

# Symposium on Implementation of Pathogen Reduction Technologies for Blood Components

European Committee (Partial Agreement)  
on Blood Transfusion (CD-P-TS)





# **Symposium on Implementation of Pathogen Reduction Technologies for Blood Components**

*Executive Summary*

2-3 September 2010  
Strasbourg, France

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Director of the Publication: Dr S. Keitel

Page layout and cover: EDQM

### Editing:

European Committee (Partial Agreement) on Blood Transfusion  
(CD-P-TS)

European Directorate for the Quality of Medicines & HealthCare  
of the Council of Europe (EDQM)

Council of Europe

7, allée Kastner

CS 30026

F-67081 STRASBOURG

FRANCE

Website: [www.edqm.eu](http://www.edqm.eu)

For ordering: [www.edqm.eu/store](http://www.edqm.eu/store)

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Printed on acid-free paper by Bialec, Nancy, France

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# Implementation of Pathogen Reduction Technologies for Blood Components

2-3 September 2010  
Strasbourg, France

## *Executive Summary of the Symposium*

### INTRODUCTION

The symposium on Implementation of Pathogen Reduction (PR) Technologies for Blood Components was held on 2<sup>nd</sup> and 3<sup>rd</sup> September 2010 under the auspices of the European Committee on Blood Transfusion (CD-P-TS) of the Council of Europe (CoE). It was organised by the Department of Biological Standardisation, OMCL Network & HealthCare (DBO) at the European Directorate for the Quality of Medicines and Healthcare (EDQM) at its premises in Strasbourg. The symposium involved representatives of 77 blood establishments and services and regulatory authorities, as well as recognised specialists and manufacturers of PR systems. Experts from Australia, Canada, New-Zealand, Japan and the United States of America (USA) and World Health Organisation (WHO) representatives joined European colleagues from 39 countries for this event. Further to the advice of the CD-P-TS the EDQM was charged to coordinate the drafting and the publication of an executive summary for this symposium. This summary was prepared by the scientific committee to the meeting (see Appendix).

The detailed programme and presentations are downloadable at following URL  
<http://www.edqm.eu/en/Proceedings-of-International-Conferences-83.html>

## KEYWORDS

Blood transfusion, pathogen reduction, blood components, infectious disease transmission, blood safety, European Committee (Partial Agreement) on Blood Transfusion (CD-P-TS), European Directorate for the Quality of Medicines and Healthcare (EDQM), Council of Europe (CoE)

## ABBREVIATIONS

A: Amotosalen

AE: Adverse Events

APTT: Activated Partial Thromboplastin Time

BC: Buffy Coat

CCI : Corrected Count Increment

CD-P-TS : European Committee (Partial Agreement) on Blood Transfusion

CMV: Cytomegalovirus

CoE : Council of Europe

EC : European Commission

EDQM: European Directorate for the Quality of Medicines and Healthcare

EU : European Union

FFP: fresh frozen plasma

GTS : *ad hoc* working group on the “Guide to the preparation, use and quality assurance of blood components”

GVHD: Graft versus host disease

HIV : Human Immunodeficiency

IU : International Unit

MB : methylene blue

MS: Members States

NAT: Nucleic Acid Amplification Techniques

PAS: Platelet additive solution

PC : platelet concentrates

Ph. Eur. : European Pharmacopoeia

PR: Pathogen Reduction; Pathogen Reduced

PT: Prothrombin time

R: Riboflavin

RBC : Red Blood Cells

TA : Transfusion-associated

TACO: Transfusion associated circulatory overload

TRALI: Transfusion Related Acute Lung Injury

TTP: Thrombotic thrombocytopenic Purpura

U : Unit

UV : Ultra Violet

USA: United States of America

vCJD : Variant Creutzfeldt Jacob Disease

WHO: World Health Organization

WNV: West Nile virus

XMRV: Xenotropic Murine Leukemia retrovirus-like Virus

## PROGRAMME

The programme was as follows

### ***First day, September 2<sup>nd</sup> 2010***

#### SESSION A: KEY LECTURES

Background information and current status of pathogen reduction (PR) technologies implementation was presented.

#### SESSION B: SCIENTIFIC DATA FROM MANUFACTURERS

Cerus, CaridianBCT, Macopharma and Octapharma presented the latest progress in the PR technologies being developed.

#### SESSION C: INVENTORY OF TRIALS AND STUDIES PERFORMED BY COUNTRIES

Fourteen presentations discussed clinical trials performed with platelets, plasma and red blood cells (RBC) in different countries.

### ***Second day, September 3<sup>rd</sup> 2010 (restricted to authorities and blood services)***

#### SESSION D: REGULATORY AND IMPLEMENTATION STATUS OF PR TECHNOLOGIES

Seven European and three non-European authorities presented their approach to the regulation of PR technologies in their respective countries

#### SESSION E: ROUND TABLE DISCUSSION

A lively discussion took place at the end of the meeting with much participation from the audience.

## SUMMARY OF KEY POINTS

The following issues were addressed:

- The possibility to incorporate a consensus range of risk for emerging pathogens into cost-effectiveness models.
- The clinical usefulness of the endpoints used in platelet transfusion clinical trials.
- Uncertainties regarding the outcome of previous clinical studies, particularly of PR platelets and the possibility that a meta-analysis might offer some further clarity. However since different technologies exist for PR of platelet concentrates (PC), the combination of data of different technologies might be a challenge.
- The possible need to consider the treated blood component as a different component with characteristics and requirements which are probably different from those of the non-treated component. The case of pathogen reduced (PR) coagulation factor concentrates was cited.
- The question of how aggressively to move forward with implementation of the available PR technologies and issues regarding implementation in different settings.
- The general need for enhancement of haemovigilance monitoring of transfusion outcomes as well as specific safety assessment of PR treated products.
- The lack of consistency in the decisional criteria used by regulatory bodies and blood operators regarding implementation of PR technologies.
- The need that the implementation of PR technologies should be considered country by country, in relation to the risks of transfusion.
- The risk of blocking and unduly delaying progress in this field. The situation that occurred 30 years ago during the implementation of PR methods for coagulation factor concentrates was recalled.

## RECOMMENDATIONS

The following recommendations emerged:

- A document on study design should be developed, which should focus on clinical endpoints in trials of PR products (N.B. A paper on this subject is pending in *Transfusion*).
- The value of a meta-analysis of previous clinical trials of PR products should be examined (N.B. A Canadian led meta-analysis has been performed and publication is pending<sup>1</sup>).
- A proposal should be developed for a generic decisional instrument on implementation of PR technologies that could be used by National Regulatory Authorities and Blood Operators.
- It should be investigated whether it is possible to incorporate a consensus range of risk for emerging infections into cost-effectiveness models.
- The prerequisites for implementation of PR in a given blood system should be defined.
- Progress should be made in the assessment of the relative benefits and risks of PR technologies in different settings, which must then be implemented where appropriate.
- The standards for haemovigilance and post-marketing assessment of PR products should be defined and then implemented.

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<sup>1</sup> Post meeting note: *Transfusion*. 2010 Nov 8. doi: 10.1111/j.1537-2995.2010.02925.x. [Epub ahead of print] Meta-analysis of the randomized controlled trials of the hemostatic efficacy and capacity of pathogen-reduced platelets. Vamvakas EC.

## ACKNOWLEDGEMENTS

The organisers would like to express their sincere thanks to the CD-P-TS and GTS as well as to all the participants from Control Authorities, Blood services and manufacturers for their support to this initiative. The speakers<sup>2</sup> and the members of the scientific committee to the meeting (listed in the Appendix to this summary) are especially acknowledged for their active contribution to the elaboration of the programme and to the preparation of this executive summary. Dr Jean-Pierre Cazenave, Dr Miguel Lozano and Dr Sheila MacLennan are acknowledged for their expert advice and support to the EDQM secretariat in the organisation of the meeting as well as the drafting and publication of the executive summary which was coordinated by Dr Marie-Emmanuelle Behr-Gross (Scientific Officer, EDQM) supported by Ms Ahlem Sanchez (secretarial assistant, EDQM) and Ms Carole Knaup (editorial assistant, EDQM).

## SUMMARY OF SESSIONS

### *Session A: Key lectures*

#### **A1. Background information**

The speaker reviewed different approaches to reduce the risks from pathogens in transfused blood components, particularly the use of donor history and specific testing.

Donor history can be coupled to donor examination, post-donation information and haemovigilance. If donation is deferred, donor deferral registries can be maintained. The problem is that the limit of this approach may have been reached. The sensitivity of the questions is low, as is their specificity. This can lead to significant loss of healthy donors and undermine public confidence. Formal validation of the questions would be possible, although this would necessitate demanding epidemiological studies, with marker rates in deferred donors.

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<sup>2</sup> Not listed or named per request of CD-P-TS

Specific testing has been spectacularly successful in effectively eliminating transmission of hepatitis and Human Immunodeficiency Virus (HIV). In 1967, no less than 30% of multiply transfused patients developed hepatitis. Introduction of testing for hepatitis B surface antigen reduced the frequency of infection by 70%. Further progress was largely dependent on the development of specific tests for hepatitis C and, in the USA, the current rate of transfusion-linked hepatitis is effectively zero.

The emergence of HIV-linked infections took the blood transfusion community by surprise. Before a specific test could be developed, it is estimated that about 12,000 transfusion-linked infections occurred in the USA. Since the introduction of a specific antibody test in 1985, only 49 transfusion-related infections have been identified. Since the introduction of specific nucleic acid testing, the risk of transfusion-related HIV infection has dropped to an estimated 1 case per 2 million.

HIV is not the last emergent pathogen with which transfusion specialists have been faced. For example, dengue fever has started to spread in Florida. Xenotropic murine leukemia retrovirus (XMRV)-like virus is said to have entered the USA blood transfusion system. West Nile virus (WNV) has rapidly spread throughout most of the USA during the last 10 years. Chagas disease - a South American tryposomal infection - is being increasingly detected in the USA. Screening for all conceivable pathogens would hardly be practicable and would tend to lead to inadequate blood supplies.

The optimal approach might be pre-emptive PR, as this would cover a wide variety of pathogens, even those which have not been fully characterised. Current technologies require the addition of either psoralens or riboflavin (R) to blood, followed by exposure to Ultra Violet (UV) light, and disrupt the nucleic acid of all known pathogens. Such techniques will probably be generally adopted for platelet and plasma treatment. This could provide the definitive safeguard for the blood supply.

## A2. Implementation

### A2.1. Current situation in European countries

The speaker reported the results of a survey of the use of PR in 51 countries, including 47 members of the CoE. Responses were made by 36 members of the CoE and 4 other countries.

Sixteen of the Council of Europe (CoE) Members States (MS) employed PR technologies for fresh frozen plasma (FFP). Nine of these countries employed a mixture of quarantine and PR technologies - Austria, Germany, Greece, Italy, Poland, Portugal, Spain, Switzerland and the United Kingdom. Seven countries used PR technologies alone - Belgium, Finland, France, Ireland, Luxembourg, Norway and Sweden. The most frequent PR technologies were solvent detergent (SD) treatment and methylene blue (MB). Amotosalen (A) and Riboflavin (R) were hardly used.

Thirteen European countries are routinely using PR PCs. Platelet concentrates treated with PR are officially approved in Belgium, France, Germany, Portugal, Spain and Switzerland. The principle method used is Intercept (A plus UVA). Mirasol (R plus UVB) is also approved in Belgium. The use of PR platelet infusions in Alsace has been shown not to impact platelet use and to improve outcomes to transfusion.

Treatment of RBC is not yet adequately established to allow large scale introduction.

The speaker emphasized that PR is a proactive rather than a passive approach to the problem of contamination. It was effective against unknown and known pathogens at such low levels that any test would give negative results.

### A.2.2. Current situation in other countries

The speaker reviewed the use outside Europe of PR of blood components.

The situation is particularly difficult in developing countries, as viruses, bacteraemia and parasites are highly prevalent. Moreover, the principle transfused component is whole blood (>80%), for which methods of PR are not yet established. There is also a paucity of available data.

Nevertheless, relatively large quantities of pathogen-reduced preparations are used in some more prosperous countries, such as 30,000 units (U) of Theraflex - MB-treated plasma - in Russia in 2009 and 23,940 bags of Octaplas - a SD treated plasma - in Turkey between 1995 and 2010.

PR is less established in developed countries outside Europe than within Europe. Thus, in the USA, Octaplas has been submitted for registration. Theraflex is registered, but not distributed in Canada. Mirasol (R plus UVB treated platelets) is in clinical studies in Japan, Australian and New Zealand, but has not been registered.

## ***Session B: Scientific data from manufacturers (unpublished data and recent method developments)***

### **B1. Cerus corporation**

#### *Background*

PR technologies are now widely available in Europe, with multiple CE marked products available to treat both platelets (Intercept Blood System (referred to as “Intercept” thereafter), Mirasol) and plasma for transfusion (Intercept, Theraflex, Octaplas, Mirasol). The European experience with PR platelets and plasma now numbers in the millions of U, with a safety record that has been widely reported in the scientific literature. Many countries in Europe now incorporate PR into at least some proportion of their blood component production, with some already applying the treatment to 100% of plasma for transfusion.

There are no approved systems for RBC pathogen reduction as yet. However, on the basis of the completion of a Phase I Intercept RBC trial earlier this year, Cerus plans to move forward with pivotal

Phase III trials of this product in support of CE mark approval. This method is not effective enough for whole blood.

#### *Properties of the Intercept system*

The Intercept system uses UVA and the photoactive compound A to inactivate viruses not covered by current testing protocols. It has been demonstrated to inactivate influenza H<sub>5</sub>N<sub>1</sub>, WNV and corona virus (SARS), Chikungunya virus, dengue virus, and XMRV. It is not effective against all non-enveloped viruses. The Intercept Blood System inactivates high levels of both cell-free and cell-associated Cytomegalovirus (CMV). The Intercept System for Platelets is used in place of CMV negative platelets by blood centres in numerous countries.

The Intercept Blood System inactivates high levels of leucocytes, including T-cells, preventing both replication and cytokine synthesis. It is CE marked as an alternative to gamma irradiation. Intercept treatment of platelet components facilitates management of a single platelet inventory, eliminating the possibility that patients at risk for transfusion-associated (TA) Graft versus host disease (GVHD) may receive platelet components with viable T-cells.

The Intercept Blood System inactivates high levels of bacteria, both Gram-positive and Gram-negative, aerobic and anaerobic, as well as spirochetes. The Intercept Blood System for Platelets is used in numerous countries in place of microbial testing of platelets. Spores are resistant to Intercept pathogen reduction. Custer *et al* (Transfusion 2010) estimated the bacterial risk with untreated platelets as 4.8 – 12 per 1000 patients.

The Intercept Blood System inactivates high levels of protozoa, including *T. cruzi*, *Leishmania*, *P. falciparum*, and *Babesia*.

#### *Experience with the Intercept system*

Intercept is in routine use in more than 60 blood centres in 14 countries. More than 600,000 treated U have been transfused. Cerus has supported an extensive program of haemovigilance studies to

monitor the introduction of Intercept products in Europe. In studies of over 30,000 of treated platelet U and over 30,000 treated plasma U to date in a broad patient population, Intercept Platelets and Plasma have demonstrated a safety profile comparable to conventional components. Adoption of Intercept Platelets has not affected platelet or red cell component use.

Intercept Platelets are CE marked for storage up to 7 days, and clinical studies have confirmed that 7-day Intercept platelets are comparable to untreated platelets for support of thrombocytopenic patients.

Investigator studies of Intercept Platelets in routine use have demonstrated significant reductions in platelet recipient acute transfusion reactions when compared to prior periods of conventional platelet use. The results of these post-marketing studies demonstrate the potential impact of Intercept treatment on the non-infectious hazards of transfusion - in addition to protection against transfusion-transmitted infections.

The efficacy and safety of Intercept Platelets have been established in 11 trials and over 1000 patients. Similarly, Intercept Plasma has been evaluated in 6 trials with approximately 5,000 U transfused in all major indications for plasma transfusion. Treated platelets and plasma were similar to conventional products for control of bleeding. The safety profiles of treated products were not different from those of conventional platelets or plasma. The Medical Device Design Dossiers submitted for EC conforming assessment of Intercept included full Drug Dossiers to support the safety and efficacy of A. The Intercept Blood System is a Class III medical device. Intercept-treated platelets have received additional country-specific regulatory approvals in France, Germany, and Switzerland. Intercept plasma is approved in France, and under review in Germany and Switzerland. It is approved for all patient groups.

## **B2. CaridianBCT biotechnologies (referred to as “Caridian” thereafter)**

### *Introduction*

The Mirasol PR System is intended to reduce the pathogen load and inactivate residual white blood cells in donor platelet concentrates or plasma for transfusion. It is also planned to develop the system for the treatment of whole blood.

The basis of the Mirasol PRT System Technology is R + UV Light (UVA and UVB). R modifies nucleic acids upon exposure to light and makes blood pathogens unable to replicate. It is not based on covalent modification. R and its photo-products are non-toxic and non-mutagenic and are naturally present in normal blood. No new, unknown compounds are introduced into the blood supply and no new photoproducts or adducts are generated. All starting materials and photoproducts are already found in normal blood.

PR has been demonstrated for enveloped and non-enveloped viruses, Gram-positive and -negative bacteria and parasites. Whole blood pathogen reduction has been demonstrated.

### *Quality control*

QC is performed on every component batch. Parametric process monitoring and control assures that the stated performance on pathogen kill, white cell reduction and cell quality is met for each component.

### *Efficacy and safety*

Detailed toxicology studies have been performed. No adverse events (AE) have been attributed to the use of Mirasol-treated platelets in a controlled clinical trial. The average retention of all coagulation and anticoagulation factors measured at all test sites met CoE Guidelines. There are three programs to monitor post-market surveillance and haemovigilance. The product is licensed in Europe for plasma and platelets.

Surveillance data are available for 4,500 platelet transfusions and 1,000 FFP transfusions. These include no reports of AE related to Mirasol treated products. More specifically, there are no reports of TRALI (Transfusion Related Acute Lung Injury) or ALI (Acute Lung Injury), no reports of bacterial contamination in products, and no reports of increased bleeding or increased platelet component utilization after introduction. Moreover, the clinical parameters for platelet products were within historical ranges, and the correction of ProthrombinTime (PT) and Activated Partial Thromboplastin Time (APTT) after FFP use were within the expected ranges. The overall adverse event rate was 0.20%, versus historical rates of 0.34%. The events reported were Grade 1, including itching and rash.

The CE mark has been awarded.

### **B3. Macopharma**

The THERAFLEX technology is a simple and rapid procedure with irradiation (UVC irradiation wavelength 245 nm) with agitation (~40 s) There is no need for chemicals, although it is necessary to have areas of thin layers and mixing.

#### *Plasma*

THERAFLEX MB-Plasma was CE Marked as Class IIB Medical device (2000) and then Class III (2004). THERAFLEX MB-Plasma is in clinical use in 15 countries worldwide and more than 1,900,000 U have been treated with the THERAFLEX MB-Plasma system and then subsequently transfused. Macopharma is investigating both haemovigilance and post-marketing surveillance programs.

#### *Platelets*

THERAFLEX UV-Platelets was CE marked early in 2009 and is undergoing clinical trials.

Platelet additive solutions must always be used. Good tolerability has been shown. No photoactive agent must be added. Survival and recovery experiments have found no loss in viability.

### *Future developments*

Prion Removal (P-Capt filter) was CE marked in Sept 2006 and is awaiting implementation.

The red cell/whole blood PR project is in the early stages of conception. Feasibility Studies are being performed in R&D.

A Phase I study (healthy volunteers, tolerability, dose escalation) and a multicentre international phase III study are in the planning stage.

## **B4. Octapharma**

Octaplas is a coagulation-active and blood group-specific plasma preparation which has been treated with solvent and detergent, leading to the rapid and irreversible inactivation of the lipid membranes of all enveloped viruses. Non-enveloped viruses are immunologically neutralised, where neutralisation capacity depends on the virus load and the specific antibody content in the plasma pool and final container.

OctaplasLG is prepared from Octaplas with an additional affinity gel step to remove prions.

### *Quality*

Octaplas is prepared by pooling 630 to 1,520 U of single-donor FFP, to balance out donor-to-donor variations for coagulation factors and to meet the request for standardised and high quality coagulation-active plasma for infusion. Pooling also prevents AE by dilution/neutralisation of antibodies against white blood cells.

All coagulation parameters for Octaplas are within the normal range.

Octaplas is manufactured in a Good Manufacturing Practice (GMP) approved plant.

### *Approval*

Octaplas is a medicinal product for human use (EU Directive 89/381/EEC). It must comply to the specifications of the European

Pharmacopoeia (Ph. Eur.) (monograph 1646 and is subject to stringent marketing authorisation approval procedures, focusing on quality, safety and efficacy).

Octaplas is licensed in 29 countries (including Europe, Canada, Mexico) and over 6.5 million of 200 mL bags of Octaplas have been transfused to more than 2 million patients since January 1992. OctaplasLG is licensed in Germany and Australia and over 37,000 bags of OctaplasLG have been transfused to more than 12,000 patients since June 2009.

### *Therapeutic indications*

The therapeutic indications for Octaplas/OctaplasLG are:

- Complex deficiencies of coagulation factors, such as coagulopathy due to severe hepatic failure or massive transfusion;
- Substitution therapy in coagulation factor deficiencies, in emergency situations, when a specific coagulation factor concentrate (e.g. factor V or factor XI) is not available or when a precise laboratory diagnosis is not possible;
- Rapid reversal of the effects of oral anticoagulants (coumarin or indanedione types), when vitamin K is insufficient, due to impaired liver function or in emergency situations;
- Thrombotic thrombocytopenic purpura (TTP), usually in conjunction with plasma exchange;
- Potentially dangerous haemorrhage during fibrinolytic therapy, using e.g. tissue plasminogen activators, in patients who fail to respond to conventional measures.

### *Clinical studies*

At least 18 studies and retrospective analyses have been conducted to examine the efficacy and tolerance of SD plasma, covering all indications for plasma. Pharmacovigilance data and clinical studies indicate that Octaplas/OctaplasLG is extremely safe with regards to TRALI and that transfusion of Octaplas/OctaplasLG is associated with

markedly lower rates of severe adverse reactions than with control plasma.

### *Other products*

Uniplas has the same properties as Octaplas, but can be used regardless of blood group. Lyophilised plasma is in the pipeline. Its advantage is that it is available for use immediately, as it does not need to be thawed.

## ***Session C: Inventory of trials and studies performed by countries***

### ***Key lecture***

Clinical studies to evaluate platelet efficacy in hematology/oncology patients are complex and should be carefully planned. Platelet efficacy can be thought of in terms of a platelet transfusion response or in terms of cessation or prevention of bleeding in response to a platelet transfusion. Interpretation of these studies is complicated by variability in the frequency of bleeding episodes in thrombocytopenic patients undergoing therapy, the variability in number of transfusions per patient and the variability per patient in the response to platelet transfusion.

### *Transfusion response endpoints*

One measurement of a platelet transfusion response is with a corrected count increment (CCI). This is a platelet count taken usually 1 or 24 h post transfusion and corrected for the dose transfused and the size of the patient. Although this is considered a surrogate endpoint for efficacy in clinical trials, it is not commonly used by physicians in clinical practice. The CCI is useful in comparing platelet responses between patients transfused with different platelet transfusion products but it is, however, influenced by the number of preceding transfusions. To avoid this influence, it is better to assess only the first 8 transfusions or only to monitor the first 28 days of thrombocytopenia. This approach was taken in the Eurosprite and Miracle clinical trials. A CCI analysis should first be performed for

each patient and then summarised for all patients in the study (mean/median). An alternative approach is to treat CCI as a dichotomous outcome by specifying whether the CCI was  $>7500$  at 1 hr or  $>4500$  at 24 h. The advantage of treating the data this way is that it is easier to understand - but more detailed information is lost. However, there is no evidence that obtaining a specific CCI is associated with reduced bleeding and further evaluation is needed of the appropriateness of CCI as a haemostasis endpoint.

### *Bleeding endpoints*

A measure of patient bleeding is a true clinical endpoint for platelet efficacy, but a study design needs to consider which type of bleeding events to capture. One approach is to quantify the percent of patients with bleeding events. This was used in the SPRINT study. The disadvantage of this approach is that it does not capture the duration of thrombocytopenia or identify patients with multiple bleeding episodes. An alternate approach is to record the time to the first bleed. This implies that the timing of the first bleed is important, but does not capture information about the duration of thrombocytopenia and additional bleeding episodes. Yet another way to approach this issue is to capture recurrent bleeding events. This identifies which patient is bleeding, when they bleed and the total burden of bleeding during the treatment period. This methodology was used in the STOP Study (Heddle *et al* Blood 2009). The choice of the bleeding endpoints depends on which question is being asked in the study and needs to be specified before the start of the study. Measurement of bleeding in patients requires a scoring scale. The most common is the WHO bleeding scale that classifies bleeding by grades: Grade 1 Minor, Grade 2 Mild blood loss, Grade 3 Gross blood loss, Grade 4 Debilitating blood loss. Bleeding of greater or equal to Grade 2 can be considered as a composite endpoint, but there are limitations to this approach, including the fact that the WHO bleeding scale has not been validated and the clinical relevance of Grade 2 bleeding has been challenged. Alternatives to the WHO bleeding scale are being developed but will need to be validated.

### *Choice of outcomes*

The selection of either a surrogate outcome or composite outcome for a study requires careful consideration. A surrogate outcome is an easily measured laboratory value or a physical sign used in clinical trials as a substitute for a clinically meaningful endpoint (how a patient feels, functions or survives) and is expected to predict the effect of therapy. Surrogate endpoints are used because they are easier to measure. A composite outcome is a compilation of a number of outcomes that represent different serious morbidities. Surrogate endpoints are used because they can estimate the net benefit to the patients. Moreover, they make the statistical evaluation more efficient and can drive down the size of the study and avoid making an arbitrary choice between outcomes. The composite outcome should be associated with the primary objective, be biologically justifiable, meaningful to patients and represent a clinically important long term outcome. All components of the composite outcome should be of equal value.

### *Statistical considerations*

The study hypothesis needs to be carefully considered. The most common approach in PR studies is to prove non-inferiority of the treated platelet component. This has been applied to both CCI and bleeding endpoints. An important issue in non-inferiority studies has been how to set the “zone of non-inferiority”. This is the margin beyond the point estimate of the control that would be acceptable as equivalence between the two products. A standard approach to setting the zone of non-inferiority is to calculate the upper limit of 95% CI for the actual risk difference. The zone should be within this limit. In analysing these studies for non-inferiority, the type 1 error should be reduced to 0.25 and the null hypothesis should be that PR platelets are better than control platelets. There are potential ethical issues with non-inferiority studies. One ethical concern is whether we are exposing patients to an intervention if we do not have a reason to believe that it is superior but just want to prove it is not worse. Non-inferiority studies require some benefit either for the patient - such as less harm (AE) or to society - such as lower cost or resources

consumed. If a benefit cannot be identified one should not conduct a non-inferiority study.

In summary, studies on platelet efficacy are difficult to perform and need continuous improvement. Points to consider in planning these studies are: research designs that address the question, the appropriateness of the outcomes (single clinically relevant outcome vs composite outcome), methods analysis and appropriate conclusions. The foundation of good clinical research is formulating the right question to be answered. The question should include the patient population, the intervention, the comparison or control, the outcome and the timing.

## **C1. Pathogen reduction technologies for platelets**

### **C1.1. Austrian experience**

Austria has 10 separate districts for blood collection. In total the country collects approximately 500,000 whole blood U annually; 95% of these are collected by the Red Cross. PR is applied to plasma (SD and MB) and is being evaluated for platelets. The validation for platelets is proceeding in 3 centres for Intercept and validation and approval for Mirasol is scheduled for Autumn 2010 at one of the centres (Innsbruck). In vitro studies of UVC for platelets are also being conducted at Innsbruck.

In 2007, the Austrian authorities conducted an *in vitro* test of the Intercept PR methodology in platelets. Twenty one double U of apheresis platelet U were contaminated separately with seven species of bacteria (0.03-3.0 Colony Forming Unit/ml) and split. From each, pair one unit was treated with Intercept PR and the other unit served as control. Samples were taken on days 1, 2 and 5 and tested for the presence of bacteria by culture. No growth was observed in any Intercept treated U but bacteria did proliferate in the control U. In a separate study, Austrian authorities compared the effects of Mirasol treatment and UVC on platelet mitochondria through confocal microscopy studies. Mirasol treated platelets maintain

mitochondrial activity through day 5, but exhibited decrease in mitochondrial activity between days 5 and 7. Similar effects were observed with UVC treated platelets.

Clinical experience with Intercept treated platelets demonstrated a reduction in AE associated with platelet transfusion. The frequency of reported AEs in 2004 - prior to PR - was 0.8 and this was reduced to 0.4 in 2009 after the introduction of PR.

### C1.2. EuroSprite study

The EuroSprite trial was a prospective, controlled, randomised, double blind study in thrombocytopenic patients transfused either with Intercept-treated buffy coat (BC) platelets or conventional pooled BC platelets. The primary endpoint was a mean CCI at 1 h for the first 8 transfusions. A total of 103 patients were enrolled in the study. CCI at 1 h was not statistically significantly different between the two treatment arms. Clinical haemostasis, haemorrhagic AE and overall AE were not different between the treatment groups.

### C1.3. HOVON study

The Netherlands conducted their own clinical evaluation of Intercept platelets in a recent Hovon 82 study. The study involved a comparison between BC platelets stored in plasma, platelets stored in additive solution [Platelet additive solution (PAS) III] and Intercept treated platelets. This was a non-inferiority, randomised, controlled trial but not blinded to the treatment. The primary endpoint was CCI at 1 h with a non-inferiority margin of 20%. Secondary endpoints were 24 h CCI, bleeding (Grades 1-5), use of platelet and red cell products, transfusion intervals and adverse reactions. It was planned to enrol approximately 100 thrombocytopenic oncology patients per group. The study started in March 2007 and had a planned interim analysis in March 2008. The study was stopped after the interim analysis by the Data Safety Monitoring Committee, due to an excess in bleeding in the PR arm as compared to the plasma stored platelet arm. At the end of the study, the control arm had 99 patients, the PAS-III arm had

94 patients and PR-PAS III arm had 85 patients. The conclusion of the study was that platelets treated with Intercept PR have an inferior transfusion response, independent of dose and time. More patients experienced bleeding episodes in the PR arm of the study when compared to the plasma arm or the additive solution arm of the study. The CCI for PR-PAS III platelets was significantly lower and required 2-3 more BC platelets in a pool to reach the same CCI. Platelets that were stored in PAS-III without PR were not significantly inferior to plasma stored platelets.

#### C1.4. IPTAS (Italian Pathogen reduction Technology Assessment Study)

In Italy, PR is not mandatory and no guidelines for its use are in place. PR has been implemented in 15 Blood centres in 9 out of 21 Italian Regions. Two centres use Mirasol treatment and thirteen use Intercept treatment for platelets. The National Ministry of Health has sponsored a clinical trial to evaluate pathogen-reduced platelet products. This will be a non-inferiority, multicentre, controlled, randomised and prospective study comparing safety and effectiveness in 420 thrombocytopenic hematology-oncology patients transfused either with Intercept-treated platelets or Mirasol-treated platelets or conventional platelet products. The primary endpoint will focus on prevention of bleeding.

#### C1.5. MIRACLE (MIRAsol CLinical Evaluation) study

This study was conducted by Caridian (manufacturer of Mirasol pathogen treatment) and independently analysed by Dr. Nancy Heddle from the McMaster Transfusion Research Program, Canada. The study was a prospective, randomised, single blinded, non-inferiority study of patients transfused either with Mirasol PR platelets or control plasma stored platelets. The primary endpoint was CCI at 1 h. Secondary endpoints were CCI at 24 h, bleeding (WHO bleeding scale 1-4), frequency of platelet and red cell transfusions, alloimmunisation and AE. The study included 118 patients (56 PR platelets vs 54 control platelets). The conclusion of the study was that non-inferiority

of Mirasol treated platelets compared to control platelets was not demonstrated for CCI at 1 h. The secondary endpoints were not statistically different and the safety data did not identify any concerns. Additional comments on the study included a suggestion that the non-inferiority margin might have been set too tight, as previous studies with radiolabeled platelets and healthy volunteers had already demonstrated a significant loss of *in vivo* recovery after Mirasol treatment.

### C1.6. Norwegian experience

PR platelet (Intercept) use was initiated in 2003. In 2010, PR platelets are being used in 4 out of 15 major hospitals and approximately 20% of transfused platelets are PR. No bacterial testing and no gamma irradiation is used on platelets that are PR. In 2007, NAT-testing was discontinued in Norway but neighbouring countries increased their NAT testing. This year, Norway is re-evaluating its NAT testing strategy, including the use of PR platelets.

Clinical experience using PR platelets in Norway includes 1144 patients monitored for CCI after a single transfusion. Of these, 399 were transfused with Intercept platelets and 745 with plasma stored platelets. The CCI was reduced by 18% at 1 h and by 25% at 24 h. The total platelet content of PR platelets was reduced by 9%. There were no reports of serious bleeding after PR platelet transfusion.

In addition to clinical studies, Norway also conducted *in vitro* studies. A 2005 article (Transfusion 2005, 248-253) reports that Intercept treated platelets have a higher rate of platelet destruction and increased level of cytokine accumulation during storage. In 2007, the same group also reported that Intercept platelets induced spontaneous platelet activation, accelerated platelet metabolism and exhibited reduced capacity for adhesion, aggregation and degranulation. In 2010, this group also conducted a small clinical trial of 40 patients transfused with plasma stored or Intercept treated platelets. The primary endpoint was CCI. There was a significant reduction (40%) in CCI at 1 h and 24 h (70%) after Intercept platelet transfusion.

The conclusion of the team investigating PR in Norway is that the Intercept method accelerates the storage lesion and this may reduce CCI. Nevertheless, bearing in mind the possible benefits of PR, the group recommends further development and use of PR products.

#### C1.7. PrePAREs Study –( PR Evaluation and Predictive Analytical Rating Score)

In the HOVON 82 study, the Dutch blood service compared Intercept treated platelets to plasma stored platelets. A follow-up study is being planned that will compare Mirasol treated BC platelets to plasma stored platelets. This will be a randomised, single blinded, multicentre non-inferiority study with two arms: BC platelets stored in plasma and PR (Mirasol) platelets in plasma. The primary endpoint will be WHO  $\geq$  Grade 2 bleeding and non-inferiority will be defined as a less than 12.5 % increase in bleeding complications. The estimated size of the study will be 618 haematological/oncology patients. Secondary endpoints will be CCI at 1 and 24 h, AE, transfusion intervals and transfusion requirement and alloimmunisation rates. The study will also attempt to validate a new scoring system based on *in vitro* platelet parameters, including CD62 expression, annexin A5 binding and lactate concentration. A pre-study is currently being conducted and enrolment of the first patient into the PrePAREs study is anticipated to be in October 2010.

#### C1.8. SPRINT

This was a large randomised controlled trial (600 patients) using apheresis platelets (AMICUS) PR by A (318 patients), in comparison with control platelets (327 patients):

Primary endpoint (linked to efficacy):

- proportion of patients with grade 2 bleeding,

Hypothesis: non-inferiority

Secondary efficacy endpoints (include efficacy and safety parameters):

- CCI 1 h and 24 h;

- Interval between platelet transfusions;
- Number of platelet transfusions;

Incidence of platelet refractoriness;

- Number of RBC (RBC) transfusions;
- Number of platelet transfusion reactions;

Conclusions:

- CCI lower than with control PC;
- Intervals between platelet transfusions shorter,
- Increased number of platelets transfused
- PR platelets with function similar to the control platelets (no difference in haemostatic endpoint)
- AE associated with the transfusion of PR platelets are similar to those of control platelets

### C1.9. TESSI

Multicentre, multinational, prospective, randomised, double-blinded study.

Primary endpoint: CCI at 1 h

Hypothesis of Non-inferiority

Secondary endpoints: level of platelet count, count increments at 24 h, haemostasis and safety

Conclusion:

- The 1 h CCI of 7 day-old Intercept PC was significantly lower than, but not inferior to, conventional PC (margin of inferiority set at 30%, this level was thought not to be clinically significant)
- The 24 h CCI of 7 day-old Intercept PC was significantly lower than conventional PC

- The 24 hr platelet count for 7 day-old PR was sufficient for haemostasis:
  - Time to next PC transfusion was not different
  - Haemostasis maintained
- No difference in safety profile

*Summary of discussions following presentation of all platelet trials*

SPRINT & TESSI: These two clinical trials had populations (study and control) with similar characteristics and without statistically significant differences. Both investigated whether platelets PR by A (buffy-coat derived or apheresis) exhibit non-inferiority when compared to similar non-PR platelets. The margin of non-inferiority in the studies was different (12.5% vs. 30%). The endpoints were also different: in the first the endpoint is bleeding, in the second it is the comparison of the CCIs. Both studies proved their hypothesis for the primary endpoint. For the secondary endpoints, they conclude that there is no differences in safety (based on adverse reactions), or function (both were sufficient for haemostasis), but that there is a decrease in CCI at 24 h.

There is no evidence that CCI relates quantitatively to bleeding. It is difficult to compare studies when two arms start with a different platelet dose. It is thought that even though the platelet dose is taken into account in the calculation of CCI, this does not completely correct for the effect. Is CCI a surrogate for bleeding? - there appears to be a systematic decrease in CCI with pathogen activated platelets and one participant commented that the absolute count increment was highly correlated with bleeding.

It was suggested that if there is a reasonable increment this suggests that platelets are present and functional; the question is whether CCI is a relevant value to assess quantitative rather than qualitative differences. It might not mean that the platelets are safer if there is a higher CCI but may mean that there is not a need to transfuse as often. Perhaps the platelet count is irrelevant beyond a threshold.

One participant was worried about whether the studies were adequately powered to detect clinically significant differences in the rates of AE. Another participant advocated the use of thromboelastometry for platelet function. There was lively discussion of the significance or lack of significance of Grade 2 bleeding. The new bleeding scale being proposed by Kathryn Webert should be assessed for correlation with CCI.

In all of the studies, CCI was shown to be decreased, although there was no difference in the effect on bleeding in any study except for Hovon.

CCI is not a validated surrogate for bleeding as far as the FDA is concerned.

## **C2. PR technologies for red cells**

Red cell PR is under development. The first study was a double blinded non-inferiority study with the hypothesis that S-303 erythrocytes are not clinically different from untreated RBC. This was stopped voluntarily at phase 3, because two patients presented antibodies to acridine. The second generation S303 method is now in development and clinical studies are under way.

New studies and new methodologies should be developed before any decision can be taken by the blood establishments/authorities

## **C3. PR technologies for plasma for clinical use**

### **C3.1. Intercept studies**

Six clinical trials have been performed - 2 phase I/II and 4 phase II/III - on the activity of this plasma in acquired coagulopathy, with the hypothesis that Intercept plasma is not clinically different from untreated plasma. The conclusion is that the studies have demonstrated that the kinetics of coagulation factors are comparable to those with conventional plasma. The reduction in fibrinogen was approximately 27%, but all other factors were 78 – 97% of initial values.

It was concluded that Intercept Plasma corrects congenital and acquired coagulation factor deficiencies and supports haemostasis for minor and major bleeding. The effect of Intercept plasma was comparable to that of FFP in TTP, and the adverse reactions and events were similar during 2 years of follow up.

Only 203 patients were enrolled in these 4 studies, and 4358 U were administered.

### C3.2. Finnish experience

Finland started to use SD-FFP in 2007 and since last year all U used are SD PR. SD-FFP has been transfused to all patient groups and has also been used to prepare reconstituted blood for exchange transfusion in neonates. The main advantages are the uniformity of quality and coagulation factor content, and the decrease in the incidence of serious allergic reactions. TRALI and anaphylactic reactions have not been observed.

Hospital blood banks and clinicians are happy with the safety and efficacy of the component.

### C3.3. Norwegian experience

Norway has used SD-FFP since 1993, including in children. Since 2005, the health authorities have also accept single donor pathogen PR plasma and quarantine plasma.

There has been no documented transmission of infectious disease by plasma; over the same period there was also no documented transfusion of transmitted infections by red cells or platelets except transmission of Hepatitis A virus (HAV), Varicella and Parvovirus B19 by red cells. There were also no notifications of TRALI (which are linked to transfusion of red cells or platelets) and logistics in blood services were improved.

### C3.4. Austrian experience

Austria recently decided to switch from quarantine plasma to the MB technology for plasma PR. The advantages are that no quarantine period is now needed and that clinical studies showed a decrease in AE (possibly due to filtration pre-freeze).

Many different technologies can be used to inactivate plasma: solvent-detergent (SD), MB (MB), R and A.

In general, different European countries have totally or partially adopted one of these technologies.

It seems that they are generally well accepted, particularly the SD and MB technologies. The efficacy is the same as with non-treated U, but with a lower level of adverse reactions.

### *Conclusions of Session C*

Views on the use of PR products differ between countries, as do the estimated risks of transfusion of blood components. These differences are particularly marked with respect to the use of PR platelets, but less so with PR plasma.

Naturally the costs of these technologies have great weight in the decision process. But this is not the only issue. Most countries consider that long term studies and an active haemovigilance programme must be fundamental to the implementation of these new technologies.

Close collaboration between the different countries using these technologies is of fundamental importance if we are to achieve a real understanding of the advantages and disadvantages of these technologies and to reach well founded decisions about their introduction.

## ***Session D: Regulatory and implementation status***

### **D1. European national authorities**

#### **D1.1. Federal Agency for Medicines and Health Products, (AFMPS, Belgium)**

The process for the implementation in Belgium of a new system such as PR (PR) technologies requires a CE mark system, laboratory and clinical studies, consideration of budgetary implications and the decision of Minister of Health and Social Affairs (after advice from the Senior Health Council (SHC)).

In Belgium, PR of FFP became mandatory in 1994, with the SD (SD) method. Because of the risk of vCJD, PR of individual plasma U has been preferred since 2002 and became mandatory in 2003. In 2004, MB was approved. In 2010, 87,242 PR FFP U were distributed; 98% of these were MB-FFP, 2% A. SD-FFP is a medicinal product and makes up only a small percentage.

For PC, A-PC was implemented in 2003 in one centre. In 2006 a feasibility study started and in 2008 the SHC recommended the universal implementation of PR for all PC. In June 2009, a Royal Decree made the implementation of PR mandatory for PC by 1 July 2010. However, in 2010, SHC recommended deferral of universal implementation of PR-PC until 1 July 2011.

The minimum content of platelets has to be  $3 \times 10^{11}/U$  and the maximum storage of PC was laid down as 5 days.

In 2009, 68,910 PC were distributed. 43% of these were A-PC and 57% had been microbiologically screened. The price in 2010 of an adult dose ( $4 \times 10^{11}$ ) of leucoreduced PC is 381.19 €, and of PR is 487.32 € (plus 14 € for NAT testing).

## D1.2. French Agency for the Safety of Health Products (AFSSAPS, France)

In France, A-PC was approved by AFSSAPS in October 2003 in Intersol and in April 2010 in SSP+. R (R) PC was CE marked in October 2007 and has been under evaluation by AFSSAPS since June 2008.

The approved characteristics of A-PC in France are:

- residual leucocytes  $< 1 \times 10^6$
- pH at the end of storage 6.4 – 7.4
- residual A:  $\leq 2 \mu\text{M}$
- platelet dose per unit 2.2 -  $5 \times 10^{11}$
- storage: up to 5 days

A decision was taken by the Ministry of Health in July 2007, after consultation with AFSSAPS, that it was considered premature to recommend full implementation of PR. Instead, it was decided to implement PR in selected sites and overseas departments (areas at risk for emerging epidemic agents: Chikungunya, dengue, Chagas). PR for PC was implemented in 4 out of 17 regional establishments: Alsace (100% in November 2006), La Réunion (March 2006), Martinique (July 2007) and, Guadeloupe-Guyane (July 2007).

The haemovigilance data collected in 2009, showed a rate of AE of:

- BC derived A-PC (11,586 U transfused): 1/ 5,793
- BC derived PC in plasma (13,194 U transfused): 1/13,194
- Buffy-coat derived PC in platelet additive solution (PAS, 51,869 U transfused): 1/ 7,398
- Apheresis A-PC (10,181 U transfused): 1/3,393
- Apheresis-PC in plasma (119,865 U transfused): 1/ 2,305
- Apheresis-PC in PAS (56,706 U transfused): 1/ 5,670

Current status of PR technologies for FFP in France:

- SD treatment is approved since 1992;
- MB treatment was initially approved in October 2003 and the current process was approved in September 2007;
- A treatment has been approved in December 2006 and there is a currently on-going freeze dried plasma evaluation by Centre de Transfusion Sanguine des Armées (Army Blood Transfusion Center, CTSA).

SD-FFP transfused in France is produced in Bordeaux in batches of 100 plasmapheresis donations of the same A, B or O group. The final component is prepared in bags of more than 200 mL with a leucocyte count lower than  $1 \times 10^4$ /L. After thawing, the factor VIII levels of the plasma must be  $\geq 0.7$  IU/mL. Storage is for maximally one year after collection, at temperatures  $\leq -25^\circ\text{C}$ .

MB-FFP is only prepared from plasmapheresis FFP and is frozen within 12 h of collection. After thawing, factor VIII must be  $\geq 0.7$  IU/mL. Since a removal step for MB is mandatory, the residual MB must be  $\leq 30$   $\mu\text{g}/\text{L}$ .

The implementation of PR for FFP occurred after a decision taken by the Ministry of Health in January 2007 that PR for FFP should be implemented as soon as possible. This was completed by EFS by September 2008. As a consequence, the situation in June 2010 was:

- MB-FFP: 63%
- SD-FFP: 20%
- A-FFP: 17%

The CTSA decided in November 2008 to implement plasma treated with A.

The haemovigilance data reporting for 2009 produced the following AE:

- MB-FFP (204,814 bags transfused): 1/14,629

- SD-FFP (142,533 bags transfused): 1/ 28,506
- A-FFP (22,933 bags transfused): 0 in 22,933

An allergy expert group convened by AFSSAPS to analyse the 2009 haemovigilance data concluded that the incidence of allergic reactions was significantly higher with MB-FFP compared to other PR FFP.

### D1.3. Paul Ehrlich Institute (PEI, Germany)

The three main pillars of transfusion safety are donor selection, donor testing, and PR technologies.

The current regulatory situation in Germany regarding blood components (BC) preparation is as follows:

- Blood components for transfusion need a marketing authorisation as proprietary medicinal products and every blood establishment can apply for drug licensing. A prerequisite for marketing authorisation is a manufacturing license.
- A prerequisite for the application of pathogen PR BC is the CE mark of the PR system used.

Several blood establishments have obtained marketing authorisation for PR platelets and PR single donor plasma. SD-plasma has a national marketing authorisation.

Before a PR technology is approved in Germany, the following points are carefully considered:

- Preclinical studies  
These must provide convincing proof that the PR agent is non-toxic.
- Viral reduction studies  
Low reduction capacity is not necessarily a reason to refuse an application
- Bacterial reduction studies  
Spiking experiments with suitable strains should follow 2 strategies, employing both high and low counts.

- Studies on blood component quality

Information used to estimate the quality and shelf life of cellular components treated with PR should be based on:

- metabolic studies
- structural studies
- functional parameters

A meticulous description of the manufacturing process is required for an application, since this affects the final component.

- Clinical studies

For a clinical study to be valid, the manufacturing process must be described and laid down in detail, using Good Clinical Practice (GCP) conditions.

It is recommended that homogeneous patient groups should be carefully selected.

Clinical studies must be carefully planned.

Simple designs are preferred.

One sufficiently powered trial is better than a series of small underpowered trials.

Clinical endpoints are favoured, rather than laboratory endpoints.

In the case of non-inferiority trials, clinical and statistical justification is needed for the non-inferiority margin specified.

- Post-marketing measures:

These may give only weak evidence of component safety.

Nevertheless, active post-marketing vigilance may increase knowledge of the safety profile of the PR principle.

#### D1.4. National blood center (Greece)

Greece has 11 million inhabitants, 9 blood centres and 101 blood banks.

The National Authority has currently approved PR for 40% of the FFP, although only 11.7% is PR with MB. The Blood Transfusion Committee

has strongly recommended the implementation of PR technologies for FFP and PC.

In 2008, 152,992 U of platelets were transfused (11.2% collected by apheresis).

86 serious reactions were reported in 2008, almost 80% of which were linked to RBC transfusion. Two bacterial infections and 2 hepatitis B virus infections transmitted by transfusion were reported.

Between 2000 and 2010, a significant reduction in the incidence of allergic, anaphylactic and total reactions was recorded following transfusion of MB-FFP (1/22,400 total adverse reactions), in comparison to FFP (1/1,652).

It is planned that three centres (Athens, Crete and Ionannina) will start an evaluation plan for PR for PC.

#### D1.5. Blood transfusion service (Slovenia).

Slovenia had 2,008,516 inhabitants in 2006. Currently there are 3 blood establishments, which collected 95,390 whole blood donations in 2009, 60% of these being in Ljubljana.

The decision to implement PR for PC was taken in 2007 and the system selected was Intercept. Implementation took place during 2008 and was completed in 2009.

The rationale for implementing PR of PC was:

- Improved safety
- Avoidance of bacterial detection
- Prolonged storage
- Precaution for emerging pathogens
- Consistency with plasma PR
- Avoidance of irradiation

PC prepared by apheresis and by pooling 5 BCs are being used and treated U are stored for up to 7 days. Currently 66% of the BC-PC and 34% of the apheresis PC transfused are treated with PR.

The analysis of the number of PC issued for each haematology patient has shown an increase of 18%, from 3.07 U in 2006 to 3.64 U in 2010. A significant decrease in the outdated rate of the PC has been observed after implementing PR, from 15.7% in the past to 5.93% now.

After transfusing 519 PC to 87 patients, only 1 transfusion reaction was reported. This was generalised urticaria, that vanished after appropriate antihistaminic therapy.

Currently PR PC are approved by the competent authority, as additionally manipulated standard blood components (analogously to irradiated components).

Summary: PR using A/UVA has been successfully implemented. This exhibits acceptable preparation time, volume losses and platelet recovery, leaving residual A levels below the prescribed limits. The post-transfusion 24-h CCI showed acceptable increments and no adverse effects were reported after transfusion of 99.8% PR PC.

#### D1.6. Swissmedic (Switzerland)

Switzerland is moving towards nationwide PR of FFP and platelets

- PR for FFP with MB is registered. Swissmedic has decided that implementation at each blood centre will depend on its resources.
- 15 bacterial reactions have been attributed to platelet transfusion, including 3 fatal reactions caused by *Klebsiella* (2) and *E.coli* (1), with an incidence 1 death/40,000 platelets or 1 death every 1.6 years. In response, Swissmedic has decided that all PC should be PR.

Three blood centres (corresponding to 50% of all platelets produced) have already implemented PR with A. Full implementation in all blood centres is foreseen by the end of 2011.

#### D1.7. United Kingdom blood transfusion services

FFP for children is imported from abroad and pathogen reduced by MB. SD FFP, also sourced from outside the UK, is used for TTP patients.

Implementation of screening of platelets for bacterial contamination has just started in England and this activity will be completed by the end of year 2010.

The conditions for implementing PR technologies for platelets are well defined and some clinical trials using A have been performed

The safety and efficacy of platelets treated with the Intercept and Mirasol technologies have been compared with bacterial screening (Bact Alert and Pall EBDS) using risk modeling. Alternative strategies to reduce the risk with platelet transfusion (arm cleansing, blood diversion, reduction in shelf life) are also under examination.

The incidence of contamination, the clinical efficacy of PR platelets, operational issues, the impact on supply and the prevention of newly emerging infections have all been investigated.

As the technology is expensive and its benefits are not fully proven, PR technologies will not be implemented at this time; clinical efficacy will be monitored in further studies.

## **D2. Non-European Authorities (North America, Japan)**

### **D2.1. Center for blood and tissues evaluation health Canada**

Statements:

- PR technologies are relatively safe.
- The “tolerable” risk/benefit ratio for PR technologies is unclear.
- Data on implementation and experience must be shared.

The Canadian authorities have approved the PR technology for FFP, and have had many pre-submission meetings on the platelet technologies.

Canada has already a very high level of safety as regards the blood components produced, with a very low risk of infection.

Bearing this in mind, we can ask whether another layer of safety is “necessary”, and at what cost?

Active haemovigilance is fundamental in reaching a wise decision.

#### D2.2. Pharmaceutical and Blood Safety Bureau, Ministry of Health, Labour and Welfare (Japan)

In Japan the Ministry of Health, Labour and Welfare is responsible for supervising the Japanese Red Cross which performs the blood collections and for the approval of manufacturing of blood components.

In 2008, the Blood Advisory Committee, a subsidiary body to the Government Council, advised Japanese Red Cross on the use of PR technologies.

In 2008-2009, the Japanese Red Cross proposed introducing PR technologies for platelets, to replace 6 month -quarantine plasma and chose the R technology.

In 2009-10, the Blood Advisory Committee advised Japanese Red Cross to start preparing for clinical trials pending in-depth review of clinical data obtained through clinical trials and Post-marketing surveillance abroad.

#### D2.3. Center for Biologics Evaluation and Research (CBER, FDA, USA)

Statements:

- Benefits should outweigh the risks.
- Current risks should be reduced.
- Bacterial sepsis should be reduced.
- Future (emerging) risks must be reduced.
- The efficacy and transfusion response must be favourable.
- Safety - alloimmunisation and adverse reactions - must be favourable.
- There is not enough data to implement the PR technologies.
- The best target to estimate the benefit of PR should be the bacterial contamination of the component U.

After assessing the advantages and disadvantages of the PR technologies, and comparing with the methodologies that are in place in blood components for safety and efficacy, and taking into account the results of clinical trials and the experience of other countries, the USA authorities reached the following decision: further clinical trials of current technologies are needed to resolve the FDA's concerns over decreased efficacy and increased AE seen with PR platelets.

### ***Summary and conclusions of session D***

The two countries of North America agreed that there is a need for more clinical trials. Active haemovigilance for the safety and efficacy of PR platelets could demonstrate the added value of PR technologies.

Japan, on the other hand, emphasised the high level of risk of platelet transfusion and decided for full implementation of PR technologies.

In Europe there is no common position among the various countries. Some consider these technologies to be safer than bacterial screening, whereas others believe that they have some risks and do not recommend their use unless and until the results of further studies show these risks to be appreciably less important than the advantages, taking in account the health of the patients.

The implementation of these technologies should be considered country by country, in relation to the risks of transfusion.

### ***Session E: round table discussion - conclusions***

The session chair introduced the discussion noting that the goal of the symposium is to develop input to CD-P-TS and GTS (*ad hoc* working group on the “Guide to the preparation, use and quality assurance of blood components”) that might lead to revision of the CoE's position on PR as stated in Recommendation Rec (2003)<sup>11</sup> of the Committee of Ministers to member states on the introduction of pathogen inactivation procedures for blood components as well as a corresponding revision of the “Guide to the preparation, use and quality assurance of blood components”.

The session chair first asked the panellists to comment on the priorities for continued work after the meeting.

A panel member responded that themes had emerged regarding uncertainties in the clinical trials, and if more trials are to be done, there is a need to focus on their design. He asked, “What is the gold standard against which PR products should be assessed?” Ethics require that endpoints should be informative, but questions have been raised about the meaning of CCI and bleeding measures as endpoints. Significant differences in selected margins of non-inferiority, which have ranged from 12-30%, are also an issue. Additionally, if decisions are based on safety as well as efficacy of platelets, don't we need to design trials to better assess safety? In summary, he suggested that a short paper could be developed around the design of clinical studies. This would result in less debate about the meaning of trial outcomes.

A second panel member put the central question as to whether we are in a position to make a broad recommendation in favour of PR. On the one hand, there is concern that the field will die out if we wait another 10 years to implement these technologies. Alternatively, we may need more information. He asked for a show of hands of how many of the participants would favour “quick” movement to a goal of 100% implementation of PR, e.g. within 2-3 years, without gathering additional data. A majority of those present appeared to favour the converse, namely more research.

Another panel member commented that the level of development of blood systems varied greatly across Europe, precluding a blanket recommendation on a shift to PR. In some systems, the change needed now is from a “mom and pop” service type model of blood collection to a model of “manufactured products.”

A fourth panel member commented that roll-out of PR needs to be linked to a systematic program of controlled post-marketing studies as well as enhanced haemovigilance.

A participant countered that in many situations in Europe, introduction of PR could increase blood safety. Blood organisations

need to consider the current safety of their products, their patient populations and the local risks of emerging infections. Cost effectiveness of PR might vary from setting to setting.

A fifth panel member remarked that regulatory agencies had reached different decisions on approval of PR technologies, despite having reviewed the same data, and that it is unclear what processes each used to address the issues. She suggested that the CD-P-TS could recommend a set of criteria for decision making about implementation of PR.

The first panel member returned to the question of post market surveillance and concurred that highly effective systems are needed if we are really to understand the safety of PR treated products. However, he pointed out that if we lack the same robust data on the current products, we may merely discover problems with the current products that are not actually attributable to PR. He concluded that we need equally effective safety surveillance for the current products.

A participant questioned the meaning of “effective implementation.” She informed the meeting that there are 42 countries that do not even screen all blood donations for HIV and HCV and that 47% of blood in the developing world is not tested in a quality assured manner. Therefore, prerequisites should be defined for implementation of PR; for example, whether the system is hospital based, whether staffing is adequate and also trained in quality systems. Consideration should be given to the strategy for “roll-out” even in systems that are ready to implement.

The session chair agreed that the important thing is to move forward rationally, more so than the speed of change. She reiterated the need for full systems of surveillance to establish the risks and benefits of component use. For example, we have good safety information on PR treated plasma, but lack data on the efficiency of the clinical use of plasma. Also, we have reasonable data on the value of platelet transfusions, but give these products to only 10-15% of transfusion recipients, implying that full benefit of PR necessitates a technology to treat red cell products. She noted that determining the medical value

of PR in the developed world would benefit decision making in the developing world too.

Another participant asked how we can explain the additional benefits of PR given the unknowns related to their long term use. He noted that the present margins of concern (i.e. safety risks) are very low and asked what the public messages should be.

A third participant responded that this issue comes down to a choice between pursuit of maximum safety despite costs or basing the decision to implement on an overall cost-effectiveness consideration as a “more rational model.” He noted the advice of the Canadian Consensus Conference to implement PR in parts while striving for maximum component safety. Conversely, if one looks at the net risk to patients, the relative risk from platelets is low compared with that from red cells, so attention should be on red cell products.

The second panel member remarked that the question whether to use a PR component is framed differently for the individual patient for a blood operator or for a government decision maker.

Another participant observed that people are neither solely rational nor emotional, but both at once. He stated that the first priority is to go forward with PR (i.e., if there is no use, there is nothing to study further.) He pointed out that the recipients of the 40% of untested blood in developing countries would in all probability prefer a PR treated component. If there are too many barriers, this will prevent industry development. The key questions are the relevance of CCI and the bleeding scales that are used in clinical trials. Nevertheless, Switzerland went to PR after two cases of bacterial transmission from a single split apheresis platelet concentrate. France implemented PR for platelets in La Réunion at the time when 60% of the population had infections with Chikungunya virus, because the political imperative for safe blood was great.

A participant commented that, like NAT, PR technologies definitely can improve component safety, but that the efficacy of the PR products could be improved. She agreed with the earlier remarks that

specifications are needed for safety and efficacy evaluations of the products, but that this should be followed quickly with a new CoE recommendation (i.e. more supportive of PR). Mechanisms should be in place in MS for rapid implementation of PR if epidemiological data indicate a need to improve component safety.

Another panel member agreed with the previous speakers on the need to go forward since the systems are already working in many countries. She reminded the group of the lesson from AIDS, namely that the same kind of discussions (which delayed implementation) occurred regarding pasteurisation of Factor VIII.

Also a very recent notification to the PEI of a case of HIV transmission from transfusion despite negative serology and NAT test results on the donor was mentioned.

The session chair summarised the recommendations heard so far as follows:

- A proposal to develop a document on study design focusing on clinical endpoints in trials of PR products;
- A proposal for a generic decisional instrument that could be used by National Regulatory Authorities and Blood Operators;
- The prerequisites for implementation of PR in a given blood system should be defined.

There was a general feeling that we need to move forward, but possibly at different speeds in different settings

A participant asked whether there could be agreement on a model to take emerging infectious diseases (EID) into consideration in assessing the cost-effectiveness of PR technologies. He noted that cost-effectiveness models already exist, but suggested that a range could be placed around the risk of an EID in these models.

The session chair responded that this question could be brought to the CD-P-TS for a discussion.

A participant re-emphasised the need to standardise the approach to post-market surveillance. For instance, there is a need to establish surveillance at sentinel sites that have not yet implemented PR to obtain baseline data. Standards are also needed how to calculate adverse event rates, i.e., per patient or per transfusion episode.

A participant commented that per patient reporting is best, as is used in the Scandinavian database on transfusion outcomes (ScanDat).

A participant remarked on the need for an overview, or integration of the results of the many, often small, clinical studies of PR products. He suggested the possibility of a meta-analysis and also the possibility to integrate the design of the currently planned prospective trials.

A participant informed the group that a meta-analysis of PR platelets has been submitted for publication. She further noted that “Consort Guidelines” exist for reporting the power of safety analyses in clinical trials.

The session chair questioned whether the CD-P-TS might itself have the capacity for carrying out a meta-analysis. Based on the foregoing discussion, she added the following points to the list of recommendations heard at the Symposium:

- Standards for haemovigilance and post-marketing assessment of PR products should be developed;
- A meta-analysis of previous clinical trials of PR products should be performed.

In closing the meeting, it was stated that the CD-P-TS would take up issues as appropriate and would interact in the normal fashion with the GTS group and the EC. The importance of cooperation that would avoid duplication of efforts was emphasised and appreciation was expressed for any suggestions that could enhance cooperation and save resources.

# APPENDIX

## Scientific Committee

CAZENAVE Jean-Pierre  
Etablissement Français du Sang  
10 Rue Spielman  
FR - 67085 Strasbourg Cedex - France

DE ANGELIS Vincenzo  
Udine University Hospital  
P. le S. Maria della Misericordia, 15  
IT - 33100 Udine - Italy

DE WIT Jeroen  
Sanquin Blood Supply Foundation  
Plesmanlaan 125  
PO Box 9892  
NL - 1006 AN Amsterdam - The Netherlands

EPSTEIN Jay  
Office of Blood Research and Review  
HFM 300, 1401 Rockville Pike  
US - 20852-1448 - Rockville - United States of America

FLANAGAN Peter  
New Zealand Blood Service  
71 Great South Road  
Private Bag  
NZ – 92071 Auckland – New Zealand

FLESLAND Oystein  
Asker and Baerum Hospital  
PO Box 83  
NO – 1309 Rud - Norway

GANZ Peter  
Health Canada  
Building n° 6, 3<sup>rd</sup> floor, Room 3364  
AL o6o3C3, Tunney's Pasture  
CDN - KIA OL2 Ottawa Ontario - Canada

HEIDEN Margarethe  
Paul Ehrlich Institut  
Paul Ehrlich Strasse 51-59  
DE – 63225 Langen - Germany

LOZANO Miguel  
Hospital Clinic Provincial  
Villarroel 170  
ES – o8o36 Barcelona - Spain

MACLENNAN Sheila  
NHS Blood and Transplant  
Leeds Centre  
Bridle Path  
GB - LS15 7TW Leeds – United Kingdom

NASCIMENTO Fatima  
Service Immuno Hemoterapia  
Parque da Saude de Lisboa  
Av. Do Brasil 53, Pav 17  
PT – Lisboa - Portugal

NORDA Rut  
Klinisk immunologi och transfusionsmedicin  
Uppsala University Hospital  
Akademiska Sjukhuset  
SE – 751 85 Uppsala - Sweden

POLITIS Constantina  
Ministry of Health and Social Solidarity  
3 Garnofsky Str.  
GR – 11742 Athens - Greece

*EDQM Staff members*

BEHR-GROSS Marie-Emmanuelle  
BUCHHEIT Karl-Heinz  
SPIESER Jean-Marc  
KEITEL Susanne



*For further information concerning the work of the Council of Europe / EDQM in the area of blood transfusion please contact:*

Dr Marie-Emmanuelle Behr-Gross  
Department of Biological Standardisation,  
OMCL Network & HealthCare  
EDQM, Council of Europe  
7 allée Kastner  
CS 30026  
F-67081 STRASBOURG  
FRANCE  
Tel: +33 (0)3 90 21 41 08  
Fax: +33 (0)3 88 41 27 71  
E-mail: [marie-emmanuelle.behr-gross@edqm.eu](mailto:marie-emmanuelle.behr-gross@edqm.eu)

**Director of the Publication**  
Dr S. Keitel

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**European Directorate for  
the Quality of Medicines &  
HealthCare (EDQM)  
Council of Europe**

7 allée Kastner  
CS 30026  
F-67081 STRASBOURG  
FRANCE  
Tel: +33 (0)3 88 41 30 30  
Fax: +33 (0)3 88 41 27 71  
E-mail: [info@edqm.eu](mailto:info@edqm.eu)  
Internet: <http://www.edqm.eu>

[www.edqm.eu](http://www.edqm.eu)  
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