Pathogen inactivation of labile blood products

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Introduction

Selection of donors and screening of donated blood and plasma have greatly diminished the risk of blood products to transmit viral or other infectious agents. The introduction in some countries of prestorage leucocyte depletion and the hepatitis C virus nucleic acid amplification test have further improved the safety of the blood supply. However, all these methods have their limits. Moreover, several newly emerging infectious agents with uncertain pathogenicity and mode of transmission have been described. Thus, there is a need for methods aimed at the inactivation of pathogens in labile cellular blood products. In fact, such procedures are being developed and some of them are in advanced preclinical or already in clinical stages. A working group of the SP-HM Committee on Blood Transfusion and Immunohaematology of the Council of Europe has performed a Co-ordinated Research Study on Pathogen Inactivation of Labile Blood Products. The present review summarizes some of the findings included in this study, which will be published in extenso in November 2000.

Threat to the blood supply

Transmission of viral diseases by labile blood products cannot totally be excluded, since tests used for donation screening are insensitive during the "window period", i.e. the time between infection and seroconversion of a donor. Even direct tests for virus constituent parts, such as surface antigens and nucleic acids, have a sensitivity threshold that allows some contaminated components to escape detection. The aggregate risk of acquiring HBV, HCV or HIV from a donor passing all current serological tests is one per 34,000 donations. If one assumes that an average transfusion episode results in exposure of a given patient to blood products from 5 donors, the risk for a patient of receiving a virally contaminated blood product may be as high as one in 6,800. Evidently, in countries with less rigorous testing requirements, particularly in developing countries, this risk is substantially higher.

An equally important threat is bacterial contamination of cellular blood products. In many countries, bacterial sepsis today is probably the most frequent infectious complication of blood and especially platelet transfusions. Prospective studies showed that the frequency of bacterial contamination ranged between one in 500 to one in 1,700 for random-donor platelet concentrates, and one in 19,519 for single-donor platelets. In bone marrow recipients the frequency of infection was one per 350 pooled platelet transfusions, and symptomatic bacteriæmia developed in 14 of 161 patients. Bacterial contamination of red cell concentrates poses a significant risk as well, although it occurs less frequently than that of platelet concentrates.

Various parasitic diseases may also be transmitted by labile cellular blood products. Of greatest concern are post-transfusion malaria and particularly Chagas disease, but others are also known to contribute to the transfusion risk in special circumstances.

Labile blood products

The composition, as well as the criteria for blood donor selection, donation testing, manufacturing and quality control are defined in the Guide to the Preparation, Use
Obvious candidates for pathogen inactivation are red blood cell concentrates (RBC), platelet concentrates (PC), and fresh frozen plasma (FFP). Actual studies are focused on these products. Since the addition of any compounds to labile blood products is likely to affect their functional properties, an assessment of their quality before and after pathogen inactivation is crucial, and has to be performed by a battery of in vitro tests. In addition, their safety and efficacy have to be studied in vivo in animals and humans.

Table I: microbiological targets

<table>
<thead>
<tr>
<th>Viruses</th>
<th>envelope</th>
<th>non-envelope</th>
</tr>
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<tbody>
<tr>
<td><strong>envelope</strong></td>
<td>HIV-1, HIV-2, HTLV-I, HTLV-II</td>
<td>HAV, parvo B19, TTV</td>
</tr>
<tr>
<td>CMV, HHV-6, HHV-8, EBV</td>
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<tr>
<td>HBV, HGV</td>
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<table>
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<tr>
<th>Bacteria</th>
<th>Gram-positive</th>
<th>Gram-negative</th>
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</thead>
<tbody>
<tr>
<td><strong>Gram-positive</strong></td>
<td>Staphylococcus epidermidis</td>
<td>Yersinia enterocolitica</td>
</tr>
<tr>
<td>Staphylococcus aureus</td>
<td></td>
<td>Pseudomonas fluorescens</td>
</tr>
<tr>
<td>Coagulase negative staphylococi</td>
<td></td>
<td>Salmonella enteritidis</td>
</tr>
<tr>
<td>Streptococcus viridans</td>
<td></td>
<td>Citrobacter freundii</td>
</tr>
<tr>
<td>Enterococcal species</td>
<td></td>
<td>Serratia marcescens</td>
</tr>
<tr>
<td>Bacillus cereus</td>
<td></td>
<td>Enterobacter cloacae</td>
</tr>
<tr>
<td>Coliform bacteria</td>
<td></td>
<td>Flavobacterium species</td>
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<table>
<thead>
<tr>
<th>Protozoa</th>
<th>Plasmodium vivax</th>
<th>Trypanosoma cruzi</th>
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<tbody>
<tr>
<td>Plasmodium falciparum</td>
<td>Babesia microti</td>
<td></td>
</tr>
<tr>
<td>Plasmodium malariae</td>
<td>Toxoplasma gondii</td>
<td></td>
</tr>
<tr>
<td>Plasmodium ovale</td>
<td>Leishmania donovani</td>
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<table>
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<tr>
<th>Others</th>
<th>Treponema pallidum</th>
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</table>

<table>
<thead>
<tr>
<th>Prions</th>
<th>Treponema pallidum</th>
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Microbiological pathogen targets for inactivation include all enveloped and non-enveloped viruses, bacteria and parasites known to be transmitted by blood products. In addition, newly emerging infectious agents need consideration. An overview of the most prominent agents is given in Table I. It is important to realize that viruses such as HIV, can be cell-free in plasma, cell-associated in/on leucocytes, and in latent pro-viral form integrated into the genomic nucleic acids of leucocytes. Evidently, inactivation processes should be effective against all these forms. In addition to HIV and hepatitis B and C viruses, the human T-cell leukaemia/lymphoma viruses, parvovirus B19, herpesviridae such as cytomegalovirus, Epstein-Barr virus and others, as well as hepatitis A virus need consideration. More recently, hepatitis G virus and another transfusion-transmitted virus (TTV) have emerged as potential threats4.

A wide range of micro-organisms have been cultured from contaminated platelet and red cell concentrates (Table I). These bacterial contaminants multiply in blood products during storage at room temperature or in the cold, and may cause life-threatening infections and septic shock in the recipients. The most prominent agents in platelet concentrates include Staphylococcus epidermidis and coagulase-negative staphylococci, but also Salmonella enteritidis, Bacillus cereus and Serratia marcescens. The pattern of bacterial species observed in red blood cells includes unusual gram-negative micro-organisms with the capacity to proliferate at low temperatures (psychrophilic bacteria) during storage. Typically, they include Yersinia enterocolitica, Pseudomonas fluorescens, Citrobacter freundii and Serratia marcescens5. Parasitic diseases that can be transmitted with labile blood products include malaria, due to the plasmodium genus, and, most importantly, Chagas' disease caused by Trypanosoma cruzi. Other, rare parasitic agents that have been described in the literature are Babesia microti and Toxoplasma gondii. Finally, prions, i.e. the agents of Creutzfeldt-Jakob Disease (CJD) and the variant of CJD (vCJD) have to be mentioned in this context, even if there is no evidence for transmission of spongiforme encephalopathies by blood products in man.

Contaminating leucocytes as pathogens

Leucocytes contaminating labile blood products are not considered as infectious pathogens per se, but they are targets for inactivation for reasons summarized in Table II. Leucocytes may harbour and transmit cell-bound infectious agents, notably viruses such as CMV, HIV and HTLV-I, and cause infectious disease. Furthermore, by secretion of pro-inflammatory cytokines, cells of the
monocyte/macrophage and granulocyte lineages often induce febrile non-haemolytic transfusion reactions (FNHTR). In immunocompromised patients, viable donor T lymphocytes are known to cause fatal transfusion-associated Graft-versus-Host-Disease. Moreover, by alloimmunization to donor HLA antigens, leucocytes often induce refractoriness to platelet transfusions in thrombocytopenic recipients, thereby aggravating their bleeding tendency. In addition, many studies have shown that allogeneic blood transfusion could induce immunomodulation, in particular immunosuppression, predisposing recipients to postoperative infection and possibly to a higher rate of tumor recurrence. Finally, in recent years, animal experiments have suggested that leucocytes, particularly B-lymphocytes, might be involved in promoting transmissible spongiform encephalopathies, such as vCJD.

**Methods in clinical use for pathogen inactivation**

This paragraph reviews the procedures which are already in use for inactivation or elimination of pathogens in labile blood products. A synopsis is presented in Table III.

### Solvent/detergent (S/D) treatment of FFP

The lipid envelope of transfusion-relevant viruses is destroyed by the combination of an organic solvent and a non-ionized detergent [tri (n-butyl) phosphate and Triton X-100], whereas non-enveloped viruses are not affected. A series of studies showed that the content and the biological function of most plasma proteins were well preserved, but some sensitive proteins, particularly protein S, $\alpha_2$-antiplasmin and the high-molecular multimers of vonWillebrand factor were found to be damaged to some degree. Since 1991, S/D treated FFP prepared from pooled plasma (up to 2000 donations) has been clinically used in a number of countries and has a good efficacy and safety record. However, clinicians sometimes consider pooling of plasma donations a potential disadvantage, since contamination by the non-enveloped human Parvovirus B19 may pose problems. In fact, Parvovirus B19 seroconversions have recently been observed in a clinical trial of S/D FFP.

The S/D technology cannot be applied to cellular blood products, since the reagents would disintegrate the lipid bilayer of the cell membrane and destroy the cells.

### Methylene blue treatment of FFP

The virus inactivating properties of methylene blue (MB) in combination with visible light have been known for a long time. MB is a positively charged hydrophilic dye with a high redox potential.

Investigators at the German Red Cross Blood Transfusion Service of Lower Saxony have developed a procedure using MB for virus inactivation of FFP, which is
based on the addition of 1 μmole MB to single-donor units of FFP, and illumination with visible light for one hour. The treatment inactivates enveloped model viruses for HBV, HCV and HIV. MB also affects the function of several labile plasma proteins including coagulation factor VIII. Since 1992, this blood product was successfully used on a large scale in clinical medicine: by the end of 1998 more than 1 million units of MB-treated FFP were transfused in Germany and more than 300,000 Switzerland. However, the Paul Erlich Institute has recently expressed concern about approval of the method. In order to improve the method, a combination with leucocyte filtration was proposed, (i) to remove the potentially genotoxic methylene blue and its metabolites formed by illumination, and (ii) to eliminate residual leucocytes resisting freezing and thawing.

Leucocyte depletion and ultraviolet B irradiation

Leucocyte depletion with appropriate filters reduces the leucocyte content in PC and RBC to less than 1x10^6 per unit, as specified in the Council of Europe Guide to the preparation, use and quality assurance of blood components, and in national guidelines. Leucocyte depletion may be performed at the bed-side, i.e. immediately before the transfusion. This method allows specific targeting of leucodepleted products to patients who need them. However, quality assurance issues, like the filter performance with leucocytes desintegrated during RBC storage, are difficult to deal with. The alternative preferred for quality considerations is pre-storage filtration of RBC and PC, i.e. filtration within one day after collection, at the blood component processing site by personnel of the blood transfusion service. Recently, animal experiments have suggested that leucocytes, particularly B-lymphocytes, might be involved in promoting transmissible spongiform encephalopathies, such as vCJD. As a consequence, health authorities in some European countries have introduced universal leucodepletion of all blood products, in order to minimize a potential risk for the public. Appropriate prestORAGE leucocyte depletion by filtration was shown to prevent transfusion-associated CMV-infection and to greatly reduce FNHTR, but studies demonstrating that this technology also excludes cell-bound HIV and HTLV-I infectivity are still lacking. Furthermore, lymphocyte reduction by prestorage leucocyte depletion apparently does not eliminate the risk of transfusion-associated GVHD. Exposure of leucocytes to UV light was shown to damage HLA class II related surface structures on lymphocytes and monocytes, and to abolish proliferative responses to mitogens and alloantigens and viability. Clinical trials including patients after bone marrow transplantation or patients with haematological malignancies showed that transfusion of UVB irradiated platelets stopped haemorrhage and reduced the rate of HLA antibody development. A large comprehensive multi-institutional group has reported a comparison of UVB irradiated and leucodepleted platelets in 530 adult patients with acute myeloid leukaemia undergoing chemotherapy for remission induction. Patients were randomized to receive either unmodified pooled random donor PC (control arm), leucocyte depleted pooled random donor PC, UVB irradiated pooled random donor PC, or leucocyte depleted single donor apheresis PC. The overall incidence of HLA antibodies was 45% in the control group and 17 to 21% in the three other study groups (p<0.001). There was no significant difference between the study groups. The overall incidence of alloimmune platelet refractoriness was 13% in the control group, as compared with 3 to 5% in the three other study groups (p=0.03). Thus, UVB irradiation as well as leucocyte depletion by filtration significantly reduced the development of HLA antibodies and prevented platelet refractoriness during chemotherapy for acute myeloid leukaemia. However, both procedures do not totally eliminate the risks associated with leucocytes in labile blood products.

Procedures under development

Procedures for pathogen inactivation in development can roughly be subdivided in photoactivation methods and in more recently developed new technologies. Photoinactivation methods are powerful tools for pathogen inactivation, based on the use of photosensitizers and defined light sources. Photosensitizers are organic dyes with light absorption properties. Upon illumination they become excited to a higher energy level and can react with a substrate or with other molecules. The mechanisms by which microbial pathogens are inactivated are described in the literature. Briefly, some of these dyes mediate photodynamic reactions: they primarily generate active oxygen species, which may alter various cell-associated structures and disrupt viral envelopes. Other reagents induce photochemical reactions: they are able to penetrate into the cells and to irreversibly modify nucleic acids of viruses, bacteria, protozoa and leucocytes in the absence of oxygen. However, one given compound may mediate both types of reactions, and the mechanisms, by which the reagents interact with biological structures are not fully understood. New technologies also utilize compounds that
react with cellular or viral nucleic acids and irreversibly modify them. Some of the newly developed compounds do not require activation by external energy sources. Table IV summarizes the most important compounds, that are currently under investigation.

### Porphyrins

Porphyrin-like compounds have been used in oncology for treatment of malignancies. Most porphyrins are amphiphilic and localize in membranes, suggesting a preference for inactivating lipid-enveloped rather than non-enveloped viruses. Haematoporphyrin derivative and dihaematoporphyrin have proven to be efficient in the inactivation of various enveloped viruses in tissue culture and whole blood, whereas non-enveloped viruses were not affected, again suggesting that the major target for the effect is the viral envelope. Benzoporphyrin is a potent photosensitizer with a strong absorption peak at 690 nm and a high affinity for lipoproteins. It was shown to inactivate VSV (Vesicular Stomatitis Virus; a model virus for enveloped viruses) and free as well as cell-associated HIV with limited damage to erythrocytes. However, experimental studies on these compounds have come to a halt, since other photosensitizers appeared to be more promising.

### Phenothiazines

The virus inactivating properties of methylene blue (MB) in combination with visible light have been known for a long time. This positively charged hydrophilic dye with a high redox potential absorbs UV and visible light and has an absorption maximum between 661 and 667 nm. Upon excitation by light, MB produces singlet molecular oxygen (type II mechanism), which may act as the principal mediator of virucidal effects. However, excited MB can also react directly with the substrate to yield highly reactive free radicals (type I reaction). MB binds to proteins and lipoproteins present on the membrane of lipid-enveloped viruses, as well as to nucleic acids.

Due to its hydrophilic nature, the MB does not readily penetrate into cells, and can thus not be used for photoinactivation of intracellular pathogens. More recently, another phenothiazine, 1,9-dimethylmethylene blue (DMMB) was shown to be a promising candidate for virus inactivation of RBC: this more hydrophobic compound penetrates into cells, and has an approximately 10-fold higher affinity for nucleic acids than MB. Phototreatment using this compound and white light with a fluence rate of 5 mW per cm² inactivates a variety of intracellular and extracellular model viruses and *Trypanosoma cruzi*. The predominant mechanism of action is singlet oxygen formation (type II mechanism). Unlike MB, DMMB has little damaging effect on the integrity of RBC. Evidently, more experimental data is needed.

German investigators have started to explore properties of thionine for photodecontamination of PC. Thionine can be excited by light at 590 nm. Its virus inactivation efficiency was tested for enveloped model viruses including HIV-1, BVDV (Bovine Viral Diarrhea Virus), VSV, SFV (Semliki Forest Virus), and for SV-40 (Simian Virus) as an non-enveloped virus.

Under the conditions used a virus reduction of 4-6 log
steps was noticed. The quality of the platelets was well preserved after 5 days of storage. Thionine thus appears to be useful, and will be further investigated.

**Phthalocyanines**

Photodynamic properties of phthalocyanines have been systematically investigated. Aluminum phthalocyanines (AlPc) and its sulfonated derivatives AlPcS$_2$ and AlPcS$_4$, very effectively kill various model viruses added to RBC or whole blood. Non-enveloped viruses are not affected, suggesting that the major target is the virus envelope. However, haemolysis, although modest under appropriate conditions, was considered to be a constraint. In a new series of phthalocyanines introduced in 1994, the central aluminum atom was replaced by a silicon atom. The virus killing activity of these compounds exceeded that of AlPcS$_4$, but the RBC damage inflicted by them was also more pronounced. An interesting phthalocyanine was the silicon containing Pc$_4$, a hydrophobic compound, which had to be emulsified for virus inactivation of RBC. It effectively inactivated enveloped model viruses. Pc$_4$ also killed peripheral blood mononuclear cells and neutrophils by induction of apoptosis. Erythrocyte damage could be reduced by addition of appropriate quenchers of type I photodynamic reactions, but still remained substantial. For this reason, phthalocyanines were not considered for clinical trials.

Merocyanine 540 (MC 540) is a photosensitizer that has been tested for purging of leukaemia and lymphoma cells from autologous bone marrow transplants. Experiments with RBC showed that a wide range of viruses were sensitive to photoinactivation with merocyanin 540. However, substantial haemolysis could not be avoided, possibly because the absorption peak at 540 nm overlaps with that of haemoglobin. Treatment of PC with MC 540 and light resulted in activation of the platelets, as demonstrated by the presence of microaggregates, and spontaneous release of serotonin. For these reasons, studies with MC 540 were not continued.

**Psoralens**

Psoralens are extensively being studied for photodecontamination of PC. Interest in psoralens was based on prior human use for the treatment of chronic psoriasis and later for cutaneous T cell lymphoma, where these compounds were found to be safe and efficacious. Oral psoralen followed by total body exposure to long wave ultraviolet light A (UVA) irradiation was introduced as a treatment for severe psoriasis in the 1970s and is commonly known as PUVA. The first psoralen investigated for inactivation of infectious pathogens in PC was 8-MOP. The principal mechanism of action of all psoralens is intercalation with pyrimidine base residues of nucleic acids. Upon illumination this step is followed by the formation of covalent mono- and di-adducts between psoralen and nucleic acid strands and cross-linking, by which replication of nucleic acids is prevented. 8-MOP efficiently inactivated cell-free and cell-associated viruses, as well as gram-positive and gram-negative bacteria. 8-MOP is no longer explored today: its most evident disadvantage is a relatively low affinity for nucleic acids and the competitive binding to plasma proteins affecting the virus inactivation capacity.

Aminomethyltrimethylpsoralen (AMT) was more efficient than 8-MOP; but in order to maintain appropriate platelet functions, the oxygen tension had to be reduced during treatment, or quenchers of reactive oxygen species had to be added. AMT is not further developed because of its mutagenicity. Among a large number of other psoralens, that were synthesized and screened for their ability to inactivate viruses and bacteria, for preservation of in vitro platelet function after photochemical treatment, and for absence of toxicity and mutagenicity, the novel psoralen S-59 was identified. Experiments with PC containing up to 5x10^11 platelets in 300 mL of 35% plasma and 65% platelet additive solution (PASIII) demonstrated that this photochemical treatment inactivated cell-free and cell-associated HIV and other enveloped viruses, including model viruses for hepatitis B and C. In addition, gram-positive and gram-negative micro-organisms were killed, and in vitro platelet function was adequately maintained for 7 days after treatment. These experiments were done at ambient room temperature without need for oxygen reduction or quenchers. It was concluded from these studies, that due to the high nucleic acid-binding efficiency of S-59, infectious pathogens are rapidly inactivated in PCs at low doses of UVA light, whereas in vitro and in vivo platelet functions are not significantly affected. The S-59 procedure is also intended for pathogen inactivation of FFP.

S-59 and UVA light treatment also inactivates leucocytes, including T lymphocytes in PC and FFP. Their proliferative capacity is abrogated and cytokine synthesis is completely inhibited. Experimental findings in a murine bone marrow transplant model suggest that the procedure prevents graft-versus-host disease. Furthermore, prestorage treatment of PC prevents accumulation of cytokines and has thus the potential to reduce the risk of febrile non-haemolytic transfusion reactions. Hopefully, the clinical trials will show to what extent these and other leucocyte-mediated transfusion-associated risks will be influenced by S-59 and UVA treatment.
Riboflavin

This interesting new technology using Riboflavin, i.e. vitamin B2, is still in an early phase of development. The principle, i.e. cross-linking of nucleic acids of infectious pathogens by riboflavin and UV light is comparable to that of the psoralens. Riboflavin also binds to albumin and other plasma proteins.

The procedure appears to inactivate enveloped viruses, but has the potential to inactivate leucocytes as well. The damage inflicted to platelets is still an open issue. Functions of plasma proteins (FFP) are preserved in presence of ascorbate. The toxicology of riboflavin and its photo products has been extensively studied and they are generally regarded as nontoxic.

Inactine

Inactine compounds, or ethylene imines, are electrophilic reagents that selectively bind to and irreversibly modify nucleic acids. Very few data have been published so far.

The procedure is applicable to RBC and FFP. There is evidence that it efficiently inactivates both enveloped and non-enveloped viruses (>5 log_10 reduction). According to the report, Inactine treatment does not affect the function of the red blood cells in vitro and in vivo. Survival rates of Inactine treated and untreated red blood cells were similar in a baboon model.

Important open issues are the toxicological properties and residual levels of these compounds and their metabolites in blood products.

FRALE (S-303)

The novel class of components termed Frangible Anchor Linked Effectors (FRALE) irreversibly crosslinks nucleic acids in a manner similar to that of S-59, but without requiring light for activation. With its anchor moiety the complex attaches to nucleic acids, and its effector moiety crosslinks nucleic acids. The two components are joined by a linker moiety. FRALE penetrates red blood cells and decomposes after pathogen inactivation.

There is little published information. In vitro tests provided evidence that FRALE efficiently inactivated cell-free and cell-associated HIV, other enveloped viruses including model viruses for hepatitis B and C, as well as gram-positive and gram-negative bacteria. Moreover, the integrity of the red blood cells appeared to be preserved. Animal models showed that recovery of FRALE treated red blood cell was comparable to that of untreated cells.

Clinical trials and comments

A number of pathogen inactivating procedures are currently (March 2000) in clinical trials. Studies with psoralen S-59 treated PC have been started several years ago.

Today, phase I and II trials are completed or in advanced stages. Viability, as well as recovery of S-59 treated platelets were found to be adequate.

This pathogen inactivation procedure has moved into phase III trials, which take place in the U.S. as well as in several European countries, and involve large numbers of patients with acquired thrombocytopenia and clinical bleeding.

In addition, phase I trials have been performed with S-59 treated FFP.

Subsequently, its tolerability, safety and efficacy are being assessed in patients with congenital and acquired deficiencies of coagulation factors and in patients with thrombotic thrombocytopenic purpura.

Pathogen inactivation of RBC with FRALES (S-303) has also been studied in phase I trials, where post-transfusion recovery, half-life, side effects and the potential to induce neoantigens have been analyzed.

Currently, phase II and III studies are planned in the U.S. and in European countries in patients who need chronic RBC support.

Furthermore, a program with Inactine treated RBC has recently entered phase I trials.

So far, these studies have demonstrated that the procedures are safe, and that the pharmacodynamic as well as pharmacokinetic properties of the pathogen inactivated labile blood products are within or close to the normal range. However, as long as the clinical trials are not completed, details on the performance of the procedures are not available.

Thus, at present, it is still too early to assess their value. Certainly, the manufacturers need to demonstrate beyond any doubt that the procedures are safe, i.e. that the compounds and their metabolites have no toxicity for patients, and furthermore, that the addition of these compound does not significantly alter properties of the labile blood products.

But in addition to that, we need to know whether the introduction of these methods brings some additional benefit: thus, the cost-benefit ratio will be an important issue to be addressed before the introduction of such pathogen inactivation methods in the blood transfusion service can be recommended.

We certainly hope that they bring us one step closer to the theoretical "zero risk" of blood and blood products.
References


