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**ISBT 2011**

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International Society of Blood Transfusion, Europe

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Lisbon, Portugal

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# Table of Contents

## ORAL PRESENTATION

Time	Title & Authors	Page
<b>Tuesday, June 21st, 09.00 - 10.30, S15 - Pathogen inactivation</b>		
09.45 – 10.00	<b>Validation and Implementation of the INTERCEPT Blood System for Platelets for Pathogen Inactivation of Apheresis and Buffy-Coat Products at One of the Biggest Regional Blood-Centers of Switzerland</b> D Goslings, P Lodemann, G Yavuzcan et al.	5

## POSTER PRESENTATIONS

**On Display During Exhibition Hours:** Poster Hall, Pavilion 3, Blood products - 3.4 Pathogen inactivation

**Poster Walk:** Monday, June 20th, 18.15 - 19.15

Poster #	Title & Authors	Page
<b>INTERCEPT Blood System for PLATELETS</b>		
P-193	<b>First Validation and Implementation of the Orbisac System in a Swiss Blood Center within the Scope of Introducing the Pathogen Inactivation System INTERCEPT</b> D Goslings, A Valek and BM Frey	6
P-252	<b>Pathogen Reduction Treatment Using Amotosalen and Ultraviolet-A Light: Process Control</b> A Castrillo Fernández, C Arcas Otero, MI Rodríguez Calvo	7
P-264	<b>Cumulative Clinical Data of INTERCEPT Blood System™ for Platelets Demonstrate Ability to Replace Gamma Irradiation in Routine Clinical Use for TA-GVHD Prevention</b> L Lin, A Stassinopoulos, L Corash	8
P-269	<b>Two Years Of Experience With The Transfusion Of Pathogen Inactivated Platelets Using The INTERCEPT Blood System™ And 7 day Storage</b> D Domanovic, M Cukjati, A Milojkovic	9
P-271	<b>Hemostatic Efficacy of Platelet Components Treated with Amotosalen-UVA Pathogen Inactivation and Stored for 5 and 7 Days Prior to Transfusion</b> L Corash, C Sherman, W Reed et al.	10 - 11
P-272	<b>Validation of Double Dose Pooled Platelet Products for Pathogen Inactivation with the INTERCEPT Blood System and Storage for up to 7 Days</b> M R Abedi, AC Doverud	12
<b>INTERCEPT Blood System for PLASMA</b>		
P-174	<b>Analysis of Functional Activity of a Large Panel of Coagulation Factors in Fresh and Previously Frozen Plasma Treated with the INTERCEPT Blood System</b> M Yáñez Izquierdo, E Fernandez Fontecha, MA Moya San Pedro et al.	13 - 14
P-254	<b>The Influence of Different Holding Conditions of Coagulation Parameters of Plasma After Pathogen Reduction with the INTERCEPT Treatment</b> B Baumann-Baretti, G Jaster, B Brys et al.	15 - 16
P-268	<b>Photochemical Treatment of Fresh Plasma. Evaluation of Functional Activity of Coagulation Factors and Inhibitors</b> F Dias, M Bini-Antunes, M Pereira et al.	17
<b>INTERCEPT Blood System for RED BLOOD CELLS</b>		
P-262	<b>In Vitro Evaluation of Pathogen Inactivated RBC Using the S-303 Treatment System</b> A Erickson, R Henschler, K Janetzko et al.	18 - 19



## Validation and Implementation of the INTERCEPT Blood System for Platelets for Pathogen Inactivation of Apheresis and Buffy-Coat Products at One of the Biggest Regional Blood-Centers of Switzerland

D Goslings, P Lodemann, G Yavuzcan, A Glauser, A Valek, B M Frey

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**BACKGROUND:** The INTERCEPT™ Blood System for platelets (plts) is CE marked since 2002 and has been approved by Swissmedic in 2009. The Swiss Red Cross has decided to introduce pathogen inactivation with the INTERCEPT System in its centers. The blood transfusion service Zurich is one of the first centers in Switzerland to validate the technology for introducing it into routine production. To ensure highest degree of effectiveness of the pathogen inactivation process the input products have to meet certain guard bands. Also, a platelet product has to fulfill additional pre-conditions to meet Swiss regulations.

**AIMS:** The objective of this validation program was to study existing production steps and potentially required optimizations for platelet concentrates (PC) from Buffy-Coats (BC) or apheresis in order to meet both sets of requirements. It included also the thorough analysis of the end-products in terms of volume, platelet dose and amount of contaminating cells.

**METHODS:** Buffy Coats were produced from whole blood (450mL) using MacoPress Classic Separators. To get 1 PCBC, 5 ABO/Rh-matched BCs were pooled with SSP+ as additive solution (PAS). Apheresis PCs were produced using the Amicus or Trima device with InterSol as PAS. 13 PC were evaluated before and after INTERCEPT treatment with either the small volume (SV) or the large volume (LV) disposable set. Volume, platelet content and loss, residual white blood cells (WBC), erythrocytes (RBC) as well as residual amotosalen were determined.

**RESULTS:** For PCBC (n=7) the mean platelet dose before INTERCEPT was  $4.0 \times 10^{11}$  (range 2.9-5.0) in 327mL (range 297-347) of 37-39% plasma with SSP+. Residual RBC were  $0.9-2.6 \times 10^6/\text{mL}$  and residual WBC at  $0.044-0.099 \times 10^6/\text{unit}$ . After treatment mean platelet dose was  $3.7 \times 10^{11}$  (range 2.7- 4.5) in 315mL (range 286-333) and residual RBC were at  $0.30-0.73 \times 10^9/\text{unit}$  and WBC at  $0.016- 0.137 \times 10^9/\text{unit}$ . Average production-losses were 12mL (range 7-17mL) and the mean plts loss was 7.8% (range 4.2 -10.7%). For apheresis products (n=6), the mean platelet dose was  $3.1 \times 10^{11}$  (range 2.6-3.8) in 284mL (range 277-289) of 33-38% plasma with InterSol. RBC were at  $0.4-1.0 \times 10^6/\text{mL}$  and WBC at  $0.014-0.210 \times 10^6/\text{unit}$ . After treatment the mean platelet dose was  $2.9 \times 10^{11}$  (range 2.4-3.3) in 268mL (range 257-279) with  $0.07-0.23 \times 10^9/\text{unit}$  of residual RBC and  $0.000-0.154 \times 10^6/\text{unit}$  WBC. Production-losses were 9-20mL with a mean plt loss of 9.2% (range 6.3-14.0). Values for residual amotosalen after adsorption in the compound adsorption device (CAD) were in the range of  $0.19-0.52 \mu\text{M}$ , independent of the disposable set used (SV with a CAD time of 4 -16 hours, LV disposable set with a CAD time of 6-16 hours).

**SUMMARY/CONCLUSIONS:** All BC and apheresis products met the guard bands for the INTERCEPT process with the SV or the LV disposable set. All pathogen inactivated products (apheresis and BC) were in compliance with the Swiss specifications ( $\geq 2.4 \times 10^{11}$  plts/unit,  $< 5 \times 10^9$  RBC/unit and  $< 1 \times 10^6$  WBC/unit). Residual amotosalen was quite below the threshold of  $2 \mu\text{M}$ . Production-losses were within the expected range. Implementation of the INTERCEPT technology was easy and our validation study was positive for all parameters measured. Production for routine use started successfully in January 2011.

## First Validation and Implementation of the Orbisac System in a Swiss Blood Center within the Scope of Introducing the Pathogen Inactivation System INTERCEPT

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**BACKGROUND:** Due to rising demands of platelets (plts), the capacity to produce platelet concentrates (PC) from Buffy-Coats (BC) needed to be increased at our facility. In addition, the decision to treat 100% of PC with the pathogen-inactivation system INTERCEPT™ extended the production time significantly. These facts made it necessary to optimize the efficiency of PCBC production. Two systems for semi-automation of PCBC production were tested and we decided on the OrbiSac System from CaridianBCT® since it allows among other things automated pooling of BCs. Two machines were in place for this validation.

**AIMS:** One goal was to produce more PCBC in a shorter period of time with the same staff. Furthermore, the PCBC had to meet the process entry requirements for INTERCEPT, called guard bands (volume 255-420mL,  $2.5-6.0 \times 10^{11}$  plts/unit,  $<1 \times 10^6$  WBC /unit,  $<4 \times 10^6$  RBC/mL, 32-47% plasma). Finally after INTERCEPT the products had to meet Swiss specifications ( $\geq 2.4 \times 10^{11}$  plts/unit,  $<5 \times 10^9$  RBC/unit,  $<1 \times 10^6$  WBC/unit,  $\text{pH} \geq 6.4$  after 5d). Focus was here on pH since we validated INTERCEPT extensively before and were now mainly interested to see if PC from OrbiSac have an acceptable pH after 5d.

**METHODS:** Efficiency: The manufacturing process with the OrbiSac System was compared to the efficiency of the current process (manual pooling of BCs followed by soft spin centrifugation and a 2<sup>nd</sup> expression with a MacoPress including in-line leukoreduction). INTERCEPT- compatibility: BCs were produced from whole blood (450mL) using MacoPress Classic separators. To get 1 leukoreduced PCBC, 5 ABO/Rh-matched BCs and 250ml SSP+ as additive solution (PAS) were processed with the OrbiSac System. The products (n=18) were analyzed for guard band specifications and some of those products (n=6) were further treated with INTERCEPT after approx. 2h resting time. 3 additional PCBC were manufactured and processed with INTERCEPT without resting time to create a putative worst-case scenario concerning pH after 5d.

**RESULTS:** The measured platelet content of PCBC (n=18) before INTERCEPT was  $3.7 \times 10^{11}$  (range 2.8-5.2) in 335mL (range 314-353) containing 37% plasma (range 34-42) in PAS. RBC were  $1.2 \times 10^6$ /mL (range 0.3-2.1) and WBC were  $0.017-0.166 \times 10^6$ /unit. All 6 PCBC further processed with INTERCEPT after a resting time (n=6) met Swiss specifications including pH (range 7.0-7.1). 1 of the 3 runs without resting before INTERCEPT did not meet the specifications for plts/unit ( $2.3 \times 10^{11}$  instead  $\geq 2.4 \times 10^{11}$ ). All other Swiss specifications and the guard bands were met including pH (range 7.0-7.1). Investigations on the failed run showed that the platelet content of the initial BCpool was already poor. The two OrbiSac devices increased production capacity after implementation from 20 to 30 PCBC/day while manufacturing time was reduced from 13h to 9h and staff involved was reduced from 4 to 2 operators.

**SUMMARY/CONCLUSIONS:** The OrbiSac System is well suited to efficiently produce PCBC for the INTERCEPT System. All PCBC met the INTERCEPT process entry criteria. After INTERCEPT, one PCBC did not meet Swiss specifications for platelet content which was very likely due to a poor BCpool and not related to separation by OrbiSac or the INTERCEPT Process.

## Pathogen Reduction Treatment Using Amotosalen and Ultraviolet-A Light: Process Control

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Universal use of pathogen reduction treatment (PRT) such as amotosalen and UVA light (INTERCEPT™, Cerus Co) of platelet component (PC) as part of routine operations offers the advantage that all PC components in the inventory are treated with an effective broad spectrum pathogen and leucocytes inactivation process. Process control of blood components is important to insure issuance of properly treated components and we have studied some aspects related with this treatment.

**MATERIAL AND METHODS:** The Transfusion Centre of Galicia (CTG) provides blood components for approximately 2.7 million inhabitants and issues approximately 14,000 PC per year. In 2008, the CTG implemented routine use with INTERCEPT to treat PC, from apheresis and from pooling buffy coat (BC). During INTERCEPT™ treatment there is platelet and volume loss, that is due in part of repeat transfers into different containers and to CAD incubation. From the outset we worked in the same conditions in relation to PC obtention before using INTERCEPT™. We meet all requirements of PRT as: additive solution –PAS III- ratio plasma/PAS, range of volume, RBC content, platelet dose was increased from  $2.5 \times 10^{11}$  (lower limit) to  $2.7 \times 10^{11}$ . Last year the method of processing whole blood was changed using top & bottom bag to prepare PC from BC (before top & top bag). We did some adjustments in centrifugation and fractionation equipment to improve component production. We evaluated the volume and platelet dose in PC from apheresis and pool-BC before and after PRT. The number of platelet was counted on a haematology analyser, Sysmex XT-2000i. In the evaluation phase and subsequent evaluation, functional and metabolic parameters has been tested.

**RESULTS:** The values are shown on the included table.

**CONCLUSIONS:** In our nearly three years of experience, PRT has provided some advantages like:

- The storage life of PC has increased to 7 days, giving us later expiration date.
- The elimination of gamma-irradiation.
- Some logistic advantages particulary for the weekends and holiday periods.

PRT requires additional labour, space and quality control. We suggest to increase the platelets to approximately  $3.5 \times 10^{11}$  before amotosalen-UVA treatment to achieve  $3 \times 10^{11}$  per unit at least in 75% of units tested. All PC had  $< 1 \times 10^6$  leucocytes/unit (by flow cytometry). Now, treated PC from pooling BC has high and consistent content of platelet, 89% of units have more than  $3 \times 10^{11}$  per unit. In the case of apheresis 8.3% of units do not fulfil the requirements of platelet dose.

	PRE INTERCEPT		POST INTERCEPT		% loss volume	% loss PQ	FINAL TREATED PC	
	Volume	PQ $\times 10^{11}$	Volume	PQ $\times 10^{11}$			units $\geq 3 \times 10^{11}$	units $< 2.5 \times 10^{11}$
<b>(5 BC)</b>								
top & top N= 250	353±18	3.3±0.4	325±19	3 ±0.4	7.6 ±3	8.4 ±3	55%	1.7%
top & bottom N= 320	360±19	3.7±0.4	335±20	3.4 ±0.4	7.2 ±2	8 ±4.5	89%	0.31%
<b>Apheresis</b>								
N= 330	299±11	3.3±0.4	277±12	2.9 ±0.4	7.4 ±2	9.8 ±7	47%	8.3%

## Cumulative Clinical Data of INTERCEPT Blood System™ for Platelets Demonstrate Ability to Replace Gamma Irradiation in Routine Clinical Use for TA-GVHD Prevention

L Lin, A Stassinopoulos, L Corash

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**BACKGROUND:** The INTERCEPT Blood System™ (IBS) for platelets received CE Mark registration as a Class III Medical Device in 2002 for pathogen inactivation treatment of platelet components. IBS has been in routine clinical use for 8 years in Europe, Russia, and the Middle East. Prior to CE registration of INTERCEPT™, gamma irradiation was the standard method used to prevent transfusion-associated graft versus host disease (TA-GVHD). A specific indication for INTERCEPT treatment to replace gamma irradiation for prevention of TA-GVHD received CE Mark approval in 2008. Subsequently, country-specific regulatory agencies including the Paul Ehrlich Institute (PEI) of Germany, the Agence Française de Sécurité Sanitaire des Produits de Santé (Afssaps) of France, and the SwissMedic of Switzerland separately approved the use of INTERCEPT in place of gamma irradiation for prevention of TA-GVHD for all patient populations at risk. Approval of IBS to replace gamma irradiation was supported by in vitro and in vivo studies including a clonal T cell proliferation assay by limiting dilution analysis demonstrating robust inactivation of T cells by INTERCEPT treatment to the same level as gamma irradiation, but with a 3000-fold efficacy margin. Additional complimentary assays demonstrated high levels of genomic DNA modification (1 adduct/83 base pairs), complete inhibition of cytokine synthesis, and elimination of early activation antigen presentation. In vivo animal studies confirmed that INTERCEPT inactivated T-cells could not initiate TA-GVHD in immuno-compromised recipients.

**AIM:** To evaluate the efficacy of INTERCEPT for prevention of TA-GVHD in clinical use.

**METHODS:** We analyzed 8 years of cumulative experience obtained from clinical trial and routine use of INTERCEPT treated platelet components, without gamma irradiation, transfused in a broad patient population. Data were obtained from clinical trial databases and hemovigilance (HV) studies. The populations studied were enriched for immune-compromised hematology-oncology patients at risk for TA-GVHD, and hematopoietic stem cell transplantation (HSCT) recipients.

**RESULTS:** The cumulative frequency of TA-GVHD for patients transfused with INTERCEPT platelet components in place of gamma irradiation included hematology-oncology, HSCT recipients, and pediatric patients from 24 centers in 12 European countries (Table 1). A significant number of HSCT patients were evaluated and no cases of TA-GVHD were reported. In addition to the Phase III and HV studies, blood centers have purchased INTERCEPT kits representing production of more than 500,000 platelet components to date. Most blood centers using INTERCEPT have discontinued gamma irradiation and rely on the inactivation process to provide protection against TA-GVHD. No cases of TA-GVHD have been reported by these centers in association with transfusion of INTERCEPT platelet components.

**CONCLUSION:** Cumulatively, the clinical experience supports use of INTERCEPT treatment in place of gamma irradiation to prevent TA-GVHD in at risk patients.

**Table 1: Summary of TA-GVHD Incidence in Patients Receiving Non-Gamma Irradiated INTERCEPT Platelet Components in Clinical Trials and Hemovigilance (HV) Studies**

Study	Number of Transfusions	% Non-gamma irradiated	Total Number of Patients	Hem-Onc Patients	HSCT Patients	Incidence of TA-GVHD
Phase III Trials <sup>4</sup>	575	100%	87	82	28	0
HV1 <sup>5</sup>	5,106	97.3% <sup>1</sup>	651	378	47	0
HV2 <sup>6</sup>	7,437	98.9% <sup>2</sup>	1,400	748	121	0
HV <sup>3</sup>	6,991	95% <sup>3</sup>	2,062	974	310	0
Mt. Godinne <sup>7</sup>	3,645	100%	186	186	186	0
Pediatric <sup>8</sup>	500	100%	83	48	10	0
Basel <sup>9</sup>	551	100%	46	38	15	0
Lübeck <sup>10</sup>	560	100%	52	52	17	0
Strasbourg <sup>11</sup>	55,104	100%	~8,000	~4,400	not available	0

1. Prior to CE Mark gamma replacement approval 139 of the 5,106 products (2.7%) performed in Trondheim, Norway were gamma irradiated. 2. Prior to Afssaps's approval, a small number of products (82 of 7,437, or 1.1%) performed in France were also gamma irradiated. 3. Based on data up to Jan 2011. 4. van Rhenen et al. *Blood*. 2003;101: 2426-33. Janetzko et al. *Transfusion*. 2005;45: 1443-52. 5. Osselaer et al. *Transfusion*. 2008;48: 1061-71. 6. Osselaer et al. *Vox Sang*. 2008;94: 315-23. 7. Osselaer et al. *Vox Sang*. 2010;99:428. 8. Van haute I, et al. *Vox Sang*. 2006;91: 177. 9. Stebler C, et al. *Vox Sang*. 2007;93: 172. 10. Schlenke P, et al. *Vox Sang*. 2007;93: 171. 11. JP Cazenave. 2010. *Bull Acad Natle Med*.

## Two Years of Experience with the Transfusion of Pathogen Inactivated Platelets Using the INTERCEPT Blood System™ and 7 Day Storage

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**BACKGROUND:** The INTERCEPT BLOOD System™ is the leading technology in routine use for pathogen inactivation (PI) of plasma and platelet components (PCs). It utilizes amotosalen, to target DNA and RNA in pathogens and leukocytes. After illumination with UVA light, covalent bonds are formed between amotosalen and the nucleic acids preventing nucleic acid replication and transcription.

**AIMS:** The aim of this study was to review and summarize our experiences in the preparation and usage of PI PCs using INTERCEPT system which was introduced into in routine in our institute to improve overall safety of platelet (plt) transfusions, to prolong storage to 7 days, protect against emerging pathogens, to avoid bacterial detection and gamma-irradiation and to have one system enabling also for pathogen- inactivation of plasma.

**METHODS:** We used retrospective data from years 2009 and 2010 concerning processing, quality control, storage and transfusion of PI PCs in our Blood Transfusion Centre. The data from an active haemovigilance program are also part of this analysis.

**RESULTS:** The total number of PI PCs analyzed was 10785. From these 7383 (68,5 %) were pooled buffy coat (BC) PCs and 3402 (31,5 %) apheresis (AP) PCs. During this period we issued 9716 PCs: 6521 (67,2 %) pooled BC PCs and 3195 (32,8 %) AP PCs. The overall expiry rate was 9% ( 11 % BC PC ; 6% AP PC ). AP PCs were INTERCEPT treated on the day of collection. Pathogen-inactivation of the BC PCs was performed one day after collection. Validation of the PI process showed platelet (PLT) counts, pH values on day 7 and residual amotosalen values in acceptable ranges with 6 % volume reduction and 90% PLT recovery on day 1. The quality control showed median volumes of 359 (341 – 377) mL for the BC PCs and 285 (272 – 295)mL for AP PCs. Median PLT number was 368 (253 -523)  $\times 10^9$  /BC PC and 307 (248 - 392)  $\times 10^9$  /AP PC. The median pH values on day 7 were 7,03 (6,71 – 7,12) in BC PCs and 6,87 (6,70 – 7,08) in AP PCs. The median response to transfused PI PCs (n=25) measured as CCI (24h) was 8960/ $\mu$ L (794 / $\mu$ L – 20717/ $\mu$ L) and posttransfusion platelet recovery (PPR ) (24h) was 15,67 % ( 1,97 % - 61,0 %). As part of the hemovigilance program we analyzed the outcome for 422 transfusions of PCs to 80 patients (average 5.82 PCs /patient). Only 1 (0,2 %) acute transfusion reaction (generalized urticaria) was reported and successfully treated with antihistaminic therapy. There were no reports from the clinic on diminished bleeding control or lower efficacy of transfused PLTs. No death, episodes of TRALI or TA-GVHD were reported.

**SUMMARY:** Our two year experience of routine use of INTERCEPT treated PCs shows good compatibility with existing production concerning preparation time, acceptable volume losses and PLT recoveries and compliance with official regulations. Post-transfusion CCI and PPR (24h) showed satisfactory values. Transfusion of INTERCEPT treated PCs in clinical routine to all patients was very successful with 99, 8% of transfusions without reported adverse effects.

## Hemostatic Efficacy of Platelet Components Treated with Amotosalen-UVA Pathogen Inactivation and Stored for 5 and 7 Days Prior to Transfusion

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**BACKGROUND:** In some countries, bacterial contamination of platelet components (PC) limits PC storage to 4-5 days to reduce the risk of transfusion-related sepsis (TRS). Bacterial detection is only partially effective in preventing release of contaminated PC. Pathogen inactivation (PI) of bacteria facilitates storage of PC to 5 and 7 days limiting TRS risk, reducing PC wastage, and increasing PC inventory. The hemostatic efficacy of 5 and 7 day-old PC has not been characterized.

**AIMS:** Data from 3 randomized, controlled, double blind clinical trials (RCT) were analyzed to characterize, specifically, the hemostatic efficacy of 5 and 7 day old PC transfused to hematology-oncology patients.

**METHODS:** All patients who received a transfusion of 5 or 7 day-old PI-PC (INTERCEPT™, Cerus BV, Amersfoort, Netherlands) or conventional PC (C-PC) were identified within the database of 3 RCT: EuroSPRITE (Blood 2003;101:2426), SPRINT (Blood 2004;104:1534), and TESSI (Vox Sang 2010;99:13). Outcomes analyzed for hemostatic efficacy included: hemorrhagic adverse events (AE) within 24 hr of 5 and 7 day-old PC transfusion, RBC use within 24 hr of 5 and 7 day-old PC transfusion, and days to the next PC transfusion (interval). Hemorrhagic AE were determined by trained personnel, blinded to treatment, using daily per protocol assessments (WHO criteria). Surrogate outcomes included 1 hr CI and CCI. Data from each study were analyzed separately due to varying observation periods and total transfusion exposures across the RCT. Distributions of parameters between respective treatment groups were compared by Wilcoxon rank-sum or log-rank tests at the 0.05 significance level.

**RESULTS:** 727 patients who received 5 or 7 day-old PI-PC (N = 371) or C-PC (N =356) were identified from 3 RCT. The proportion of patients with hemorrhagic AE and the proportion of patients requiring RBC transfusion were not increased by treatment (PI-PC vs. C-PC) for 5 or 7 day-old PC (**Table 1**). Median transfusion doses ( $10^{11}$ ) were lower for 5 day-old PI PC resulting in reduced median 1 hr CI ( $10^9/L$ ) and CCI ( $10^3$ ) and shorter interval (days) to the next PC transfusion (**Table 2**). For 7 day-old PC, when median PC dose was comparable between treatment groups, median 1 hr CI and CCI were improved for PI-PC; and transfusion interval was not affected by PI (**Table 2**).

**SUMMARY and CONCLUSIONS:** 5 and 7 day-old PI-PC supported hemostasis, measured by bleeding and RBC use, comparable to C-PC. Based on these data, CI and CCI did not predict or correlate with hemostatic efficacy, consistent with data from the PLADO study (N Eng J Med 2010; 362:600). When dose was controlled, the interval to the next PC transfusion was similar for PI and C PC. A synthesis of bleeding assessments, RBC use, and transfusion interval provided evidence that 5 and 7 day-old PI-PC were therapeutically effective with the added benefit of broad spectrum pathogen inactivation.

**Table 1: Frequency of Hemorrhagic AE and RBC Transfusion**

Study	EUROSPRITE (5d)		SPRINT (5d)		TESSI (7d)	
	N	PI (35)	C (27)	PI (231)	C (233)	PI (105)
<b>Grade</b>	<b>Proportion of Patients With Hemorrhage (%)<sup>1</sup></b>					
<b>0</b>	66	67	54	60	85	81
<b>1</b>	31	30	33	29	10	15
<b>2</b>	3	4	7	7	5	3
<b>3 or 4</b>	0	0	6	4	1	1
	<b>Proportion of Patients Requiring RBC Transfusion (%)<sup>2</sup></b>					
<b>No</b>	74.3	74.1	75.8	78.0	76.2	78.3
<b>Yes</b>	25.7	25.9	24.7	22.0	23.9	21.6

1.  $p > 0.05$  for 5 and 7 day-old PI-PC versus C-PC

2.  $p > 0.05$  for 5 and 7 day-old PI-PC versus C-PC

**Table 2: Impact of PC Dose On CI, CCI, and Transfusion Interval**

Study	EUROSPRITE (5d)		SPRINT (5d)		TESSI (7d)	
	PI (35)	C (27)	PI (231)	C (223)	PI (105)	C (106)
<b>N</b>						
<b>Dose<sup>1</sup></b>	3.2	4.0	3.5	3.9	4.1	4.1
<b>CI<sup>2</sup></b>	19.0	27.5	16.0	27.0	17.0	20.0
<b>CCI<sup>3</sup></b>	11.6	12.2	9.2	13.4	7.3	8.8
<b>Interval<sup>4</sup></b>	2.5	3.0	1.2	2.0	1.8	1.9

Comparisons for PI-PC versus C-PC by study.

Dose ( $10^{11}$ ), CI ( $10^9/L$ ), CCI ( $10^3$ ), Interval (days).

1. EuroSPRITE,  $p = 0.002$ ; SPRINT,  $p < 0.0001$ ; TESSI,  $p = 0.97$

2. EuroSPRITE,  $p = 0.06$ ; SPRINT,  $p < 0.0001$ ; TESSI,  $p = 0.12$

3. EuroSPRITE,  $p = 0.43$ ; SPRINT,  $p < 0.0001$ ; TESSI,  $p = 0.06$

4. EuroSPRITE,  $p = 0.75$ ; SPRINT,  $p < 0.0001$ ; TESSI,  $p = 0.72$

## Validation of Double Dose Pooled Platelet Products for Pathogen Inactivation with the INTERCEPT Blood System and Storage for up to 7 Days

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**BACKGROUND:** The INTERCEPT Blood System™ for platelets allows for pathogen inactivation in apheresis and buffy coat-derived platelet components. Production of buffy coats can be cost saving and makes platelet production less dependent on apheresis donors. The newly introduced dual-storage bag set enables for the production of two pathogen-inactivated platelet components from a pool of 7 buffy coats.

**AIMS:** The objective of this study was to analyze the feasibility of pooling 7 buffy coats to produce a double dose platelet product suitable for the INTERCEPT™ process and their compliance with the acceptance criteria for manufacturing (local and EU guidelines) and for support of patients according to clinical practice guidelines and standard platelet infusion methods in Sweden. The quality of the produced split units was determined over the storage period of 7 days.

**METHODS:** Buffy coats were produced from whole blood ( $450 \pm 45$  mL) using the Optipress II device (Fenwal). Seven ABO-matched buffy coats were pooled with 300 mL of SSP+ additive solution (MacoPharma). Twelve buffy coat pools were evaluated before and after INTERCEPT™ treatment and in vitro parameters (volume, platelet count, glucose, lactate, swirling, pH value, O<sub>2</sub> consumption and CO<sub>2</sub> production) were analyzed at days 1 or 2, 4 or 5, and 7 of storage.

**RESULTS:** The mean volume of buffy coat pools (n=12) was  $601 \pm 6$  mL. Target values for the resulting pooled platelet products were  $5.5\text{-}7 \times 10^{11}$  platelets in a volume of 370-420 mL SSP+ with 32-47% plasma. Red blood cell (RBC) threshold was at  $<4 \times 10^6$ /mL and maximum residual white blood cell (WBC) concentration at  $1 \times 10^6$ /unit. After sampling, the volumes for all products were below 420 mL. Before INTERCEPT™ treatment, the mean volume was  $404 \pm 8$  mL with  $5.65 \pm 0.61 \times 10^{11}$  platelets. The products contained  $1.2 \pm 0.4 \times 10^6$  RBC/mL and  $0.11 \pm 0.1 \times 10^6$  WBC/unit. The products were split directly after treatment. The resulting platelet components had a mean platelet dose of  $2.56 \times 10^{11}$  on day 1/2 (in  $192 \pm 5$  mL) and  $2.43$  and  $2.44 \times 10^{11}$  platelets on day 4/5 and 7 respectively, reflecting a total loss of about 5% during storage. The mean pH value was 6.9 on day 1/2, 7 on day 4/5 and 6.8 on day 7 of storage. Lactate concentration increased from 9.1 to 12 and 15.8 mM/mL and glucose content decreased from 5.2 to 3.7 and 1.9 mM/mL from day 1/2 to day 4/5 and 7 respectively. Over the 7 days of storage, the mean pO<sub>2</sub> level was 21.4, 21.7 and 21.2 mm Hg and the mean pCO<sub>2</sub> level was 4.3, 2.5 and 3.1 mm Hg on day 1/2, 4/5 and 7 respectively.

**CONCLUSIONS:** Production of pools of 7 whole blood-derived buffy coats for treatment of double dose platelet components is feasible with only minor losses. All pools produced in this study met the guard bands for the INTERCEPT™ treatment. Pathogen inactivation with the dual-storage bag set allows for the production of two components for transfusion which are in accordance with the local and EU guidelines. Analyses of the in vitro parameters show that these products are suitable for transfusion even after storage for up to 7 days.

## Analysis of Functional Activity of a Large Panel of Coagulation Factors in Fresh and Previously Frozen Plasma Treated with the INTERCEPT Blood System

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**BACKGROUND:** The INTERCEPT Blood System™ (IBS) for plasma is a CE mark registered Class III medical device for the pathogen inactivation (PI) of viruses, bacteria, parasites and leukocytes in plasma. Plasma components treated with INTERCEPT have been in routine clinical use in many blood centers in Spain since 2007. PI technology for therapeutic plasma must fulfill several essential requirements: 1) Inactivation of a broad range of pathogens, 2) Preservation of coagulation functions, and 3) Compatibility with routine blood bank operations.

**AIMS:** The aim of this study is to evaluate the plasma quality after INTERCEPT treatment following three processing procedures, 1) freshly collected plasma treated with INTERCEPT and frozen within 8 hours of collection, 2) freshly collected plasma stored overnight, treated with INTERCEPT and frozen within 24 hours of collection, and 3) previously frozen plasma, thawed, treated with INTERCEPT and frozen within 8 hours of thawing.

**METHODS:** For each experimental condition, eight apheresis plasma components (385-650 mL) were collected (Haemonetics, MCS2) and treated with INTERCEPT according to the manufacturer's instructions. Samples were taken before and after INTERCEPT treatment, and after one month of frozen storage at -30°C. Samples were then tested for quality including PT, aPTT, Fibrinogen, factors (F) II, V, VII, VIII, IX, X, XI, XII, antithrombin (AT), protein C, and protein S.

**RESULTS:** All collections of plasma prior to INTERCEPT treatment met the input requirements of 385-650 mL with  $<4 \times 10^6$  RBC/mL. The mean volume of the final INTERCEPT plasma product, residual amotosalen, WBC, RBC and platelet counts met the requirements of European guidelines. Results of plasma clotting time and coagulation factors are presented in **Table 1 and 2**. The proportion of factor activity retained in INTERCEPT plasma relative to untreated baseline was comparable among the three processing procedures. Immediately after treatment, retention of clotting time and coagulation factors of INTERCEPT plasma were 80-108%, 80-105% and 72-107% for 8 hr, 24 hr and frozen plasma respectively. The mean levels of the most labile F VIII were 87, 78 and 69 IU/dL for 8 hr, 24 hr and frozen plasma, respectively. Following one month of storage, the factor activities remained within the therapeutic range.

**CONCLUSION:** INTERCEPT plasma retained adequate levels of critical plasma coagulation activities. The effect of INTERCEPT treatment on plasma activities is comparable among three procedures. The processing flexibility ensures smooth operation in the blood bank setting while providing a safe and high quality plasma product for transfusion.

**Table 1: Functions of IBS-plasma prepared from fresh plasma and frozen within 8hr or 24 hr (n=8)**

Assay	8 Hr IBS-Plasma			24 Hr IBS-Plasma		
	Untreated	Immediately After Treatment	After 1 Month Frozen Storage	Untreated	Immediately After Treatment	After 1 Month Frozen Storage
PT (ratio)	1.0 ± 0.1	1.0 ± 0.1	1.0 ± 0.1	1.0 ± 0	1.1 ± 0	1.1 ± 0.1
aPTT (sec)	31 ± 2	32 ± 3	33 ± 3	32 ± 3	33 ± 3	34 ± 2
ATIII (U/dL)	100 ± 6	94 ± 6	92 ± 4	98 ± 8	92 ± 7	91 ± 9
PC (U/dL)	107 ± 19	93 ± 15	91 ± 13	106 ± 17	90 ± 11	90 ± 15
PS (U/dL)	114 ± 22	115 ± 23	101 ± 20	116 ± 16	117 ± 18	102 ± 11
FI (mg/dL)	358 ± 71	308 ± 62	308 ± 77	346 ± 43	278 ± 39	274 ± 39
FII (U/dL)	88 ± 9	88 ± 8	85 ± 8	93 ± 12	85 ± 8	83 ± 9
FV (U/dL)	95 ± 20	93 ± 18	91 ± 18	97 ± 11	90 ± 9	89 ± 9
FVII (U/dL)	96 ± 17	93 ± 14	91 ± 15	85 ± 18	81 ± 16	78 ± 16
FVIII (U/dL)	116 ± 21	98 ± 14	87 ± 12	103 ± 31	83 ± 14	78 ± 14
FIX (U/dL)	120 ± 17	111 ± 17	107 ± 16	114 ± 13	101 ± 13	99 ± 13
FX (U/dL)	84 ± 7	84 ± 8	80 ± 8	95 ± 8	88 ± 7	85 ± 8
FXI (U/dL)	119 ± 25	105 ± 17	96 ± 16	110 ± 14	94 ± 9	97 ± 10
FXII (U/dL)	110 ± 10	118 ± 26	103 ± 14	103 ± 36	81 ± 28†	87 ± 29

† statistically significant differences ( $p < 0.05$ ) were observed comparing to 8 hr fresh plasma

(continued on page 14)

**Table 2: Functions of IBS-plasma prepared from previously frozen plasma (n=8)**

Assay	Previous Frozen IBS-Plasma		
	Untreated	Immediately After Treatment	After 1 Month frozen Storage
<b>PT (ratio)</b>	1.0 ± 0.1	1.1 ± 0.1	1.1 ± 0.1
<b>aPTT (sec)</b>	31 ± 1	33 ± 2	34 ± 2
<b>ATIII (U/dL)</b>	98 ± 6	93 ± 7	92 ± 7
<b>PC (U/dL)</b>	107 ± 18	96 ± 23	97 ± 17
<b>PS (U/dL)</b>	113 ± 14	115 ± 14	118 ± 14
<b>FI (mg/dL)</b>	303 ± 29	258 ± 27†	254 ± 30
<b>FII (U/dL)</b>	97 ± 10	87 ± 10	86 ± 8
<b>FV (U/dL)</b>	98 ± 13	94 ± 13	93 ± 10
<b>FVII (U/dL)</b>	93 ± 19	86 ± 19	84 ± 18
<b>FVIII (U/dL)</b>	99 ± 24	72 ± 20†	69 ± 23
<b>FIX (U/dL)</b>	116 ± 18	97 ± 15†	93 ± 21
<b>FX (U/dL)</b>	103 ± 9	93 ± 10	90 ± 10
<b>FXI (U/dL)</b>	104 ± 18	89 ± 15†	86 ± 16
<b>FXII (U/dL)</b>	127 ± 20	104 ± 16	100 ± 14

† statistically significant differences ( $p < 0.05$ ) were observed comparing to 8 hr fresh plasma

## The Influence of Different Holding Conditions of Coagulation Parameters of Plasma After Pathogen Reduction with the INTERCEPT Treatment

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**BACKGROUND:** Pathogen-inactivation (PI) as a pro-active approach to blood safety has been widely discussed in literature. In the case of plasma, the preservation of the coagulation factors as well as a functioning coagulation has to be demonstrated. How the holding conditions until the start of PI may influence the quality of coagulation factors is not precisely known.

**AIM:** This study evaluated the influence of the different holding condition of coagulation factors regarding their functionality in plasma treated with the INTERCEPT Blood System (I-FFP).

**METHODS:** Plasma units (600 mL, n = 32) were collected from qualified volunteer donors. They were derived directly from fresh apheresis collections (Haemonetics PCS2; Haemonetics, Braintree, MA). All of the major blood groups were represented. The units were kept at room temperature prior to INTERCEPT treatment (Cerus Europe, BV Amersfoort); the INTERCEPT treatment was finished within (1) 6 hours (n = 12, I-FFP A) (2) 20 hours (n = 6, I-FFP B) and (3) the INTERCEPT treatment was started after thawing plasma which was kept at room temperature for 6 hours, frozen to  $-30^{\circ}\text{C}$  and then stored for 7 days at  $-32^{\circ}\text{C}$  or below (n = 14, I-FFP C). Samples of the plasma were taken before and after INTERCEPT treatment and stored at  $-32^{\circ}\text{C}$  or below prior to analyses of the coagulation parameters; Plasma coagulation function was assessed at three time points: prior treatment, immediately after treatment and after 30 days of frozen storage.

**RESULTS:** After INTERCEPT treatment the mean levels of fibrinogen, factor (F) V, FVIII, FXI and von Wille brand complex showed no significant differences between the different holding conditions and times prior inactivation. I-FFP A exhibited shorter mean prothrombin time, activated partial thromboplastin time, higher mean levels of fibrinogen, F V, F VIII and FXI immediately after treatment and after 30 days of frozen storage (**table 1**). Overall the retention immediately after PI and frozen storage over 1 month never dropped below 70% of the initial value; the retention of von Wille brand complex was almost equivalent in all samples (**table 2**). Lowest levels of FV, FVIII, FXI and von Wille brand complex, longest mean INR and activated Partial Thromboplastin Time (aPTT) were found when the plasma was kept for 20 hours at room temperature until INTERCEPT treatment. INR and aPPT slightly increased after treatment and 1 month frozen storage within normal values.

*(continued on page 16)*

Table 1: The effect of holding conditions and pathogen inactivation on the plasma proteins immediately after treatment

Analyte	I-FFP A		I-FFP B		I-FFP C	
	Post/ Pre-Treatment	Retention (%)	Post/ Pre-Treatment	Retention (%)	Post/ Pre-Treatment	Retention (%)
Fibrinogene (gl)	2,09/2,59	81	1,69/2,20	77	1,91/2,22	86
Factor V (U/ml)	1,00/1,13	88	0,83/0,90	92	0,94/1,15	82
Factor VIII (U/ml)	0,92/1,13	81	0,75/0,94	80	0,85/1,04	82
Factor XI (U/ml)	0,86/1,03	83	0,83/0,99	80	0,81/0,91	89
vWF-Ag (U/ml)	1,17/1,21	97	0,88/0,96	92	1,20/1,17	103
vWF-Ristocetin-Cof(U/ml)	0,91/0,94	97	0,66/0,70	94	1,06/0,97	109

Table 2: The effect of holding conditions and pathogen inactivation on the plasma proteins after 1 month of frozen storage

Analyte	I-FFP A		I-FFP B		I-FFP C	
	Post/ Pre-Treatment	Retention (%)	Post/ Pre-Treatment	Retention (%)	Post/ Pre-Treatment	Retention (%)
Fibrinogene (gl)	1,90/2,59	73	1,58/2,20	72	1,76/2,22	79
Factor V (U/ml)	0,97/1,13	86	0,72/0,90	80	0,85/1,15	74
Factor VIII (U/ml)	0,90/1,13	80	0,69/0,94	73	0,67/1,04	64
Factor XI (U/ml)	0,83/1,03	81	0,83/0,99	84	0,74/0,91	81
vWF-Ag (U/ml)	1,20/1,21	99	0,97/0,96	101	1,24/1,17	106
vWF-Ristocetin-Cof(U/ml)	1,02/0,94	109	0,74/0,70	106	1,05/0,97	108

**CONCLUSION:** An adequate preservation of coagulation factor activities and functionality was found when plasma was kept for 6 or 20 hours until PI or when PI was started after thawing plasma which was kept 7 days in frozen storage; but coagulation factor levels and stability were better preserved when the INTERCEPT treatment was started within 6 hours after collection or plasma was frozen as soon as possible after collection and the INTERCEPT treatment was started immediately after thawing. A holding time of 20 hours at room temperature until INTERCEPT treatment resulted in the lowest but still acceptable retention of coagulation factors.

## Photochemical Treatment of Fresh Plasma. Evaluation of Functional Activity of Coagulation Factors and Inhibitors

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**BACKGROUND:** The INTERCEPT Blood System (IBS)™ improves the safety of blood components by the inactivation of a high number of pathogens and leucocytes. The technology combines a psoralen molecule (amotosalen) and ultraviolet A light (UVA). The amotosalen penetrates in cellular and nuclear membranes and forms covalent crosslinks to the nucleic acid base pairs upon UVA exposure blocking DNA and RNA replication. This process should maintain the therapeutic efficacy of plasma and platelets.

**MATERIAL AND METHODS:** 54 plasma units were obtained from whole blood CDP-SAGM units by differential centrifugation. IBS treatment was performed in pools of two plasma units. Units were subsequently frozen at -18°C. Analysis of coagulation times (PT and APTT), factors and inhibitors was performed before and after IBS treatment and after 6 months of storage. We applied paired t-student test to compare results. Differences between values were considered significant when  $p < 0.05$ .

**RESULTS:** Table 1 presents the results. A statistical significant decline of all coagulation factors and inhibitors was observed, particularly for FVIII, after IBS treatment and after recovery ( $p < 0.01$ ). However the functional activity was always maintained above 70% for all factors except for FVIII whose mean recovery value was 65.9%.

**CONCLUSION:** Our results show preservation of the functional activity of all coagulation factors and inhibitors after IBS treatment, according to what is described in other previous studies in literature.

We observed a loss of FVIII functional activity after recovery although we considered it acceptable.

These results contributed to validate IBS treatment for fresh plasma units in our Department.

**Table 1: Results of the coagulation tests before and after fresh plasma treatment (IBS) and after recovery. Results are presented as mean values +/- standard deviation.**

	Before IBS treatment	After IBS treatment	After recovery
PT (sec)	11.14±0.4	11.56±0.5	11.84±0.6
APTT (sec)	27.18±2.2	30.18±2.2	33.4 ±2.7
Prot C	110.51±10.0	95.79±8.1	102.4±9.3
Free Prot S (u/dL)	93.49±11.7	86.86±9.8	85.89±12.9
Antithrombin (u/dL)	94.41±7.8	88.37±8.1	89.27±8.0
Fibrinogen (mg/dL)	264.92±35	182.18±25.8	195.22±35.3
Factor II (u/dL)	101.06±9.6	89.32±9.4	90.27±9.3
Factor V (u/dL)	106.14±9.6	100.68±12.2	95.24±18.4
Factor VII (u/dL)	95.42±12.8	82.00±15.9	87.91±19.7
Factor VIII (u/dL)	121.00±20.2	93.36±18.2	65.9±13.8
Factor IX (u/dL)	119.18±20.0	105.32±22.7	93.26±17.5
Factor X (u/dL)	106.43±11.0	92.66±9.2	101.09±17.9
Factor XI (u/dL)	105.28±20.0	92.58±24.3	98.75±12.9
Factor XII (u/dL)	113.14±30.0	94.93±24.4	92.71±20.7

## In Vitro Evaluation of Pathogen Inactivated RBC Using the S-303 Treatment System

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**BACKGROUND:** A second generation pathogen inactivation (PI) process for red blood cells (RBC) has been developed using S 303 to crosslink nucleic acids to prevent replication of contaminating pathogens and leukocytes. Glutathione (GSH) is included to quench non-specific reactions. A Phase 1 clinical study was recently completed and successfully met the primary endpoint of 24-hour recovery per the FDA criteria.

**AIMS:** Studies were conducted to determine the suitability of S-303 treated RBC for transfusion using standard EU blood bank practices and workflow. In vitro characteristics of stored PI RBCs processed using standard automation in the PI treatment process (Study 1) and variation of the PI process duration (Study 2) were evaluated.

**METHODS:** Leukocyte depleted SAGM RBC were prepared from buffy-coat depleted whole blood (500mL) held overnight (o/n) at room temperature (RT). In triplicate, three units of ABO matched RBCs were pooled and divided into 280mL units. The PI process was performed on two units and the third unit was unprocessed (Control).

Study 1: Test RBC were combined with diluent solution, treated with 20mM GSH and 0.2mM S-303, held for 18h at RT, and diluent exchanged with SAGM. The exchange step was either performed with a plasma press (Test-Manual) or Compomat G4 (Test-Automated). Study 2: The PI process was performed as above except one Test unit was held at RT for 4h (Test-4h) and the other 18h (Test-18h) prior to manual exchange. RBC units were stored at 4±2°C for 42 days and sampled at days 2 (post-PI process), 21, 35 and 42 post-collection.

For each study, repeated measures ANOVA was used to assess statistically significant differences (p-value <0.05) between Test and Control and Test conditions. Although studies were performed in triplicate, substantial differences could be detected since assessment was carried out for four time points.

**RESULTS:** All Test units had > 40 gHb/unit. In Study 1, hematocrit (Hct), pH, potassium (K<sup>+</sup>) and lactate were significantly higher in Control; whereas MCHC and hemolysis were lower (**Table 1**). In Study 2, K<sup>+</sup> and lactate were higher in Control; whereas hemolysis was lower (**Table 2**). The reduced Hct, pH, K<sup>+</sup> and lactate in Test units is due to the exchange step. Although some parameters showed statistical difference between Test and Control (p<0.05), these effects were not different whether the exchange step was manual or automated, or the hold time during the PI process was 4 h or 18 h. All parameters for Test units were within physiologic references ranges for conventional RBC.

**CONCLUSIONS:** All treated units met the EU guidelines for leukocyte-depleted RBCs (Hct, hemoglobin and hemolysis) and ATP levels were greater than 3 µmol/g Hb throughout storage. Although some parameters showed statistical difference between Test and Control, the values were within physiological range suitable for transfusion. The S-303 PI process is compatible with RBC prepared by standard EU blood bank practices, can be implemented using standard blood center practices and processing can be managed within blood center workflow. These data support further clinical development of the S-303 PI process in Europe.

**Table 1: Study #1 In vitro Characterization of RBC After 35 Days of Storage (n=3; mean±SD)**

Treatment	Day <sup>a</sup>	Hct (%) <sup>*</sup>	Hemolysis (%) <sup>*</sup>	ATP (µmol/ g Hb)	MCHC (g/dL) <sup>*</sup>	K <sup>+</sup> (mM) <sup>*</sup>
Test Manual	D2	57.6±0.3	0.12±0.04	8.5±0.6	33.9±0.3	1.23±0.41
	D21	57.6±0.5	0.42±0.02	5.8±1.0	34.0±0.3	30.15±1.21
	D35	58.6±0.9	0.60±0.07	4.0±0.9	33.3±0.6	42.47±2.17
Test Automated	D2	56.9±0.2	0.12±0.03	8.1±1.1	34.1±0.4	1.33±0.40
	D21	57.2±0.2	0.40±0.02	5.8±0.9	34.1±0.2	29.89±0.53
	D35	58.2±0.2	0.59±0.11	3.5±0.6	33.3±0.1	42.75±1.74
Control	D2	59.3±1.2	0.08±0.02	6.7±0.4	33.5±0.1	5.79±1.21
	D21	60.0±1.3	0.16±0.02	4.9±0.4	33.2±0.1	36.68±0.55
	D35	61.1±1.3	0.26±0.08	3.4±0.1	32.7±0.1	50.03±0.77

<sup>\*</sup> Repeated measures ANOVA between Test and Control effects: p < 0.05; comparisons between Test Manual and Test Automated showed no statistical significance

<sup>a</sup>. Days are measured post-donation

**Table 2: Study #2 In vitro Characterization of RBC After 35 Days of Storage (n=3; mean±SD)**

Treatment	Day <sup>a</sup>	Hct (%)	Hemolysis (%) <sup>*</sup>	ATP (μmol/ g Hb)	MCHC (g/dL)	K <sup>+</sup> (mM) <sup>*</sup>
<b>Test 4h</b>	D2	57.7±0.6	0.12±0.01	6.2±1.0	33.0±1.0	2.60±0.04
	D21	59.2±0.9	0.29±0.04	5.1±1.1	32.2±0.4	26.60±1.31
	D35	59.8±1.1	0.39±0.06	3.7±0.7	32.1±0.3	35.82±3.59
<b>Test 18h</b>	D2	57.5±0.2	0.09±0.01	7.8±1.9	33.0±0.9	1.00±0.00
	D21	60.7±4.1	0.27±0.04	5.2±1.3	33.0±0.4	27.81±1.82
	D35	59.5±0.6	0.36±0.01	3.7±0.9	32.3±0.7	34.11±5.48
<b>Control</b>	D2	57.8±1.2	0.06±0.01	5.4±0.8	33.4±0.9	4.84±0.70
	D21	60.3±1.5	0.11±0.00	4.8±1.0	32.0±0.7	31.76±2.32
	D35	61.0±0.6	0.17±0.02	3.4±0.6	32.1±0.9	42.42±4.11

<sup>\*</sup> Repeated measures ANOVA between Test and Control effects:  $p < 0.05$ ; comparisons between Test 4h and 18h showed no statistical significance

<sup>a</sup> Days are measured post-donation.







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## INTERCEPT REGULATORY APPROVALS

### **CE mark, Class III**

platelets (2002), plasma (2006)

### **France (Afssaps)**

platelets and plasma

### **Germany (PEI)**

platelets (2007\*)

plasma (2011\*)

### **Switzerland (Swissmedic)**

platelets and plasma

### **Austria (AGES)**

platelets (2010\*)

\*First blood center marketing authorization approved.

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Use of INTERCEPT is contraindicated in patients with a history of allergic response to amotosalen or psoralens. No pathogen inactivation system has been shown to inactivate all pathogens. Not approved for sale in the U.S.