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Stability of Coagulation Factors in Plasma Prepared with Photochemical Treatment (INTERCEPT) Stored for One Year

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ÉTABLISSEMENT FRANÇAIS DU SANG - ALSACE

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Introduction

Background: A photochemical treatment process using amotosalen HCl (S-59) and UVA light was developed to inactivate infectious pathogens and leukocytes in therapeutic plasma (INTERCEPT™, I-FFP). Previous studies have demonstrated inactivation of a broad spectrum of pathogens; and have evaluated clinical efficacy of I-FFP for support of patients with coagulopathies, and for plasma exchange of TTP (Table 1).

Aims: The present report describes process validation studies of the characteristics and stability of coagulation factors in I-FFP produced in a regional blood center, and stored for one year in conformance with French national standards for therapeutic plasma.

Table 1: Summary of Prior Clinical Trials

Phase	Objective	Patients
I	Safety, S-59 Kinetics	10
II	Factor VII Kinetics	27
II	Protein C Kinetics	17
II	Protein S Kinetics	16
III	Coagulopathy – Pilot	13
IIIA	Congenital Deficiencies	34
IIIB	Aquired Coagulopathy	121
IIIC	TTP	35

Figure 1: Mechanism of Action

The Mechanism of Action for plasma consists of amotosalen HCl, a psoralen molecule, and illumination with 3.0 J/cm² ultraviolet A (UVA) light treatment. The amotosalen compound penetrates cellular and nuclear membranes and intercalates into the helical regions of DNA and RNA. Covalent crosslinks to the nucleic acid base pairs form upon exposure to UVA light, blocking DNA and RNA replication. This process inactivates white blood cells and pathogens, rendering them unable to cause disease, while retaining the function of plasma, which does not require nucleic acid replication for therapeutic efficacy.

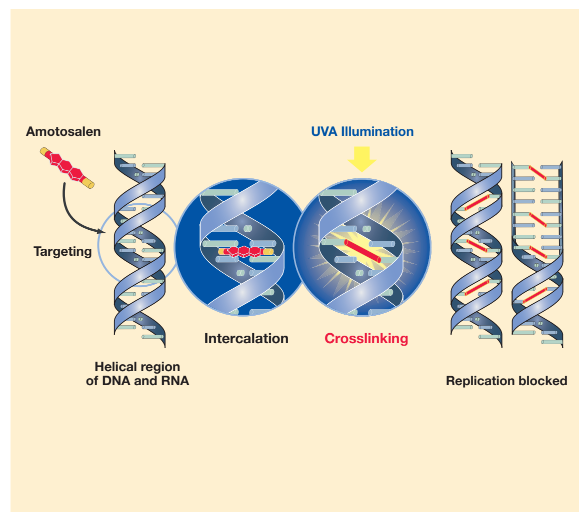
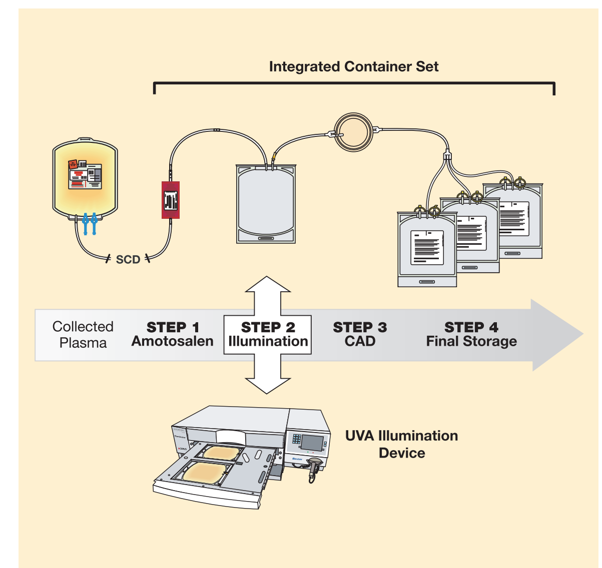


Figure 2: INTERCEPT Blood System for plasma

The collected plasma is sterile docked to the container set for processing. After addition of amotosalen (1) by gravity flow, and removal of the plasma and amotosalen containers, the plasma is illuminated with UVA light (2). Residual amotosalen and its photoproducts are reduced to low levels using a compound adsorption device (CAD) (3), before transfer to the storage containers (4).

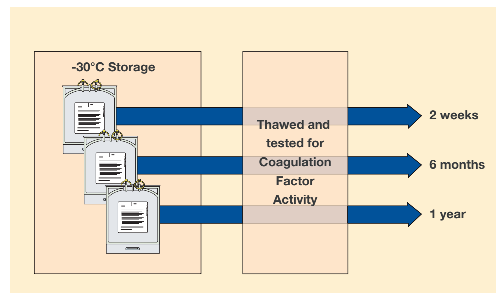


Methods

Thirty units composed of Group A, O, or B plasma (658 ± 5 mL) were collected by apheresis (MCS+. Haemonetics, Braintree, MA) using AB16 anticoagulant. Baseline samples for assay were withdrawn before photochemical preparation (635 mL plasma) with 15 mL of 6mM amotosalen and a 3 J/cm² UVA treatment. Following illumination (~8 min) and passage through a compound adsorption device (~20 min) to reduce levels of residual S-59, the treated plasma was divided into 3 equal units of ≥ 200 mL and flash frozen at –80°C, within 8 hours of collection, before transfer to –30°C for 12 month storage.

Figure 3: Study Design

Treated FFP units were withdrawn from storage after 2 weeks, 6 months, and 1 year to measure pH, total protein, albumin, IgG, IgM, IgA, fibrinogen, factors II, V, VII, VIII, IX, X, XI, XII, vWF, Proteins C and S, AT III, plasminogen, α-2 antiplasmin, D-dimers, TAT complex, PT, PTT, PF4, C3a and C5a.



Results

The average volume of units was 208 ± 3 mL. Average volume loss during processing was 6 ± 1%. All units had residual cellular content of platelets < 1x10⁹/L, WBC < 1x10⁴/L, and RBC < 1 x 10⁹/L. After 1 year of storage, total protein (60g/L), albumin (38g/L), IgG (8.4g/L), IgA (1.9 g/L) and IgM (1.0 g/L) were unchanged from baseline. After 1 year of storage, mean values for fibrinogen (g/L), coagulation factors (IU/dL), coagulation inhibitors (IU/dL), and markers of activation (C3a, C5a, d-dimer, and TAT) were within the ranges defined for therapeutic plasma.

Table 2: Coagulation Factor Levels Following One Year Storage at –30°C

Factor	Activity	Factor	Activity	Factor	Activity
Fibrinogen	2.6 g/L	IX	72 IU/dL	AT III	93 IU/dL
II	74 IU/dL	VIII:c	70 IU/dL	Protein C	94 IU/dL
V	84 IU/dL	VIII:vWF	110 IU/dL	Protein S	82 IU/dL
VII	78 IU/dL	XI	70 IU/dL	Plasminogen	83 IU/dL
X	82 IU/dL	XII	70 IU/dL	α-2-PI	75 IU/dL

Conclusions

FFP prepared with the INTERCEPT system retained coagulation factor activity levels and characteristics after 1 year of frozen storage (-30°C) in conformance with French national standards for therapeutic plasma. Approximately 36 units (200 mL) could be prepared per hour of illumination time. A single UVA platform is compatible with the operational requirements of a regional blood center producing 12,000 doses (200 mL) of therapeutic plasma and 12,000 doses of platelets per year.

- **FFP prepared with amotosalen + UVA retained adequate levels of procoagulant factors for hemostatic support**
- **FFP prepared with amotosalen + UVA retained adequate levels of antithrombotic factors for hemostatic support**
- **Treated FFP was not activated by the amotosalen + UVA process**
- **Both platelets and FFP can be prepared using a single platform for pathogen inactivation**

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