4 STEM CELLS

Which "sources" of stem cells are compatible with ethics? There presently exists wide debate on embryonic stem cells and the use of embryo for therapies and research. This raises the question of consent of parents for the use of "spare" embryos from IVF procedures which may clash with their religious and moral beliefs.

Debate and degree of acceptance varies a lot from one country to another, and the subject is usually dealt with at the highest political level, beyond the reach of the medical community.

Induced pluripotent stem cells (IPS cells): "reprogrammed" cells
These raise many hopes, but there are also safety concerns (carcinogenicity of reprograming factors). IPS cells could be mainly used for autologous therapies: key change in the "paradigm" of transplant therapies, where heterologous use is predominant.

Other sources of stem cells: fetal tissues, adult stem cells, local stem cells
General concern is expressed worldwide over the safety of stem cell therapies. In particular, the issue is raised as to the risks of stem cell "tourism" (to unregulated countries).

18.1.5 PROPERTY AND ACCESS TO TISSUES AND CELLS

In relation to property and access the following issues are also raised, and BEs would need to address these complex ethical questions:

Who "owns" banked tissues and cells?

Should the donor retain some control over the use of its donated tissues or cells?

Should access to banked T&C for research purposes be open to all researchers?
Can banking providers provide "privileged" access to some research institutions?

18.2 THE QUESTION AS TO THE LEGITIMACY OF BLOOD ESTABLISHMENTS ENGAGING IN CELL THERAPY IN THE LIGHT OF ETHICAL PRINCIPLES AND DEBATES

Many ABO BEs are already engaged in cell therapies to some extent, and it is human nature to look for vindication for one's current position. But 'seeking vindication' implies that a party has been accused of being in the 'wrong' or having the wrong opinion. Rather than defending ourselves against a wrongful characterisation, we should focus on why engaging in the business of cellular therapies is the logical extension of our work in the field of Transfusion Medicine.

The goals of the practice of medicine have always been to alter or abate the course of illness, to restore health; and to avoid death. Cellular therapy has grown rapidly over the last three decades.

History: The field began with the use of haematopoietic progenitor cells (HPCs) harvested from bone marrow to reconstitute recipient haematopoiesis [9]. The field's scope was then broadened to include autologous and allogeneic peripheral blood, and then umbilical cord blood. The field now includes new sources of cells, and issues arising include the use of mesenchymal stem cells, pancreatic islet cells, skin, bone, corneas, etc.

Quality based standards for the field have been developed with the participation of professional organisations dedicated to the development of cellular therapy, the dissemination of knowledge and techniques to professionals in the field, and the development of standards and accreditation programmes.

Experience: Blood centres as entities, and their staffs of physicians, scientists, researchers, and technicians, have comprised the bulk of the memberships of the professional societies engaged in cellular therapy. In the hospital, it is still the transfusion service that provides the components and technologies necessary to support patients seeking treatment with these developing therapies. Given our current involvement, it would seem that our engagement in all aspects of cellular therapy would be in keeping with our mission to provide the best possible medical care to our patients, and further the goals of science to alleviate suffering, restore hope, and keep an untimely death at bay.

Ethical debates: Despite such a strong argument in favor of our involvement in cellular therapies, we would be foolish to ignore the ongoing debates around the moral correctness of research in the fields of cellular therapies and regenerative medicine.

Cell therapy has been defined as "the prevention, treatment, cure or mitigation of disease or injuries in humans by the administration of autologous, allogeneic or xenogeneic cells that have been manipulated or altered ex vivo" [10]. The website of a globally known producer in the industry states, in part, that "regenerative medicine is a broad definition for innovative medical therapies that will enable the body to repair, replace, restore and regenerate damaged or diseased cells, tissues and organs" [11].

Cell therapy and regenerative medicine overlap in their focus on the repair, replacement and restoration of diseased cells, tissues and organs. Debate varies in intensity depending upon the source of the treatment cells and the perceived cost benefit in submitting to treatment. In general, the debate becomes more intense as the age of the donor decreases, or as the degree of repair or restoration seems to diminish in relationship to the cost of a single treatment.

An example of the complexity of these situations is the autologous vaccine Provenge, manufactured by Dendreon Corporation. Provenge is manufactured from the autologous dendritic cells of a patient with Stage 4 castrate resistant prostate cancer. The cells are derived from the peripheral circulation and harvested by apheresis. While the patient is an adult male who has the capacity to freely consent to this treatment option, critics point to the fact that the cost of this treatment is over $90,000 and the median increase in survival is only approximately four months. This is perhaps a shocking number when one reads it in the newspaper, but it is hardly out of the ballpark amounts of money paid for medical care for a terminally ill patient.

Sibling donors: Nearly two decades ago, the world was shocked when it was revealed that a married couple with one critically ill child conceived a second child, hoping that this child would prove to be a compatible stem cell donor for the older child [12]. Thankfully, the transplant was successful and both children have grown up together in a loving relationship.

Critics at that time thought it immoral to bear one child merely to save the life of another, but some conceded that it is within the purview of the parents to make just these types of decisions. Since then the issue of whether the juvenile organ donor can ever give 'informed consent' for procedures that ultimately benefit their sibling continues to rage as a separate issue.

The debate has broadened in this first part of the 21st century. The focus has turned from parents delivering a child that, after birth, would be the organ donor, AND a child who was also able to expect and enjoy a full life of his/her own.

Embryos in research: Now the issue is that of using the cells from embryos to support medical research for the benefit of strangers, without the prospect of the enjoyment of the life of the original embryo. This debate has two prongs: 1) when embryonic stem cells are the source, some parties are concerned over the prospect of destroying pre-born (or pre-implanted) life in order to save another human being who has already exited the womb; and 2) some worry that totipotent cells are apt to be used for the cloning of human beings.

As a practical matter, a blood centre will make a decision to collect and or process cells for medical therapies, and that decision will rest on a number of factors that impact the feasibility of entering that professional arena. But whether or not a centre actively engages in collection, processing or research in this arena, the centre will continue to provide transfusion support to the recipient and/or the donor as a matter of fulfilling the core mission of the centre to further the practice of medicine in reducing the morbidity and mortality of disease.

In attempting to add more dimensions to this 'business' decision, we performed an analysis on a blood centre's participation in cell therapies from the viewpoints of both the patient and the donor of these cells. Those factors in favor of such participation included the expertise of the blood centre's physicians and nursing/collection staffs in caring for and performing apheresis on both 'ill' and healthy individuals, and the large network of blood centres in any one country. For both patients and donors, these two factors would suggest that these new therapies may be available to many more people than just those who are in proximity to a large hospital and/or academic centre.

The distance and condition under which cells and /or products may need to be transported, frequently impact when and where therapy can be undertaken. Answering these "when" and "where" questions also impacts on "who" will be able to take advantage of this treatment option.

Blood donor sites: Using the blood centres as sites for collection, infusion or manufacturing suddenly broadens access to medical care and puts the blood centre in the middle of the treatment pipeline. The minimum training requirements for staff working in this part of the industry should also assure patients and donors that they are in capable hands when submitting themselves for cellular therapies. If there are any weaknesses to this position, they are mainly on the donor's side: donating for a cellular therapy is not the same as donating blood at your local drive.

Donor considerations: Blood centres should consider that some donors may be attracted to the activity based upon their experience with a fairly quick whole blood donation, and not fully appreciate the additional risks that these activities may engender. These increased risks will require more input from a centre's Risk Management office, and the potential for liability may be the factor that prevents some centres from entering the field.

In summary: Cell therapy is already an integral part of the medical profession's armamentarium in this group's goal to reduce the incidence of morbidity and mortality due to injury and disease. It is not just that "death has become public enemy #1", to borrow the words of bioethicist Daniel Callahan, but having an illness, disease or disability that completely define one's life, has become unacceptable to physician/scientists, in particular, and to human beings in general. Blood centres have played an integral part in the furtherance of medical progress, and moving into the field of cellular therapies should be no different. This is the next logical step in the evolution of Transfusion Medicine. Rather than 'business as usual' this is an opportunity to re-assert the central role of Blood Establishments in furthering medical progress. Working in the CT field is an ethical one. In fact, it is a logical extension of the work that BEs are involved in.

REFERENCES

1. Nuffield Council. Human bodies' donation for medicine and research. 2011. www.nuffieldbioethics.org/donation.
2. DIRECTIVE 2004/23/EC OF THE EUROPEAN PARLIAMENT AND OF THE COUNCIL on setting standards of quality and safety for the donation, procurement, testing, processing, preservation, storage and distribution of human tissues and cells. http://eur-lex.europa.eu/LexUriServ/LexUriServ.do?uri=OJ:L:2004:102:0048:0058:en:PDF
3. European Commission. REPORT FROM THE COMMISSION TO THE EUROPEAN PARLIAMENT, THE COUNCIL, THE EUROPEAN ECONOMIC AND SOCIAL COMMITTEE AND THE COMMITTEE OF THE REGIONS. 2nd Report on Voluntary and Unpaid Donation of Tissues and Cells. 2011. http://eur-lex.europa.eu/LexUriServ/LexUriServ.do?uri=COM:2011:0352:FIN:EN:PDF
4. Additional Protocol To The Convention On Human Rights And Biomedicine Concerning Transplantation Of Organs And Tissues Of Human Origin. 2002. http://conventions.coe.int/Treaty/en/Treaties/Html/186.htm
5. Boo M, van Walraven SM, Chapman J, Lindberg B, Schmidt AH, Shaw BE, Switzer GE, Yang E, Egeland T and on behalf of the World Marrow Donor Association. Remuneration of hematopoietic stem cell donors: principles and perspective of the World Marrow Donor Association. Blood 2011, 117: 21-25. http://dx.doi.org/10.1182/blood-2010-07-298430
6. Committee of Ministers of the Council of Europe Recommendation Rec(2004)8 to member states on autologous cord blood banks (adopted by the Committee of Ministers on 19 May 2004 at the 884th meeting of the Ministers' Deputies). https://wcd.coe.int/ViewDoc.jsp?id=744641&Lang=en
7. European Parliament resolution of 11 September 2012 on voluntary and unpaid donation of tissues and cells (2011/2193(INI))., http://www.europarl.europa.eu/sides/getDoc.do?pubRef=-//EP//TEXT+TA+P7-TA-2012-0320+0+DOC+XML+V0//EN
8. European Court of Justice. Judgment in Case C-34/10 Oliver Brüstle v Greenpeace e.V. 18 October 2011 http://curia.europa.eu/jcms/upload/docs/application/pdf/2011-10/cp110112en.pdf
9. American Association of Blood Banks. Standards for Cellular Therapy Services. 2004. First edition http://www.aabb.org/sa/standards/Pages/ct.aspx
10. Federal Drug Administration Register. Application of Current Statutory Authorities to Human Somatic Cell Therapy Products and Gene Therapy Products, Notice, Oct 14, 1993. (Notice from the Center for Biologics Evaluation and Research, Center for Drug Evaluation and Research, Center for Devices and Radiological Health, U.S. Food and Drug Administration.) http://www.fda.gov/downloads/BiologicsBloodVaccines/SafetyAvailability/UCM148113.pdf
11. Pall Corporation. Website, 2012, Port Washington, NY. http://www.pall.com/main/Home.page
12. Furcht L, Hoffman W. The Stem Cell Dilemma: Beacons of Hope or Harbingers of Doom? (Story of the Ayala family, San Bernadino, California, 1991). 2008, Arcade Press. http://www.amazon.com/The-Stem-Cell-Dilemma-Harbingers/dp/1559708727

George Galea
Kari Aranko
Gilles Folléa

19. THE ROLE OF BLOOD ESTABLISH-MENTS IN CELLULAR THERAPIES: CONCLUSIONS, RECOMMENDATIONS

The collaborative work established by the European Blood Alliance and the Alliance of Blood Operators, presented in the previous chapters *(13 – 18)* about the role of blood establishments (BEs) in the field of cellular therapies (CT), has led to the following conclusions and recommendations.

1. **Sterling experience of BEs:** From years of experience working in a regulatory environment with highly skilled staff, all contributors felt that there was a significant future role for BEs in the cellular therapy field. BEs provide significant added value and they also have significant experience of handling donors. All their work is supported by a quality and vigilance infrastructure.

2. **SWOT and risk assessment analyses:** Cellular therapies are not a single paradigm. Cellular therapy products are governed by different legislations based on the level of manipulation and complexity of the process-requiring varying levels of investment. Each BE should perform risk assessments and SWOT (strengths, weaknesses, opportunities, threats) analyses and position themselves at an appropriate level in the CT field.

3. **Financial risks:** There are, however, risks when entering the CT arena. The level of investment required is high, financial returns are long term, and many of the early phase products/clinical trials may fail.

4. **Regional differentiations:** At this time, BEs in different parts of the world are subject to different pressures and are at different levels of involvement in the cellular therapy field. There is an impression that BEs in the EU are more engaged in the processes of more complex cell therapies than those in North America and Australia.

5. **Potential partnerships:** BEs should not compete with 'big pharma' or hospitals and academics, but rather partner with them and identify niches where BEs may excel as well as complement the offering in the CT field.

6. **Need for R & D:** R&D in CT by BEs is to be encouraged. It is acknowledged, however, that obtaining funds for this work may be problematic. Different sources/avenues for funding clinical trials and pilot work need to be actively sought. This will ensure that as the CT field grows BEs are well positioned in this area.

7. **Intellectual property rights:** BEs have a relative lack of knowledge in IP matters, and experience should be gained in this area as a matter of urgency. This is particularly relevant if developing a novel cellular therapy or if a partnership is sought. BEs should also consider joint initiatives amongst themselves to secure freedom to operate in the CT niche.

8. **Streamlining regulation:** The regulatory landscape is very complex. Although the global aims are broadly similar, the implementation of rules varies immensely from country to country, particularly within the EU. A serious attempt should be made by BEs to streamline rules as far as possible, by engaging with their own regulators and also more globally.

9. **Knowledge pooling:** A significant opportunity exists for sharing experiences amongst BEs globally. Much can be learnt from those BEs involved in CT by those BEs who wish to be involved. Some training programmes already exist and BEs should take a lead in encouraging sharing of knowledge.

10. **CT and BE synergies:** All contributors feel that working in the CT field is an ethical development and a logical extension of the work in which BEs are involved. Many BEs have already started to integrate CT activities and this should be further developed in the future.

Wim de Kort
Cees Verhagen

20. TISSUE BANKING IN EUROPE

20.1 BACKGROUND

Human tissues have been transplanted autologously or homologously for many years now. This activity has been steadily growing over the past five decades. Human tissues, solid organs not included, cover a wide range, the most frequently being stem cells, germ cells, bone, cartilage, tendons, skin, heart valves, cornea, and amnion. The tissues are harvested from post-mortem as well as living donors, each bringing along its special ethical, logistic, technical, quality assurance and quality control challenges.

Often the transplanted tissue involved merely serves an adjuvant purpose, as is the case in most allograft skin, bone and cartilage transplants. Sometimes the tissues only play a temporary role. For example, transplanted allograft skin and cartilage are gradually replaced by the patient's own tissue. In other cases, as in bone or heart valve transplants, the applied tissue plays a supportive role and is gradually covered by endothelium or covered and filled by bone tissue of the recipient. However, in many other situations, such as stem cell or cornea transplants, the tissue involved replaces the recipient's tissue and exerts its function, thereby resembling solid organ transplants.

Blood group compatibility screening and tissue typing respectively play different roles in various tissues *(see Table 1)*. The application of germ cells and the organisation of germ cell banks are distinct from the other tissues, given its specific role in reproductive medicine. Therefore, germ cell banking will not be further discussed in this paper.

Table 1: Tissues of human origin and use, non-autologous
(Source: Nederlandse Transplantatie Stichting, Leiden, The Netherlands)

Tissue	# Transplants	Role	Tissue typing	Donation type	
	per 1,000,000 inhabitants per year in the Netherlands §	**A = adjuvant; S = supportive; R = replacement**		**Autologous, A, or homologous, H; Living donor, L or Post-mortem donor, M**	
Skin	9,000 cm^2	A	No	A, H	L, M
Cartilage	<1	A	No	A, H	L, M
Amnion	<1	A, S	No	H	L
Bone	159-175	S, R	No, Rh-comp*	A, H	L, M
Ear ossicles	1-5	R	No	H	M
Tendon	1	S, R	No	A, H	L, M
Heart valve	5-10	S, R	No	H	(L)** M
Cornea	45-50	R	HLA-matched ***	H	M
Stem cells	5-10	R	HLA-matched	A, H	L
Germ cells	IVF: 900	A (IVF) R	No	A, H	L

§ The numbers do not include transplants that have been autologously harvested and used in the same surgical procedure.
* Rh-compatibility may or may not be required
** Sometimes valves from replaced hearts are suitable for transplantation
*** HLA-matching in a minority of cases required
IVF= In Vitro Fertilisation

A lot of good work is being done in blood tissue banks all over the world. However, whereas in many countries in Europe and Northern America, blood banking and transfusion medicine are fairly under control, this appears not to be the case still with tissue banking and therapeutic use of human tissues in patients. As a consequence, product quality in tissue banking is hard to assess, and the safety of recipients may not be optimal. As the concern is mainly of organisational nature, the question arises more than for the blood component domain, as to whether a focus on cost control would be helpful here.

20.2 ORGANISATIONS

Except for a few countries, tissue banks are not nationally organised. As an example, in the Netherlands there are approximately 40 governmentally registered tissue banks. According to a recent survey, in Europe alone the number of blood banks exceeds one thousand [1]. Moreover, an unknown but presumably large number of small locally organised tissue banks exist.

An explanation for this phenomenon can be found in the history of tissue banks. With the exception of stem cell banks, which by nature have to operate on an international basis, the size and operational extent of tissue banks remains relatively limited.

In the beginning, medical specialists started tissue banks in their hospitals for treatment of their own or their colleagues' patients on a local or regional scale. They were strongly and often solely motivated by professional and medical reasons. Sometimes they simply copied from colleagues; sometimes they adjusted their working procedures based on their own insights.

Funding or managerial and logistical issues did not occur to them. Competition was confined to professional and medical aspects: they simply wanted to do good work and be the best. Bigger organisations did not necessarily function better and were not what specialists were after. Within the walls of the hospitals, these specialists practised their expertise and everything worked out just fine.

In the beginning, no questions other than those related to the professional aspects of tissue transplants were asked. They (probably) all meant well and did well with regard to their products and procedures. However, frequent questions about regulatory, quality, financial and managerial issues soon arose. This was enhanced by the fact that technical and administrational errors appeared not to be totally avoidable. In addition, because screening on transplantation associated viruses was not performed routinely, the risk of transmittable diseases turned out to be a real possibility.

20.3 REGULATORY ISSUES

Today, each registered tissue bank in Europe must comply with the requirements of mainly one EC Directive [2], transposed into national rules. Some of the rules may relate to product quality, i.e. they should help maximize functionality. Other rules are there for safety reasons, i.e. meant to minimize avoidable complications. The third set of rules are meant to regulate what is or is not allowed; like those which, for instance, foster the globally promoted non-remuneration of donors, or govern conflict of interest or administrative aspects of tissue banking. As an unavoidable result, these rules could be far from the reality of donations, banking and transplantation in patients.

One special aspect of tissue (and to a certain extent blood component) banking must be mentioned here. Tissues are increasingly regarded as pharmaceutical products. This raises special requirements with regard to procuring/harvesting, processing, inventory conditions and issuing and allocation procedures. However, pharmaceutical industries are used to working with relatively large batches, containing many, up to thousands, of individual products. In tissue and organ donation, however, each donation is the single product that comprises a batch. Random sampling, therefore, is not possible and every donation has to be checked on every aspect.

20.4 QUALITY AND SAFETY ISSUES

Next to the EC and national rules and regulations, many additional quality systems are in force. They mainly include profession-based systems such as Good Manufacturing Practices (GMP), and various standards, either nonspecific, eg ISO 15189, ISO 9001:2008, or specific, eg Joint Accreditation Committee of the International Society for Cellular Therapy and the European Group for Blood and Marrow Transplantation (JACIE), International Standards for Cord Blood Collection, Processing and Release for Administration (NETCORD-FACT), standards from European Association of Tissue Banks (EATB). Compliance with these standards has been introduced as a regulatory requirement by some competent authority for tissues.

Apart from these, most tissue banks have their internal quality system. Each tissue bank may expect to undergo several governmental and non-governmental audits per year. Process and product quality control, tracking & tracing and tissue vigilance present the most important auditing issues. Quality system compliance, which should prove that you are doing the right thing in a correct and professional way, is an expensive activity. However, it is of paramount importance to ensure optimal quality and safety of tissue products for patients. With regard to present day tissue banking there are two serious quality restrictions that hamper full control.

First, the suppliers and the collecting system are difficult to control to the extent one wishes from a GMP point of view. Especially in post-mortem donations, one has to act fast in an emotionally vulnerable environment. On such occasion, often, but certainly not always, a specialised team takes care of the harvesting of tissues and organs. Detailed information on the patient and the patient's behaviour is often not available and one must rely on hetero-anamnestic information. The harvesting team often includes health care workers for whom the harvesting procedure is distracting them from their routine. Their focus is the donor, not the donation.

Second, there are as many extensive quality systems as there are independent tissue banking organisations. Consequently, inspections of many governmental and non-governmental agencies are numerous. This does not seem efficacious, either for the auditors or for the auditees, and could certainly be improved.

20.5 FINANCIAL ISSUES

A rough estimate reveals that the turnover in Euros of all these tissue banks in Europe and Northern America together is 5-10% of that of the combined blood banks. In many tissue banks the yearly turnover is (considerably) less than one million euros, and may not exceed €100.000. The largest turnover is found in stem cell banks (bone marrow, peripheral blood stem cells and cord blood banks). They operate internationally and their harvesting, laboratory tests, logistic and allocating processes are complicated and expensive.

The necessity of HLA-matching, of major importance to ensure compatibility and therefore effectiveness of the tissue transplantations, is the prime reason for the expense. Besides the costs for the primary process, many additional costs are incurred in relation to general management, quality systems, administrative affairs, human resources management, housing, occupational care et cetera. The problem with small enterprises is that all the existing rules and regulations regarding tissue banking fully apply, without exceptions.

QA/QC-systems account for more than half of their budget. Tissue banking is a complicated and difficult task, which has already led to the bankruptcy of numerous (small) tissue banks. Even large organisations do not necessarily operate on a sound financial basis and often depend on subsidies, grants and gifts. The support of hosting hospitals, universities and blood establishments has been helpful in preventing tissue banks from going bankrupt. So far, many tissue banks have been able to survive while relying heavily on the staff, administrative personnel, housing and transport systems of their hosting organisations. But these organisations experience growing budget constraints as well, This kind of situation leads many tissue banks to look for improvement in the efficiency of their organisations.

Contrary to this, the demand for tissues is growing steadily, although not at an even pace with regard to the kind of tissue. The supply of, for example, bone and skin suffices most of the time. But there are still not enough stem cells and corneas available. The change in demand is unpredictable and might alter drastically when synthetic tissues become available.

20.6 SYNTHETIC TISSUES

Vast research efforts are exerted in the field of tissue engineering, resulting in huge steps forward in understanding the human body's production of tissues. These efforts have also resulted in lots of public and media interest and wild speculation. However, tissues (and solid organs) which are synthesised in the laboratory generally do not even look like the real thing. At best, synthetic tissues take over some of the physical or biological functions of their natural counterpart fairly well, but they never fulfil all of its functions.

Purely synthetic tissues or body parts with a (predominantly) mechanical function i.e. made from synthetic polymers or metals are available for bones (joints), including ear ossicles, and heart valves *(Table 2)*. They now have a reputable and established role in medicine.

Table 2: Origin of tissues

Tissue	100% synthetic	Partially synthetic (expanded)	100% natural
Skin		x	x
Cartilage			x
Amnion			x
Bone	x	x	x
Ear ossicles	x		x
Tendon			x
Heart valve	x	x	x
Cornea			x
Stem cells		x	x
Germ cells			x

In addition, biological process based tissue is available for skin and bone tissue. Until now their role has seemed limited, although promising results for these semi-synthetic tissues are increasing. However, so far they have been (too) costly and solely produce single cell-type tissues. The idea of producing full-thickness skin containing hair follicles and sweat glands, or regular bones in the right architecture in the laboratory is very far away.

Synthetic tissues do solve some of the problems, especially regarding the source and supply control. However, large restrictions will remain in the near future.

In the realm of stem cells, expansion techniques are promising in relieving some of the supply needs, but we must still harvest at least some of them from their natural source. The human body itself is still the best source of human tissues and probably will be for the next decade (or even decades?).

20.7 DISCUSSION AND CONCLUSION

It is suggested that reorganizing health care on a free-market basis could be helpful in resolving part of the problems arising in tissue banking. In itself, this is not improper to think about, provided that we continue to stick to the ethical principles concerning utilisation of human body parts *(see chapter 4)*.

However, expectations are that, for quite a while, the availability of human tissues for therapeutic purposes will depend on donations from living and post-mortem donors. This being so, and given the principle of non-remuneration of donors, constraints will be put on the possibility of market-driven competition in tissue banking.

Making money out of other people's charity does not feel good. In addition, commercial tissue banking opens the gates to the risk of fraud and other criminal activities. Rumours about illegal organ trade are pertinent and include the trade of tissues such as cornea, bone and skin at the cost of health risk for both donor and recipient. It is a global and general opinion that such activities should be banned.

Concurrently, it is still a good idea to look at costs and cost containment. Health care is a costly activity. Economies of scale, smart logistics and uniform procedures are very powerful tools to realize cost savings. Blood banks in a number of so-called developed countries have already followed this line of reasoning successfully.

Cost control and quality control through intensive cooperation are two important methods that are relatively easy to implement concurrently. Cooperation between tissue banks will lower quality costs, both internally and externally. The best way to go forward would be to organize tissue banks on a larger – national, if suitable – scale, thus lowering the number of organisations and systems. This has already been achieved, at least partly, in a few countries, in connection with a national blood organisation (eg France, UK).

Fewer systems mean less maintenance and overhead costs, audits and fragmented governmental control. It is as simple as that. Difficult aspects to overcome are professional competition and cultural differences. Small tissue banks are highly convinced that, firstly, they operate better than all the others and, secondly, they operate cheaper than all the others.

The first statement is generally unproven. The second statement is generally wrong, because professionals are inclined to 'forget' the costs for which the small tissue banks are not directly charged, if they are charged at all. It will be of great help if 'felt competition' (pride) between national tissue banks is put aside and, in a second stage, cultural differences between countries are seen as opportunities for improvement, instead of barriers to cooperation.

Blood banks have already proved that merging and cooperation are possible and cost-effective. Above all, blood banks have been able to improve product quality and patient safety considerably by organizing themselves in larger organisations. That was twenty or more years ago. When will tissue banks follow?

In addition, we suggest that close cooperation with blood banks will enhance organisational improvement in tissue banking. Such organisation should be the first issue: Quality, safety and cost control will follow automatically, for the benefit of the patients and healthcare systems.

SELECTED REFERENCES

1. European Commission, Health & Consumer Protection Directorate-General, Directorate C – Public Health and Risk Assessment. Brussels, Feb 2007, SANCO C6 CT/ges D (2007) 360045. http://ec.europa.eu/health/ph_threats/human_substance/documents/tissues_responses_en.pdf
2. DIRECTIVE 2004/23/EC OF THE EUROPEAN PARLIAMENT AND OF THE COUNCIL on setting standards of quality and safety for the donation, procurement, testing, processing, preservation, storage and distribution of human tissues and cells. http://eur-lex.europa.eu/LexUriServ/LexUriServ.do?uri=OJ:L:2004:102:0048:0058:en:PDF

ACKNOWLEDGEMENTS

The authors wish to thank Dr Paul Strengers and Dr Carine Doggen (Sanquin Blood Supply Foundation, Amsterdam and Nijmegen respectively, the Netherlands) for their valuable and constructive remarks.

Jeroen de Wit
Gilles Folléa

21. SYNTHESIS AND FUTURE:

EBA CONCLUSIONS AND RECOMMENDATIONS

The content of this book, aimed at presenting the European Blood Alliance perspective on blood, tissues and cells from human origin, leads us to formulate the following conclusions and recommendations.

1. **Ensuring a sustainable and safe blood supply**
   As a lifesaving therapy, blood transfusion will have a long future. It will certainly take a very long time and enormous efforts in fundamental research, product development and clinical trials to find equally safe and effective alternatives for transfusion of human blood components. The challenge for scientists, operators and regulators, is thus to ensure a sustainable and safe blood supply with sufficient blood components for every patient.

2. **Ensuring self-sufficiency from voluntary non-remunerated donors**
   For reasons of safety and ethics, voluntary non-remunerated blood donors are, and should remain, the cornerstone of blood supply. However, the debate on how to achieve European self sufficiency for blood components based on the voluntary non-remunerated donors could be difficult and sometimes emotional. Nevertheless, because the situation in Europe is vulnerable, and in some areas supply is insufficient, effective ways to ensure full self-sufficiency of blood components from voluntary non-remunerated blood donors in Europe must be found and implemented.

3. **Not for profit**
   Given the crucial role of non-remunerated donors, and the EU ethical principles supporting non-remuneration, all blood establishments and blood component suppliers should be strictly not-for-profit.

4. **Ensuring professional and effective donor management**
   The need to maintain a safe and sustainable donor base is of ultimate importance and, in order to make donor management more professional and effective, priority must be given to using and sharing good practices of donor management. The professional blood operators (i.e. EBA members) should jointly invest in this area of the blood transfusion chain.

5. **Ensuring optimal use of blood components and plasma derivatives**
   From the patients' end of the transfusion chain, the optimal use of blood components and plasma derivatives in the clinical setting is also of utmost importance. This is primarily for the benefit of the patients. But it is also an ethical obligation towards the voluntary donor. This calls for further professionalisation of this side of the transfusion chain, and should include a revised perspective on clinical use with, for instance, the right to issue prescriptions being reserved to transfusion medicine trained and qualified clinical specialists.

6. **Evaluating the blood EU Directives in the perspective of their revision**
   As assessed by the European Commission, the European Directives on Blood have been effectively implemented in all the EU Member States, and have helped significantly to improve the quality of the blood supply. But after more than seven years of experience, the Blood EU Directives need thorough objective evaluation by an independent Expert Committee, which should report to the European Commission, Parliament and Council. The importance of such an evaluation is strengthened by the initiation of the revision process of the Blood Directives in 2012-13.

7. **A standard setting role for the *Council of Europe Blood Guide***
   Given the achievement of many technical developments and improved standardisation of blood chain and transfusion practices, *The Guide to the Preparation, Use and Quality Assurance of Blood Components of the Council of Europe* should be given a standard setting role. This might be the best way to link the *Blood Guide* to the *European Directives on Blood.* In this way, the *Blood Guide* could be used to specify the technical standards of blood component manufacturing, just as the Pharmacopoeia is linked to European drug legislation.

   The rationale for this analogy is that the *Blood Guide* is annually revised in a well organised expert driven process to safeguard the maintenance of up to date scientific evidence based standards. As opposed to this helpful flexibility, the process required to revise and update the EU Directives and their annexes, according to the current Comitology rules, is extremely complex and lengthy.

   This new approach, already initiated for the chapter on quality assurance of the *Blood Guide*, would facilitate the necessary update of technical standards in a fast evolving domain.

8. **Developing self-auditing and accreditation based on the *Blood Guide* binding standards**
   For blood component manufacturing, from donors to distribution to hospitals, based on this *Blood Guide*, self-auditing binding standards should be developed, and complex EMA-like procedures should be avoided. Thus, the Quality Management in Blood Establishments could be based more both on self-auditing and on a European Accreditation System for Blood Establishments. This could help to improve the Quality Assurance standard in Blood establishments and also to reduce and harmonise the Competent Authority's inspection tasks.

9. **Adapting the blood supply to the expected increasing needs**
   Taking into account current demographic changes and despite active investment in optimal use, an average increase in the use of blood components of 1 – 3 % per year could be expected. This is based on calculations of patient population, use of blood components in every age cohort, and aging of population.

   The donor population will also increase in age, and ensuring adequate matching of donor population and component collection and supply needs will become even more difficult. Close monitoring of patients' needs and their trends, and consequent donor management to anticipate adaptation of donor bases should be organised.

10. **Improving the blood supply management**
    The current blood supply management and particularly the relationships between the users (hospitals, patients) and the blood component suppliers (mainly blood establishments) should be improved. In most EU countries, this relationship has been shown to be poorly developed. The *Good practices of blood supply management,* expected from the Council of Europe in 2013, should help in this perspective.

    In parallel, robustness of stock levels of short shelf-life blood components should be improved. Further research on the extension of shelf life of blood components, with parallel studies of the clinical effectiveness of stored components, should be stimulated.

11. **Containing the potential detrimental effects of competition**
Competition between Blood Establishments for the distribution of blood components to hospitals might increase in the coming years. But if this occurs, competition should be regulated to prevent patients suffering from suboptimal supply.

To avoid such a situation, EBA recommends that every (new) supplier meets the following criteria:

I. must fully comply with the European directives and Council of Europe Blood Guide standards
II. should be submitted to the current rules of regular inspections by the national Competent Authority of the receiving state
III. should be required to deliver the full range of blood components and services usually delivered by blood establishments;
IV. should provide a guarantee that it could meet legal claims or fund the cost of disruption which could be caused by withdrawal from the activity.

In any case, the national state sponsored blood authorities must ensure that the blood supply infrastructure remains in place.

12. **Assessing cost-effectiveness of new measures**
New safety measures, new products or new process improvements should be subject to cost-effectiveness analysis before routine implementation. This evaluation aims at maintaining a sustainable access to safe and sufficient blood components for patients.

13. **Harmonising transfusion medicine training and qualification in the EU**
Education in transfusion medicine and related qualifications should be organised at European level. In the Blood Transfusion chain, four specific levels of accreditation for medical doctors are needed: I) Donor doctor; II) donor medicine expert; III) transfusion doctor; IV) transfusion medicine specialist. The curriculum for each of these levels should be set and mutual recognition of diplomas organised.

14. **Coordinating responses to crises**
Contingency planning to define response modalities in case of crisis have been set up in EU countries. For crises that could threaten the blood supply, most EU countries now use the EBA contingency planning as a basis. To complete this, the Blood operators in Europe should organise a system for coordinating responses to crises potentially threatening the blood supply.

15. **Ensuring a sustainable and safe supply of human tissues and cells**
The same conclusions drawn for blood products certainly apply to therapies using tissues and cells from human origin. It will take a long time to find alternatives for such therapies, and here also the challenge is to ensure a sustainable and safe supply of human tissues and cells.

Given their long standing experience in the field of blood components, blood establishments should play an important role in supplying tissues and cells of human origin.