

## INTERCEPT® Blood System for Plasma

### Rx Only

**Caution: Federal law restricts this device to sale by or on the order of a licensed healthcare practitioner.**

(Date of Label Implementation)

### INTENDED USE

The INTERCEPT Blood System for Plasma is intended to be used for the *ex vivo* preparation of pathogen-reduced, whole blood derived or apheresis plasma in order to reduce the risk of transfusion-transmitted infection (TTI).

### DEVICE DESCRIPTION

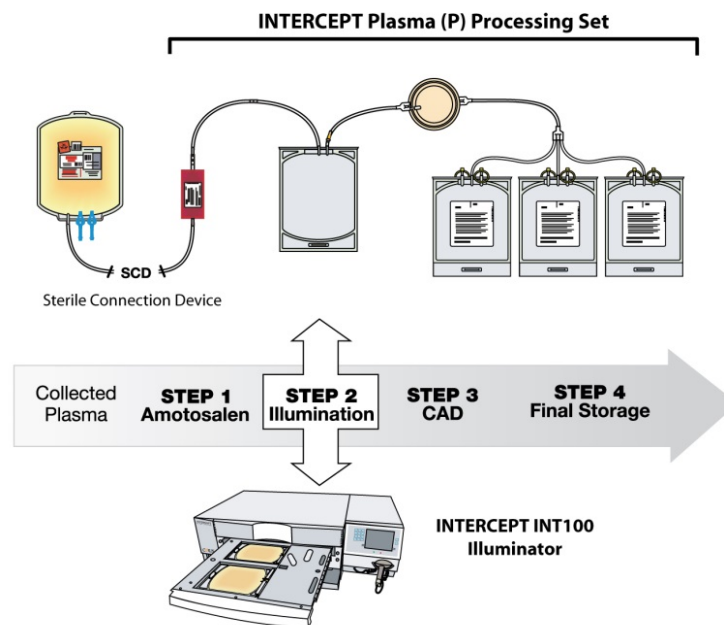
The INTERCEPT Blood System for Plasma contains a sterile, non-pyrogenic, single-use, integrated, fluid path plasma processing set (INT3110) comprised of four key components (see Table 1) and an ultraviolet (UVA) illumination device (INT100) for the *ex vivo* preparation and storage of pathogen-reduced, whole blood-derived or apheresis plasma. The INT100 is a microprocessor controlled device designed to deliver a controlled amount of UVA light, wavelength 320 – 400 nm, to up to two illumination containers simultaneously. The device is programmed to be able to control, deliver, record and store intensity and duration of light dose for each cycle.

**Table 1: Components of the INTERCEPT Plasma Processing Set (INT3110)**

Component	Description
Amotosalen (S-59, psoralen derivative) solution container	15 mL, 6 mM amotosalen in 0.924% NaCl packaged in a 20 mL, flexible, heat-sealed plastic container, with an integral light-protective overwrap and sleeve
Illumination container	Heat-sealed, plastic bag
Compound Adsorption Device (CAD)	Ground beads and binder in a sintered disk contained within ultrasonically welded housing
Plasma storage containers	Three plasma bags, ~400 mL storage capacity

The operating principle for the INTERCEPT Blood System for Plasma is illustrated in Figure 1. A container of whole blood derived or apheresis plasma is sterile connected to the INT3110 plasma processing set. The plasma flows through the amotosalen container into the illumination container. The illumination container is placed into the INT100 illumination device for UVA treatment while being mixed with horizontal agitation. Inactivation of potential pathogen or leukocyte contaminants in plasma is achieved through a photochemical treatment process in which amotosalen (S-59, psoralen derivative), a chemical capable of binding to nucleic acids, is added to the plasma and UVA illumination (320 – 400 nm wavelength) of the amotosalen-treated plasma induces covalent cross-linking of any nucleic acids to which amotosalen is bound; thereby, preventing further replication.<sup>1</sup> Treated plasma is then passed through the compound adsorption device (CAD) to remove unreacted amotosalen and free photoproducts. Finally, the plasma is distributed among two or three plasma bags for use or storage at or below -18°C. Processed plasma must be placed in a -18°C freezer within 24 hours of blood draw for pooled whole blood derived plasma or within 8 hours of apheresis collection.

**Figure 1: Illustration of the INTERCEPT Blood System for Plasma**



## DEVICE PERFORMANCE

The INTERCEPT Blood System inactivates a broad spectrum of viruses, gram-positive and gram-negative bacteria, spirochetes, parasites and leukocytes<sup>2-9</sup>. There is no pathogen inactivation process that has been shown to eliminate all pathogens. Certain non-enveloped viruses (e.g., HAV, HEV, B19 and poliovirus) and *Bacillus cereus* spores have demonstrated resistance to the INTERCEPT process.

**Table 2: Pathogen Reduction**

Pathogen	Log Reduction
<b>Virus (Enveloped)<sup>2,5</sup></b>	
HIV-1 IIIB, cell-associated	≥6.2
HIV-1 IIIB cell-free	≥6.1
DHBV <sup>a</sup>	4.4 to 4.5
BVDV <sup>b</sup>	≥4.5
HTLV-I	≥4.1
HTLV-II	≥4.7
West Nile virus	≥6.7
SARS-Associated Coronavirus	≥4.0
Chikungunya virus (CHIKV)	6.5
Influenza A virus (H <sub>5</sub> N <sub>1</sub> Avian Influenza)	≥5.7
<b>Virus (Non-Enveloped)<sup>2,5</sup></b>	
Parvovirus B19	1.8
Bluetongue virus	≥4.0
Adenovirus 5	≥5.6
<b>Bacteria<sup>2,6</sup></b>	
<i>Klebsiella pneumoniae</i>	≥6.7
<i>Yersinia enterocolitica</i>	≥6.6
<i>Staphylococcus epidermidis</i>	≥6.6
<i>Treponema pallidum</i>	≥5.4
<i>Borrelia burgdorferi</i>	≥9.9
<i>Anaplasma phagocytophilum</i> (HGE agent)	≥3.6
<b>Protozoan Parasite<sup>7,8</sup></b>	
<i>Plasmodium falciparum</i>	≥5.9
<i>Babesia microti</i>	≥4.9
<i>Trypanosoma cruzi</i>	>5.0

<sup>a</sup> DHBV model virus for HBV

<sup>b</sup> BVDV model virus for HCV

Using a limiting dilution assay (LDA), plasma processed with the INTERCEPT Blood System exhibited a 4 log<sub>10</sub> reduction of viable T cells. Using a DNA modification assay, plasma processed with the INTERCEPT Blood System demonstrated an average of one amotosalen adduct every 89 base pairs in leukocytes<sup>10</sup>.

*In vitro* Characterization of Plasma Processed with the INTERCEPT Blood System

Paired samples of plasma processed with the INTERCEPT Blood System and unprocessed (control) plasma derived from whole blood (n=62) or apheresis plasma (n=62) from healthy blood donors were compared to evaluate the *in vitro* functional activity of plasma proteins (Table 3). Apheresis plasma samples (processed and control) were frozen within 8 hours of donation, and *in vitro* tests were performed following at least 30 days of frozen storage at or below -18°C. For plasma from whole blood, three units of ABO-matched whole blood-derived plasma were pooled, and a portion of each pool was used to prepare untreated plasma control samples. Whole blood plasma was processed within 22 hours of phlebotomy, and the processed and control samples were frozen simultaneously, at or below -18°C, within 24 hours of collection.

**Table 3: *In vitro* Characterization of INTERCEPT Treated vs. Untreated Plasma**

	Apheresis Plasma		Whole Blood Derived Plasma	
	INTERCEPT (n=62)	Control (n=62)	INTERCEPT (n=62)	Control (n=62)
pH	7.38 ±0.05	7.38 ±0.04	7.38 ±0.03	7.41 ±0.05
Osmolality (mOsm/kg)	291 ±3	291 ±4	308 ±5	309 ±5
Prothrombin Time (s)	14.6 ±1.2	13.4 ±1.0	14.4 ±0.7	13.1 ±0.7
Activated Partial Thromboplastin Time (s)	28.5 ±3.1	24.8 ±2.5	27.0 ±1.7	24.2 ±1.4
Fibrinogen (mg/dL)	2.28 ±0.49	3.00 ±0.62	2.43 ±0.37	2.91 ±0.36
Factor II (IU/mL)	0.89 ±0.12	1.01 ±0.13	0.93 ±0.09	1.03 ±0.10
Factor V (IU/mL)	0.86 ±0.17	0.90 ±0.16	0.82 ±0.11	0.91 ±0.13
Factor VII (IU/mL)	0.77 ±0.23	0.97 ±0.28	0.81 ±0.13	0.99 ±0.14
Factor VIII (IU/mL)	0.92 ±0.35	1.31 ±0.46	0.73 ±0.20	0.91 ±0.25
Factor IX (IU/mL)	1.00 ±0.25	1.27 ±0.29	0.93 ±0.17	1.12 ±0.19
Factor X (IU/mL)	0.94 ±0.19	1.05 ±0.22	0.83 ±0.13	0.95 ±0.14
Factor XI (IU/mL)	0.92 ±0.21	1.08 ±0.24	0.90 ±0.13	1.02 ±0.14
vWF ristocetin cofactor activity	0.95 ±0.38 <sup>a</sup>	0.96 ±0.37 <sup>a</sup>	0.97 ±0.24	1.01 ±0.25
ADAMTS-13 (Antigenic)	118 ±25	116 ±24	128.8 ±20.6	124.7 ±17.9
ADAMTS-13 (Functional)	90 ±16	97 ±16	87.5 ±11.0	93.4 ±10.3
Antithrombin III	0.83 ±0.09	0.88 ±0.10	0.93 ±0.06	0.98 ±0.06
Protein C (IU/mL)	0.79 ±0.18	0.92 ±0.19	0.86 ±0.09	0.95 ±0.10
Protein S (IU/mL)	0.97 ±0.23	1.02 ±0.25	1.04 ±0.10	1.08 ±0.11
Alpha-2-plasmin inhibitor (IU/mL)	0.76 ±0.07	0.91 ±0.07	0.85 ±0.07	1.00 ±0.08
Thrombin-Antithrombin Complexes (µg/L) <sup>b</sup>	2.5 ±0.4	2.5 ±0.5	2.3 ±0.8	2.4 ±0.8
Factor VIIa (ng/mL)	<3.6	<3.6	<3.6	<3.6
Non-activated partial thromboplastin time (s)	104.2 ±17.9	94.0 ±11.4	91.8 ±11.4	91.8 ±10.6
C3a (ng/mL)	44.2 ±45.9	107.4 ±59.4	50.4 ±38.4	134.7 ±57.0

<sup>a</sup>n=61

<sup>b</sup>For samples below the lower limit of quantitation (LOQ), the LOQ (2.0 µg/L) was used for calculation of mean and SD.

## CONTRAINDICATIONS

- Contraindicated for preparation of plasma intended for patients with a history of hypersensitivity reaction to amotosalen or other psoralens.
- Contraindicated for preparation of plasma intended for neonatal patients treated with phototherapy devices that emit wavelengths less than 425 nm due to the potential for erythema resulting from interaction between ultraviolet light and amotosalen.

Note: include information about these contraindications in the labeling provided with transfusable plasma products prepared using the INTERCEPT Blood System for Plasma.

## WARNINGS AND PRECAUTIONS

- Only INTERCEPT Processing Sets for plasma are approved for use in the INTERCEPT Blood System for Plasma. Use only the INT100 Illuminator for UVA illumination of amotosalen-treated plasma. No other source of UVA light may be used. Please refer to the Operator's Manual for the INT100 Illuminator. Discard any plasma not exposed to the complete INT100 illumination process.
- Tubing components and container ports of the INTERCEPT Blood System for Plasma contain polyvinyl chloride (PVC). Di(2-ethylhexyl)phthalate (DEHP) is known to be released from PVC medical devices, and increased leaching can occur with extended storage or increased surface area contact. Blood components will be in contact with PVC for a brief period of time (approx. 15 minutes) during processing. The risks associated with DEHP released to into the blood components must be weighed against the benefits of therapeutic transfusion.
- Amotosalen-treated plasma may cause the following adverse reaction:

### *Cardiac Events*

In a randomized controlled trial of therapeutic plasma exchange (TPE) for TTP, five patients treated with INTERCEPT Blood System processed plasma and none with conventional plasma had adverse events in the cardiac system organ class (SOC) reported.<sup>11</sup> These events included angina pectoris (n=3), cardiac arrest (n=1), bradycardia (n=1), tachycardia (n=1) and sinus arrhythmia (n=1). None of these events resulted in documented myocardial infarction or death<sup>12</sup>. Monitor patients for signs and symptoms of cardiac events during TPE for TTP.

Note: include these "Warnings and Precautions" in the labeling provided with transfusable plasma products prepared using the INTERCEPT Blood System for Plasma.

## INSTRUCTIONS FOR USE

### Initial Setup

**Equipment Provided:** One (1) INT3110 Plasma Processing Set

**Equipment Available Separately:** INT100 Illuminator

**Equipment Required But Not Provided:** Sterile Connecting Device (SCD), Tube Sealer, Manual Tube Clamp (e.g., Hemostat)

- **INTERCEPT Processing Sets for plasma are for single use only. Do not reuse sets or components of sets.**
- This process is designed to be a functionally closed system. Treatment of plasma with INTERCEPT Blood System for Plasma does not replace applicable standards for processing in open and closed systems.

### Blood Collection

Apheresis or whole blood derived plasma may be used. Plasma volume must be within the range of 585-650 mL and red blood cell (RBC) content must be less than  $4 \times 10^6$  RBC/mL for adequate processing with this system.

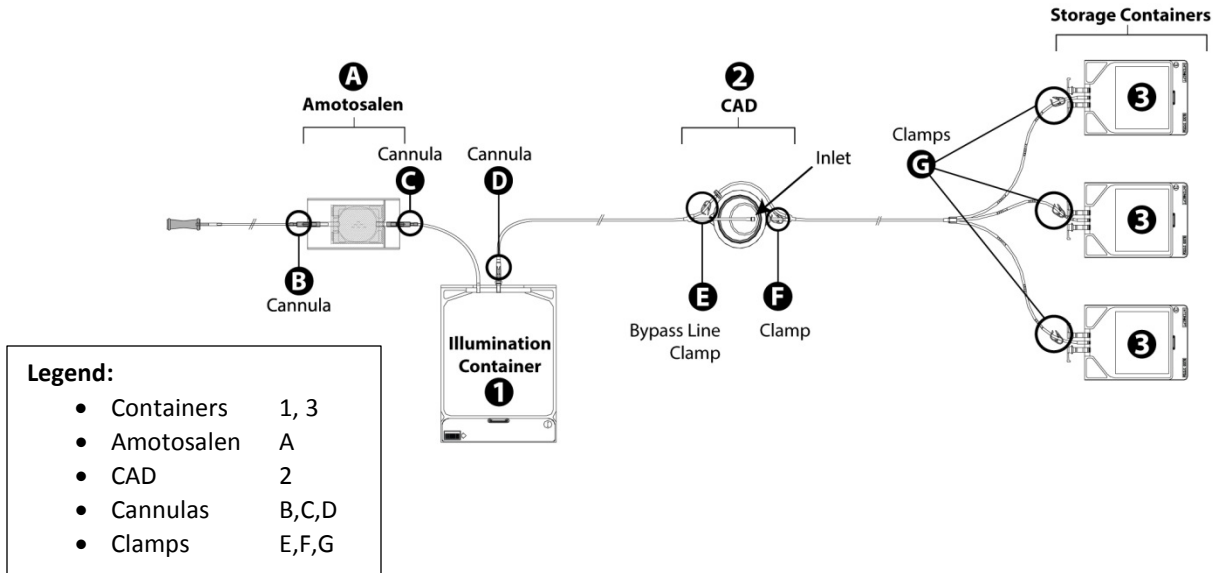
When pooling of plasma is required to meet the volume specification, pool plasma in a manner that maintains a functionally closed system. The INTERCEPT Blood System can accommodate pools of up to three units of whole blood derived plasma of the same ABO blood type, collected in the same anticoagulant solution.

Do NOT use previously frozen plasma.

### Plasma Processing

Refer to Figure 2 for labeling and identification of set components.

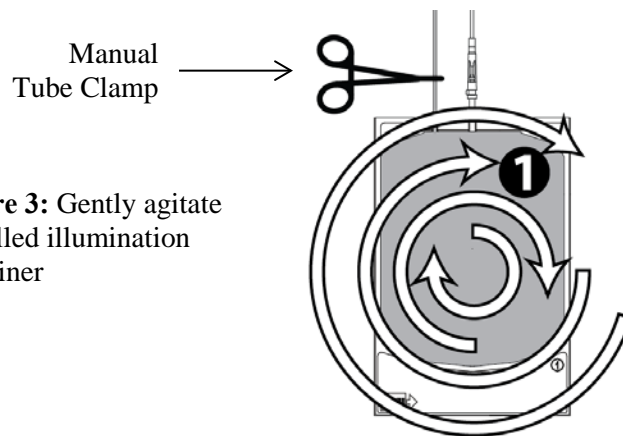
**Figure 2: INTERCEPT Processing Set for Plasma**



### I. Amotosalen Addition

**NOTE:** Amotosalen in contact with skin may result in photosensitization in the presence of ultraviolet light. If skin exposure occurs, flush exposed skin with water.

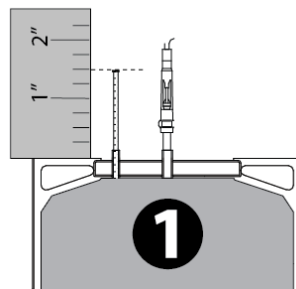
1. Remove set from package.
2. Weld tubing from plasma container to amotosalen container (A) tubing using SCD.
3. Disassemble set from organizer and remove rubber band. Save rubber band for assembly of CAD and storage containers during the illumination step.
4. If two plasma units will be produced by the INTERCEPT process, heat seal and remove one storage container (3).
5. Label storage containers (3) using appropriate donation identification. While labeling storage containers, separate them to ensure they do not adhere to one another.
6. Hang plasma container ensuring that the processing set containers/components do not come in contact with floor.
7. Break cannula (C) below amotosalen container (A) to let amotosalen flow into illumination container (1); visually verify amotosalen is present.
8. Break cannula (B) above amotosalen container (A) to let plasma flow through amotosalen container into illumination container (1).
9. Ensure that plasma drains completely from initial plasma container into illumination container (1).
10. Express air from the illumination container (1) into the amotosalen container (A).
11. When air is removed and plasma has fully drained back into the illumination container (1), manually clamp tubing above illumination container. Mix illumination container thoroughly by gentle agitation to ensure complete mixing of amotosalen and plasma (Figure 3).



**Figure 3:** Gently agitate the filled illumination container

12. Open manual tube clamp and express a small amount of plasma and amotosalen mixture into tubing, filling at least 1.5 inches of tubing. Close manual tube clamp.
13. Seal tubing between illumination container ( **1** ) and amotosalen container within the 1.5 inches of tubing (see Figure 4).

**Figure 4:** Heat seal filled tubing within 1.5 inches



14. Remove and discard initial plasma container, amotosalen container ( **A** ) and excess tubing.

**NOTE:** During illumination, tubing must be held within large compartment of illumination tray (see below).

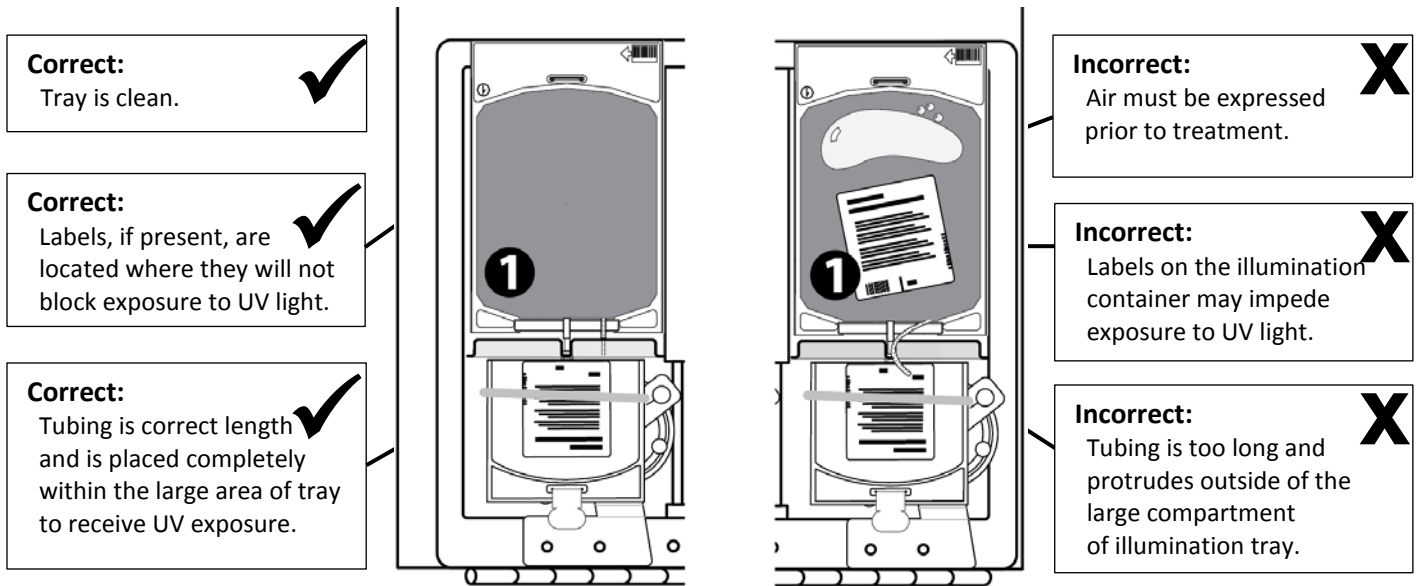
## II. Illumination

(Refer to INT100 Illuminator Operator's Manual for detailed instructions.)

**NOTE:** The inactivation process requires unimpeded light transmission through tray and illumination container. The illumination container and tubing must be within the large compartment of the illuminator tray. Tray must be clean and free from labels or other material (see Figure 5). Illumination container should lie flat in order to ensure complete illumination.



**Figure 5:** Proper way to load processing set into the illuminator tray

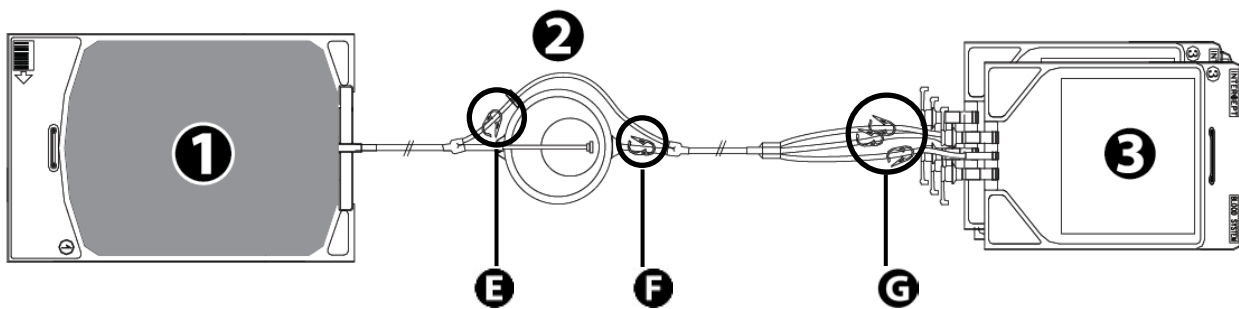


### III. Processing with Compound Adsorption Device (CAD)

Use gravity to flow plasma through the compound adsorption device (CAD) after illumination.

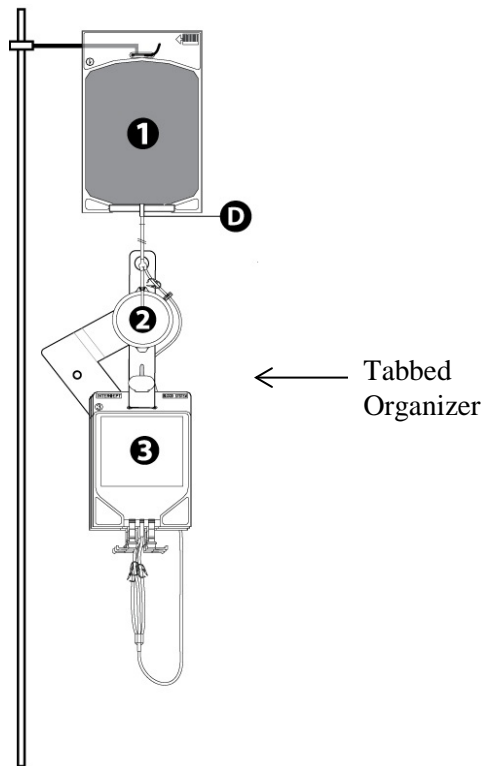
1. The position of the clamps is shown in Figure 6 below:

**Figure 6:** Clamps used during processing: ( **E** ) bypass line clamp, ( **F** ) clamp below CAD, ( **G** ) clamps above storage containers ( **3** ).



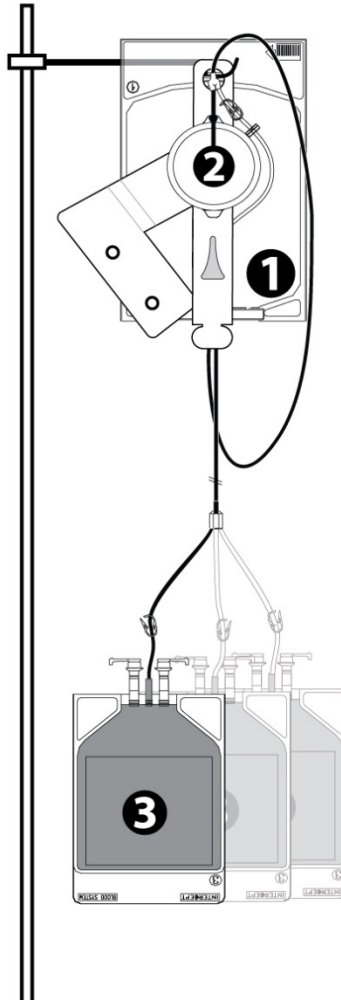
2. Hang illumination container ( **1** ), allowing CAD ( **2** ) to hang freely, with storage containers ( **3** ) kept in the tabbed organizer to keep them in an inverted position. (see **Figure 7**)

**Figure 7:**  
How to hang the  
Illumination Container



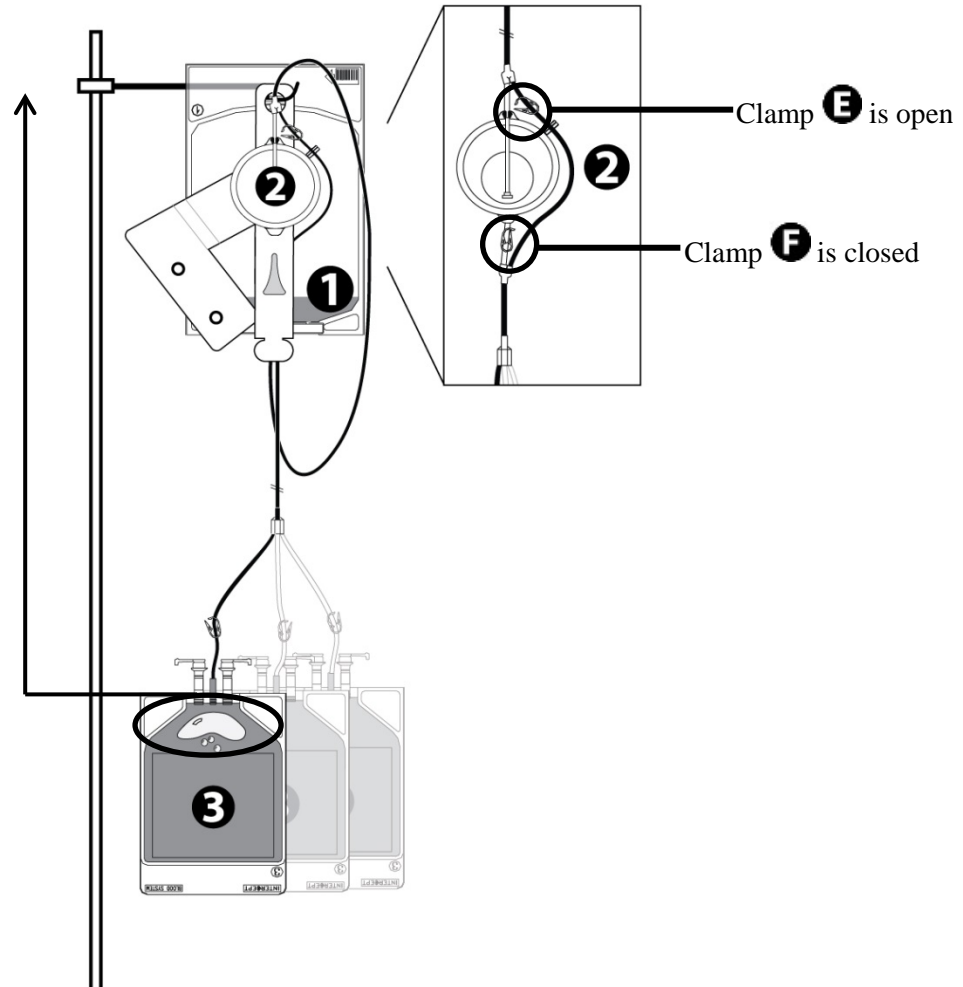
3. Close clamp ( **E** ) on bypass line; ensure all other clamps ( **F** and **G** ) are open.
4. Break cannula ( **D** ) on illumination container and allow plasma to flow through CAD ( **2** ) into storage containers ( **3** ).
5. Once plasma has emptied from illumination container and passed through CAD, close clamp ( **F** ) on tubing leading from the CAD.
6. Hang CAD ( **2** ) together with illumination container ( **1** ). Remove storage containers ( **3** ) from tabbed organizer on CAD and allow them to hang ports up. (see Figure 8)

**Figure 8:** How to hang the CAD with the illumination container

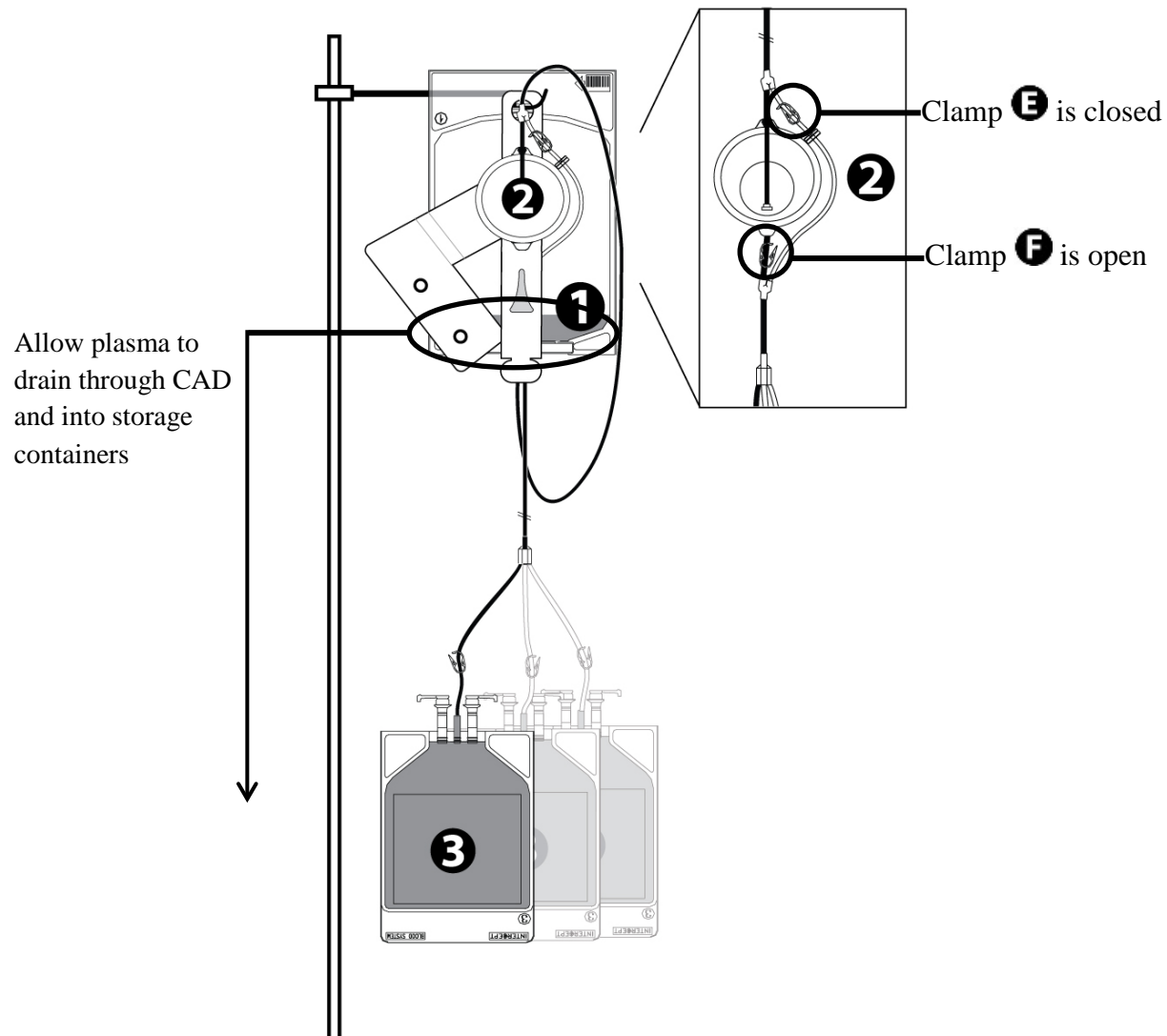


7. To ensure that storage containers are relatively free from air, express air from the first storage container into the second. Afterwards, express air from the second storage container into the third storage container.
8. Open clamp ( **E** ) on bypass line and completely express air from third storage container through bypass line, into the illumination container ( **1** ). (see Figure 9)

**Figure 9:** Express air from the third storage container into the illumination bag.



9. Close clamp ( **E** ) on the bypass line. (see Figure 10)
10. Open clamp ( **F** ) below the CAD, allowing plasma to drain into storage containers ( **3** ). (see Figure 10)

**Figure 10:** Drain plasma through CAD

11. Close clamps (**G**) on storage containers.
12. Redistribute plasma volume among storage containers, if necessary. Each storage container may hold up to a maximum of 325 mL of plasma. Redistribution of plasma may also occur after step 12 if containers are heat-sealed above the triple junction.
13. Disconnect storage containers (**3**) from set by heat sealing, allowing sufficient tubing length for segments if appropriate.
14. Discard CAD, illumination container, and any excess tubing. The INTERCEPT treatment process is now complete.
15. Seal tubing as appropriate for making segments, as needed.
16. Follow internal procedures for freezing plasma. Apheresis plasma must be frozen within 8 hours after collection. Pooled whole blood derived plasma must be frozen within 24 hours after collection of the oldest unit in the pool.

## STORAGE AND HANDLING

### *Processing sets*

- Do not use if tamper-evident package has been opened, signs of deterioration are visible, fluid path closures are loose or not intact, cannulae are broken or if there is no fluid in the amotosalen solution container.
- Protect the processing set package and tubing from sharp objects. Discard plasma product if there is a leak in the set during processing.
- Keep processing sets in the light-protective, aluminum foil pouch until time of use. Protect from direct sunlight or strong UVA light source.
- Do not store processing set above 25°C.
- Do not vent.
- Do not freeze.
- Unused processing sets may be stored for up to 20 days at room temperature (18 – 25°C) in the open aluminum foil pouch by folding and securing the open end of the pouch. Record the “Date Opened” and “Use By” date on the foil pouch label in the space provided. The processing sets removed from the aluminum foil pouch must be used within 8 hours.

### *Plasma*

- Plasma processed with the INTERCEPT Blood System must be stored in the plasma storage containers provided in the INT3110 processing sets.
- Processed plasma may be stored at or below -18°C (-0.4°F) for up to 12 months.
- Following frozen storage at or below -18°C (-0.4°F), thaw INTERCEPT Blood System processed plasma according to current license requirements and infuse within 24 hours if held at 1° to 6°C (33.8° to 42.8°F).
- Discard unused, thawed plasma after 24 hours.

## NONCLINICAL TOXICOLOGY

Nonclinical studies were conducted in mice, rats and dogs to evaluate the potential toxicity of single and repeated exposures to amotosalen, the synthetic psoralen derivative used in the INTERCEPT process to cross-link DNA and RNA. A single, intravenous injection of amotosalen alone resulted in mortality in rats at doses equal to or greater than 35,000-fold the anticipated human exposure from INTERCEPT Blood System processed plasma, on a dose per kilogram body weight basis. Lower doses (4,000- or 20,000-fold greater than the human exposure in dogs and rats, respectively) were not lethal, and resulted in transient clinical signs of toxicity (i.e. piloerection, inactivity, hunched posture and abnormal breathing in rats, and excessive salivation, convulsions, and non-lethal cardiac arrhythmias in dogs). No target organ toxicities were noted at necropsy.<sup>13</sup>

Animal experiments provided no indication of an increased toxicological risk for the use of plasma treated with amotosalen using the INTERCEPT Blood System, as compared to dosing with equivalent volumes of either homologous, untreated plasma, or saline or buffer control. Single dose studies with INTERCEPT processed plasma in dogs were non-toxic at amotosalen doses of 6,000-fold the expected clinical exposure, and repeated daily dosing in rats and dogs for 28 days with homologous plasma processed with the INTERCEPT Blood System showed no evidence of toxicity at 5,000-fold the expected amotosalen clinical exposure.<sup>13</sup>

Amotosalen was rapidly eliminated following intravenous dosing in mice and rats, with an initial plasma  $t_{1/2}$  of less than one hour. There was no evidence of amotosalen accumulation after repeated exposures over periods as long as 13 weeks. The primary route of excretion of amotosalen and its photo-byproducts was fecal.

No effects on fertility parameters were noted in male or female rats repeatedly dosed with amotosalen. In studies evaluating the effects of amotosalen dosing of pregnant rats or rabbits on embryo-fetal or peri-postnatal development, and in one study of neonatal rats dosed with amotosalen, there was no evidence of teratogenicity, or other reproductive or developmental toxicities.<sup>14</sup> No evidence of genotoxicity or mutagenicity was observed in the *in vitro* or *in vivo* mutagenicity studies of amotosalen.<sup>15</sup> In transgenic mice heterozygous for the p53 tumor suppressor gene, there was no evidence of carcinogenicity after repeated, three times weekly dosing for 6 months with amotosalen in plasma, at cumulative weekly doses approximately 150 times the human exposure from a single infusion of INTERCEPT processed plasma.<sup>13</sup>

## CLINICAL STUDIES

The safety and effectiveness of plasma prepared with the INTERCEPT Blood System were investigated in six clinical studies and two post-marketing studies including 704 patients treated with INTERCEPT Blood System processed plasma.

The tolerability, safety, and amotosalen clearance after transfusion of INTERCEPT Blood System processed plasma to healthy subjects was evaluated. This was an open label, step-wise ascending dose escalation (100, 200, 400, and 1000 mL) crossover trial; 15 healthy volunteers received autologous plasma processed with the INTERCEPT Blood System or untreated Fresh Frozen Plasma (FFP).<sup>16</sup> For patients receiving the processed plasma, the peak concentration of amotosalen at 1,000 mL was 11.5 ng/mL with a mean concentration at 16-24 hours of  $0.52 \pm 0.10$  ng/mL and a terminal half-life of 138.5 minutes. Comparison of coagulation factor activity following transfusion revealed no differences between transfusion of processed plasma versus FFP. No clinically relevant adverse events were observed in subjects exposed to INTERCEPT processed plasma at doses as high as 1,000 mL.

The transfusion of INTERCEPT processed plasma to healthy subjects anticoagulated with warfarin sodium was evaluated.

The effect of processing plasma with the INTERCEPT Blood System on vitamin K dependent coagulation factors was assessed in a prospective randomized, single-blind crossover, PK and safety trial in 27 healthy volunteers, receiving autologous plasma.<sup>16</sup> Autologous plasma samples, obtained by apheresis, were split and then either processed or frozen as FFP. Following a four day regimen (7.5 mg/day) of warfarin sodium to reduce vitamin K dependent coagulation factors, subjects received approximately 1,000 mL of processed plasma or FFP in random order. Blood samples to assess vitamin K dependent factor levels were drawn over 24 hours following transfusion. After a two-week washout period, subjects received the second transfusion with contralateral product following an identical warfarin regimen. No statistically significant differences for clearance, recovery, half-life, mean residence time, or volume of distribution for Factor VII were observed between processed plasma and FFP. Additionally, no differences in recoveries of other vitamin K dependent factors (FII, FIX, and FX) were observed. No clinically relevant adverse events were observed in subjects anticoagulated with warfarin sodium and transfused with 1,000 mL of INTERCEPT Blood System processed plasma.

The transfusion of INTERCEPT processed plasma to patients with multiple coagulation factor deficiencies was evaluated.

The first study in patients was a small pilot study that evaluated the efficacy and tolerability of INTERCEPT Blood System processed plasma versus untreated FFP in patients with acquired coagulation factor deficiencies.

This was a double-blind, prospective, randomized trial. This cohort of 13 patients (6 INTERCEPT processed plasma and 7 untreated FFP) primarily included patients with liver disease. Patients received a single transfusion of up to 2 liters of either INTERCEPT processed plasma or untreated FFP. There was no difference in the response of the prothrombin time (PT) or activated partial thromboplastin time (aPTT) at any time point after transfusion between INTERCEPT Blood System processed plasma and untreated FFP. No unexpected adverse events were observed in patients exposed to INTERCEPT Blood System processed plasma (604 to 1589 mL). One serious adverse event of pulmonary edema related to transfusion of 1589 mL of INTERCEPT processed plasma was reported. This event resolved with diuretic therapy.

Transfusion of INTERCEPT processed plasma to patients with acquired coagulopathy due to liver disease with and without liver transplantation was assessed.

Patients with acquired coagulopathy associated with liver disease requiring plasma transfusion to support either a major or minor surgical procedure (N=121) were evaluated for changes in PT and aPTT adjusted for the dose of plasma and patient's body weight, in a prospective, multi-center, randomized, controlled, double-blind clinical trial.<sup>17</sup> Fifty-one of the patients in the trial were enrolled for plasma transfusion support associated with orthotopic liver transplantation (OLT). The mean number of plasma units in the two groups was similar ( $12.4 \pm 13.4$  for INTERCEPT processed plasma and  $15.8 \pm 15.7$  for conventional plasma). The changes in PT and aPTT were not significantly different between patients who received processed plasma compared to FFP. Likewise, recovery of Factor VII was not significantly different between the two groups. Hemostatic evaluations using the prespecified modified WHO 5 point bleeding scale showed no statistically significant difference between groups receiving processed plasma or FFP. The mean numbers of RBC, platelets and other blood components were similar in both groups of patients. The average total dose of INTERCEPT Blood System processed plasma for all patients was  $2.8 \pm 3.0$  L compared to  $3.6 \pm 3.6$  L for untreated plasma. The average dose of INTERCEPT Blood System processed plasma for patients undergoing liver transplant was  $4.8 \pm 3.7$  L compared to  $5.2 \pm 3.6$  L with untreated plasma. There was no excess treatment related morbidity observed for patients supported with processed plasma compared to those supported with conventional plasma. Specifically, no differences were observed for the incidence of hepatic artery thrombosis, accelerated fibrinolysis, or thromboembolic events.

The transfusion of INTERCEPT processed plasma to patients with congenital coagulation factor deficiencies was conducted in a multi-center study.

A single-arm, Phase 3, open-label, multi-center, intent-to-treat study was conducted in 34 male or female patients  $\geq 2$  years of age with congenital coagulation factor deficiencies requiring FFP including Factors I, II, V, VII, X, XI, XIII, or deficiencies in anticoagulant proteins, Protein C or Protein S. Patients received transfusions of INTERCEPT Blood System processed plasma for pharmacokinetic analysis of the relevant deficient protein or for therapeutic indications.<sup>18</sup> Post-transfusion recovery of proteins was comparable to published *in vivo* recovery data for conventional FFP except for fibrinogen, Factor VII and Factor XI. The respective terminal half-lives and clearances for patients with deficiencies in coagulation Factors V, VII, X, XI, or anticoagulant Protein C were comparable to literature references. Terminal half-life results for fibrinogen, prothrombin and Factor XIII were lower relative to the medical literature. Prolonged pre-transfusion prothrombin time (PT) and activated partial thromboplastin time (aPTT) values decreased to within normal clinical ranges following transfusion. This study was not powered to evaluate efficacy in specific congenital factor deficiencies. The dosing regimen for specific congenital factor deficiencies has not been established. Nineteen of 34 patients experienced an adverse event related to plasma transfusion. Some patients received multiple transfusions during the two year study with a mean total transfusion volume of INTERCEPT Blood System processed plasma of 2,648 mL (range of 140 to 13,014 mL). The related adverse events were: skin rash (7), urticaria (19), bronchospasm (3), hemoglobinuria (1), chills (7), and nausea (4). The only adverse event classified as severe was 1 episode of nausea. One serious adverse



event of airway swelling was reported 3 hours after transfusion in a patient undergoing multiple attempts of intubation prior to general anesthesia.

The transfusion of INTERCEPT Blood System processed plasma to patients with Thrombotic Thrombocytopenic Purpura by therapeutic plasma exchange was studied.

In a prospective, randomized, controlled, double-blind trial, 35 patients with Thrombotic Thrombocytopenic Purpura (TTP) were evaluated for remission following therapeutic plasma exchange (TPE) with either plasma processed with the INTERCEPT Blood System or FFP.<sup>11</sup> The suggested TPE dose was a 1-1.5 plasma volume exchange per day (40-60 mL/kg/day). Remission was defined as platelet count  $>150 \times 10^9/L$  for two consecutive days without deterioration in neurologic status within 30 days of the first TPE. Both treatment groups (82% of patients transfused with processed plasma and 89% of patients transfused with FFP) achieved remission within 30 days ( $p = 0.658$ ). Median time to remission and relapse rates were not statistically different. The median volume of INTERCEPT processed plasma exposure was 35,400 mL. The only reported excess treatment related morbidity was in the Cardiac SOC. These events included: angina pectoris (3), cardiac arrest (1), bradycardia (1), tachycardia (1), and sinus arrhythmia (1). None of these events resulted in myocardial infarction or death.

The post-marketing experience with transfusion of INTERCEPT Blood System processed plasma to patients with Thrombotic Thrombocytopenic Purpura was evaluated in two specialized treatment centers using a two-period sequential cohort design.

In a retrospective study examining patients with TTP (N=31), 61% of patients treated with INTERCEPT Blood System processed plasma and 46% of patients treated with FFP achieved remission within 30 days ( $p = 0.570$ ). Also, 78% of patients treated with INTERCEPT Blood System processed plasma achieved remission within 60 days, with a median time to remission of 15 days.<sup>19</sup> The mean total exposure to both INTERCEPT Blood System processed and untreated plasma was comparable (32 L and 28 L respectively). No significant differences in related adverse events or related serious adverse events were observed between groups. The incidence of treatment emergent adverse events in the Cardiac SOC, including electrocardiographic abnormalities, was not increased for patients treated with INTERCEPT processed plasma. The incidence of treatment emergent serious adverse events in the Cardiac SOC was similar for patients treated with processed plasma and conventional plasma, respectively (cardiac arrest 1 vs 2; arrhythmia 0 vs 1; bradycardia 0 vs 1; nodal rhythm 0 versus 1; ventricular fibrillation 0 vs 1; acute coronary syndrome 1 vs 0; and angina pectoris 1 vs 0).

The post-marketing experience with transfusion of INTERCEPT Blood System processed plasma to patients undergoing liver transplant was assessed in a regional liver transplant center using a two-period sequential cohort design.

In a retrospective study of patients undergoing liver transplant secondary to acute or chronic liver disease, 335 liver transplants were performed in 328 patients with plasma transfusion support. The study examined blood product consumption, treatment differences in FFP volume transfused, total platelet dose transfused, and RBC components transfused from the time of surgery through post-operative day 7, as well as safety outcomes, such as hepatic artery thrombosis (HAT) within nine days of transplant and mortality within seven days of transplant. One hundred seventy four transplants in 171 patients were supported with INTERCEPT Blood System processed plasma, and 161 transplants in 157 patients were supported with conventional FFP. The median volume of INTERCEPT Blood System processed plasma (2,160 mL) required for transfusion support was not different from that of conventional plasma (1,969 mL). Similarly, the number of RBC and platelet components transfused to all patients supported with plasma were not different between the processed and conventional plasma cohorts. Overall, no clinically relevant differences were detected between the treatment groups in efficacy or safety measures.<sup>20</sup> The median exposure to INTERCEPT Blood System processed plasma was 2,160 mL. The only adverse events monitored in this study were hepatic artery thrombosis (HAT) up to 9 days after initial exposure to

processed plasma, and mortality. The incidence of HAT was not increased after exposure to INTERCEPT Blood System processed plasma compared to conventional plasma, (2.3% vs 5.0% respectively). Likewise, mortality was similar for processed and conventional plasma, (4.6% vs 3.7%).

## HEMOVIGILANCE (POST-MARKET) EXPERIENCE

### *Cerus Hemovigilance Study*<sup>21</sup>

An observational, prospective, uncontrolled, hemovigilance study conducted by Cerus evaluated 57,171 INTERCEPT Blood System processed plasma components transfused to 9,669 patients in 22,101 transfusion episodes. The primary endpoint of the post-market hemovigilance study was the number of transfusion episodes with at least one acute transfusion reaction (ATR) during routine use of INTERCEPT Blood System processed plasma. Thirty-two subjects (0.3%) experienced an ATR following 41 separate transfusion episodes (0.2%), including five subjects (0.05%) who experienced an ATR following more than one transfusion episode. The most common signs/symptoms of those ATRs were urticaria, chills, rash, and pruritus. Most ATRs were considered to be mild. Six ATRs were assessed as serious and possibly or probably related to study transfusion; the symptoms of these reactions were consistent with recognized transfusion reactions and included three instances of allergic reaction or symptoms of allergic reaction (e.g. rash, tachycardia, hypotension, respiratory symptoms, chills), two instances of fluid overload and one report of respiratory distress.

### *Post-marketing Experience in France*<sup>22-25</sup>

During the 3 year period after implementation of INTERCEPT Blood System processed plasma for routine use in France, the rates of acute transfusion reactions (ATR) for INTERCEPT plasma have been comparable to those of other plasma components, i.e., approximately 0.4 events per 1,000 plasma components.

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