THERAFLEX MB-PLASMA

LEAD THE WAY IN BLOOD SAFETY

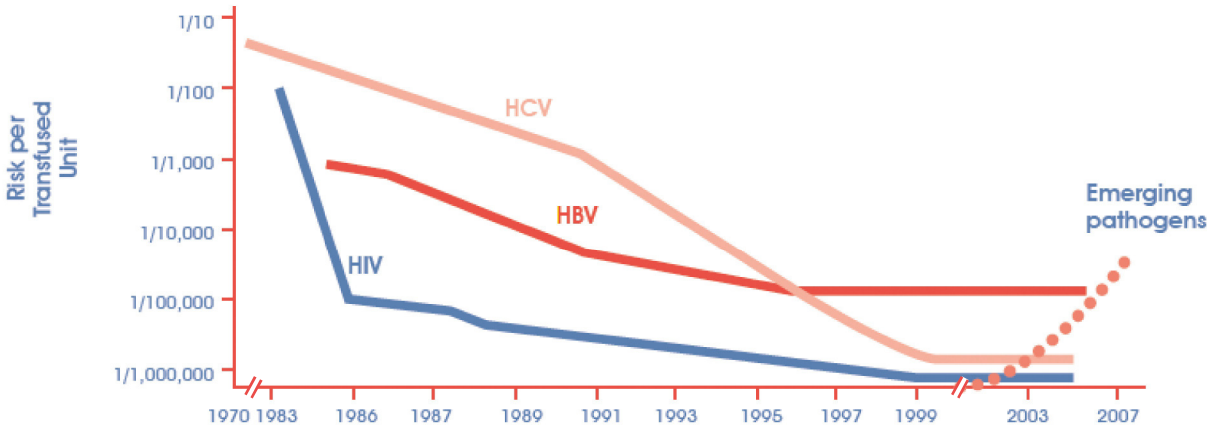
TRANSFUSION
macopharma
DESIGNED FOR LIFE

WHAT ARE THE DRIVERS OF BLOOD SAFETY?

The safety of fresh frozen plasma (FFP) in developed countries has improved significantly over the past two decades due to stringent donor selection criteria and improved screening tests.
In certain countries, safety is further enhanced by leucodepletion and pathogen inactivation. The greatest concern driving the development of pathogen reduction technologies is the prevention of blood supply contamination by new pathogens or new strains of known pathogens for which no tests currently exist. Additionally the accumulation of separate measures such as bacterial screening + viral testing + NAT + gamma irradiation increases the overall cost of blood components.
Pathogen inactivation raises the safety margin by inactivating pathogens that have gone undetected during screening due to seroconversion window periods or false results (negative or positive test).
Ultimately, pathogen inactivation provides a proactive approach, inactivating emerging pathogens before they enter the blood supply chain and before screening tests have been developed and implemented[1].

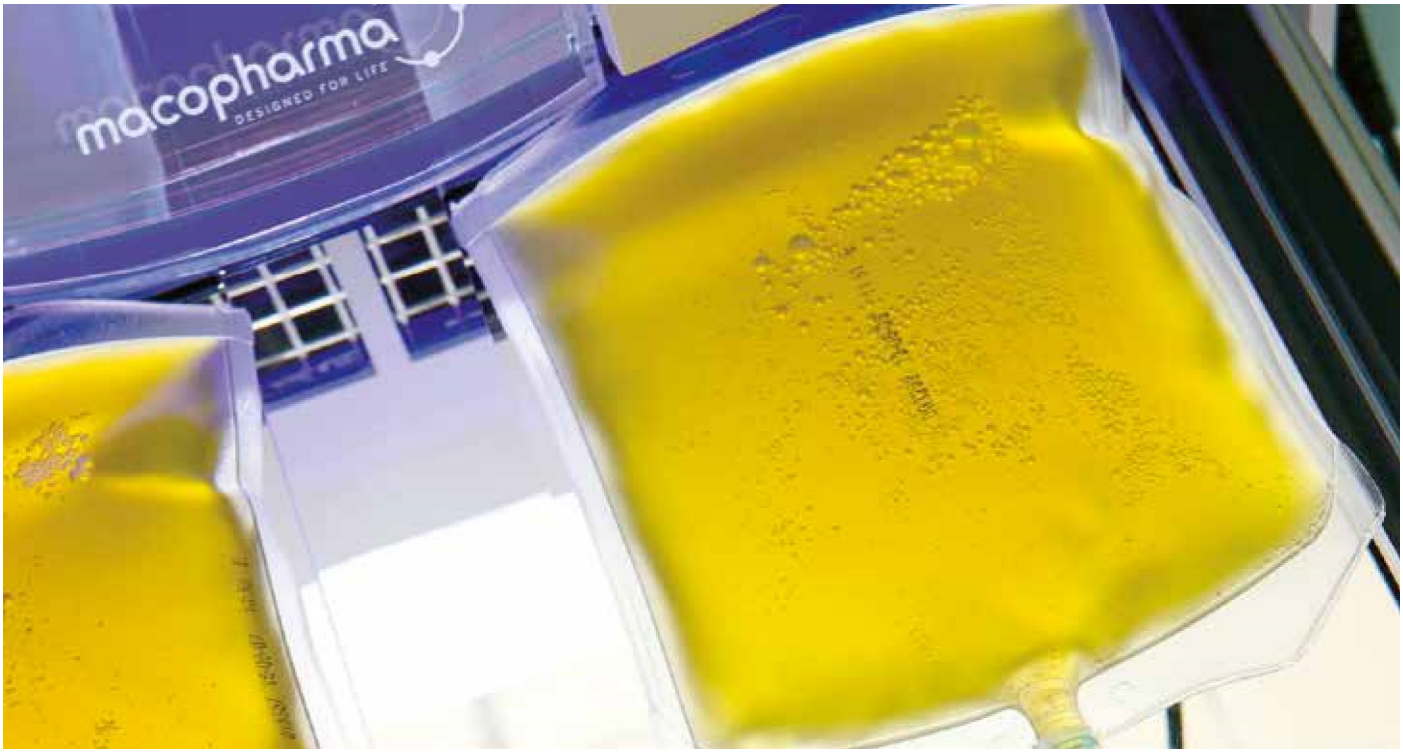
The SAFEST & USER-FRIENDLY technology for effective pathogen inactivation in SINGLE UNITS OF PLASMA

Transfusion-transmitted infections: risk per unit transfused.



Modified from Klein et al.[2]

THE THERAFLEX MB-Plasma PROCESS: ULTIMATE SAFETY FOR FFP TRANSFUSION

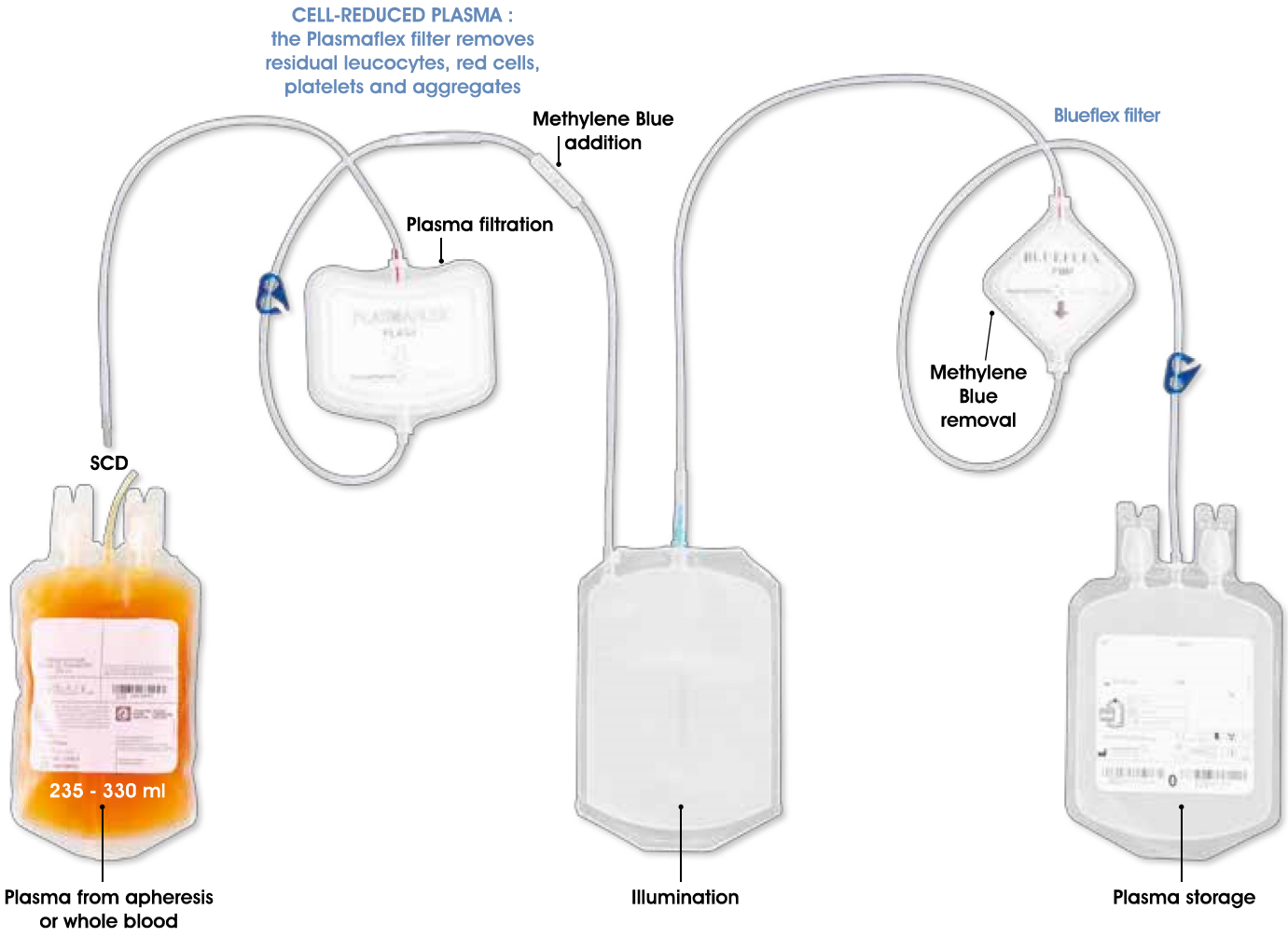


The THERAFLEX MB-Plasma kit incorporates a dockable set suitable for both whole blood and aphaeresis plasma. The process requires a simple dry set consisting of:

- a Plasmaflex filter for leucodepletion, removal of residual red cells, platelets and aggregates,
- a Methylene Blue pill (85μg anhydrous MB chloride),
- an illumination bag,
- a Blueflex filter for MB and photoproduct retention,
- and a storage bag.

The initial plasma volume range to be connected to the THERAFLEX MB-Plasma system is 235ml-330ml.

THE THERAFLEX MB-Plasma SYSTEM:
A user-friendly and effective pathogen inactivation technique against enveloped and non-enveloped viruses for single units of plasma.



The MacoTronic B2: the newest generation of illumination device for THERAFLEX MB-Plasma

FAST
- Short illumination cycle (~ 15 min.) due to optimal wavelength (630nm) of LED sources (light-emitting diodes)

SMALL
- Optimal dimensions for bench usage
- 2 bags / cycle
- Operated by touchscreen

SAFE
- Import/export with Local Information System (LIS) through the MacoTrace Data Management System
- Full GMP-Procedure
- Full IT reporting of illumination cycle

MECHANISM OF ACTION

Methylene blue is a phenothiazine-based photosensitizer with particular affinity for guanosine-cytosine pairs.

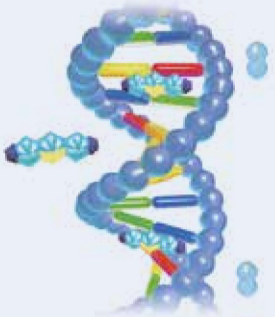
Methylene Blue molecule

FOCUS ON METHYLENE BLUE

- Methylene Blue has a monograph in the European Pharmacopeia (9th edition, 2017) and the US Pharmacopeia (USP 39-NF 34, 2016)
- Methylene Blue is in clinical use for organ staining, as disinfectant drug and for reversal of methemoglobinemia in very high concentrations (1,000 to 10,000 times higher than used in the THERAFLEX MB-Plasma)

It intercalates into viral nucleic acid and subsequent illumination generates singlet oxygen leading to guanosine oxidation and destruction of the viral nucleic acid preventing viral replication.[3,4]

1 Intercalation of Methylene Blue into nucleic acid



Methylene Blue pill MacoPharma (85µg / unit of plasma)

2 Visible light

3 Formation of singlet oxygen

4 Destruction of the viral nucleic acid

THERAFLEX MB-Plasma THROUGHPUT WITH THE MACOTRONIC B2

This is an example of a potential process design. Tailor made solutions corresponding to individual customer requirements are offered by Macopharma.

Simple and fast procedure (3 steps)
With a total processing time (1 MacoTronic B2) = 44'55"
Flexibility
- **Time between collection & freezing ≤ 24h**
- **Immediate availability of the treated plasma**

PROCESS SPECIFICATIONS

Preparation before illumination (sterile connection, plasma filtration, MB dilution, purge, seal off)	
Total time	15 min 30 sec
Hands-on time	4 min

Illumination process (loading, cycle, labeling, unloading)	
Total occupation time of the illuminator	16 min 45 sec
Hands-on time	1 min 45 sec

Preparation after illumination (transfer, purge, seal off)	
Total time	12 min 40 sec
Hands-on time	40 sec

TOTAL PROCESSING TIME	**44 min 55 sec**
TOTAL HANDS-ON TIME	**6 min 25 sec**

PROCESS THROUGHPUT

Design: 1 FTE* / 3 MacoTronic B2	
Hourly throughput	18.25 bags/hour
Daily throughput	146 bags/day**
Annual throughput	37,960 bags/year**

* FTE = Full Time Equivalent
** 8 hours a day, 260 worked days per year

PLASMA QUALITY AFTER THERAFLEX MB-Plasma TREATMENT

Plasma quality is maintained after treatment:

- No influence on complement system, inhibitors of coagulation, fibrinolysis markers or ADAMTS13
- Coagulation factors and activation are only moderately affected (Fibrinogen, Factor V, VIII, XI) and remain within the specifications set by the Council of Europe Guidelines
- Moderate enhanced thrombin time and aPTT
- Very little effect on the strength of clot formation as assessed by thrombelastometry (Cardigan et al., Transfusion 2009)[16]

PLASMA QUALITY MAINTAINED

The clinical indications for THERAFLEX MB-Plasma are in most cases the same as for standard FFP .

PLASMA PARAMETERS OF WHOLE BLOOD-DERIVED PLASMA AFTER MB TREATMENT:

PARAMETER	NORMAL VALUES	THERAFLEX MB-PLASMA (MACOPHARMA)
Fibrinogen (FI) (Clauss) g/l	1.5 - 3.5	**1.91[5], 2.11[6], 1.97[7], 2.00[8], 1.95[9], 2.4[10], 2.3[11], 2.14[21], 2.23[22], 2.35[23], 2.31[23], 2.29[23]**
Prothrombin (FII) U/ml	0.7 -1.3	**0.96[5], 0.98[9], 0.99[10]**
Factor V U/ml	0.7 -1.3	**0.86[5], 0.79[12], 0.84[6], 0.76[7], 0.79[9], 1.01[10], 1.02[11]**
Factor VII U/ml	0.7 -1.3	**0.98[5], 1.02[8], 1.01[9], 1.03[10]**
Factor VIII U/ml	0.5 -1.5	**0.74[5], 0.88[6], 0.83[7], 0.66[8], 0.62[9], 0.81[10], 0.90[11] 0.74[21], 0.80[22], 1.08[23], 0.70[23], 0.67[23]**
Factor IX U/ml	0.5 -1.5	**1.15[5], 0.88[7], 0.96[9], 1.00[10]**
Factor X U/ml	0.7 -1.3	**1.02[5], 1.01[9], 1.06[10]**
Factor XI U/ml	0.7 -1.3	**0.76[5], 0.84[7], 0.52[8], 0.75[9], 0.82[10], 0.82[11]**
Antithrombin U/ml	0.7 -1.3	**0.94[5], 0.96[7], 1.12[10], 0.87[11]**
Protein C U/ml	0.7 -1.3	**0.96[5], 0.89[7], 1.10[10], 0.95[11]**
Protein S U/ml	0.7 -1.3	**1.12[5], 0.991[9], 0.75[10], 0.94[11]**
vWF cleaving protease U/ml	0.8-1.2	**1.11[10], 1.311[9], 0.74[9], 0.50[11]**
PT (sec)	11 -15	**13.1[5]**
INR	0.9 -1.3	**1.08[5], 1.0[10]**
APTT (sec)	23 -35	**34.1[5], 40[8], 34[10]**
Prothrombin Fragments F1+2 (nM/L)	0.4 -1.4	**1.220[5], 0.85[9], 1.03[11]**
Total protein (g/l)		**59[5]**
Albumin (g/l)		**36[5]**
K^+ (mMol/l)		**3.2[5]**

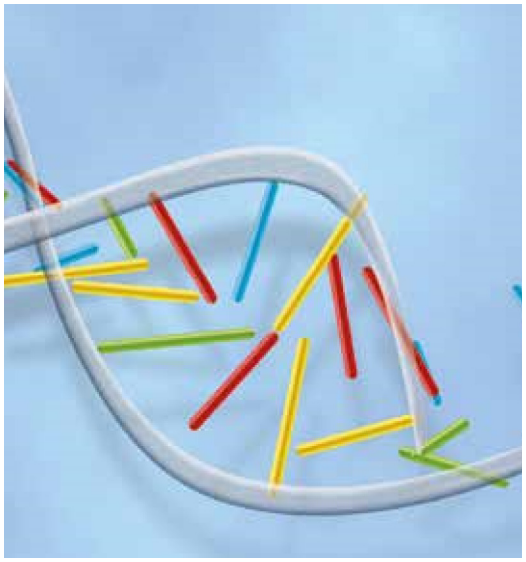
SAFETY PROFILE OF THERAFLEX MB-Plasma

When exposed to visible light, MB is highly effective in inactivating lipid-enveloped viruses such as HIV, HBV, HCV and the newly emergent West Nile Virus, non-enveloped viruses such as Parvovirus B19 and bacteria.

INACTIVATION OF NON-ENVELOPED VIRUSES

VIRUS	FAMILY	REDUCTION RATE (log 10)
Human adenovirus 5 (HAdV-5)	Adenoviridae	≥ 5.3
Parvovirus B19	Parvoviridae	≥ 5.0
Simian virus 40 (SV40)	Polyomaviridae	≥ 4.0
Feline calicivirus (FCV)	Caliciviridae	≥ 3.9

Efficiency on HAV and Polio: less than 1 log



INACTIVATION OF ENVELOPED VIRUSES

VIRUS	FAMILY	REDUCTION RATE (log 10)
Sindbis (SINV)	Togaviridae	≥ 9.7
Bovine herpes (BoHV-1)	Herpesviridae	≥ 8.1
Semliki Forest (SFV)	Togaviridae	≥ 7.0
Chikungunya (CHIKV)	Togaviridae	≥ 6.6
Duck Hepatitis B (DHBV)	Hepadnaviridae	≥ 6.0
Classical Swine Fever, Hog Cholera (CSFV)	Flaviviridae	≥ 5.9
West Nile (WNV)	Flaviviridae	≥ 5.8
Zika (ZIKV)	Flaviviridae	≥ 5.7
Human immunodeficiency virus 1 (HIV-1)	Retroviridae	≥ 5.5
Pseudorabies, Suid Herpes Virus (PRV)	Herpesviridae	≥ 5.5
Herpes Simplex (HHV-1)	Herpesviridae	≥ 5.5
Bovine Viral Diarrhea (BVDV)	Flaviviridae	≥ 5.4
Influenza A (H1N1)	Orthomyxoviridae	≥ 5.1
Avian infectious bronchitis (IBV)	Coronaviridae	≥ 4.9
Vesicular Stomatitis (VSV)	Rhabdoviridae	≥ 4.9
Dengue 1-4 (DENV)	Flaviviridae	≥ 4.5 - ≥ 5.8
Influenza A (H3N2)	Orthomyxoviridae	≥ 4.4
Cytomegalovirus (CMV)	Herpesviridae	≥ 4.1
Hepatitis C (HCV)	Flaviviridae	≥ 3.8

*BVDV: Model for HCV, MERS CO et ZIKA.
**PRV: Model for CMV, HBV.

A final virus content below the detection limit implies a depletion at least as equivalent as the initial virus content.

REDUCTION OF PARASITES

PARASITE	LOG10 REDUCTION	DISEASE
Trypanosoma cruzi	≥ 4.9 to ≥ 5.8	Chagas

REDUCTION OF CELLS (INCLUDING INTRACELLULAR VIRUSES)

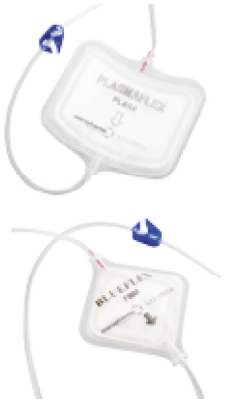
MEAN OF N=12	TEST SYSTEM	LIMIT OF DETECTION	STARTING PLASMA	AFTER PLASMAFLEX FILTRATION	END PRODUCT
Leucocytes/µl	Plasmatest FACS	< 1.3 rWBC/µl	20.4	< LD	< LD
Red cells/µl	Plasmatest FACS	< 3.0 rRBC/µl	261.0	< LD	< LD
Platelets/µl	Sysmex SF3000	< 10,000 rPLT/µl	14,250*	< LD	< LD

*4 out of 12 above 10,000 rPLT/µl
No value above the limit of detection after filtration

Plasma filtration not only decreases transfusion reactions and HLA alloimmunisation but also provides the benefit of removing cell-associated pathogens such as cytomegalovirus (CMV) and human T-cell lymphotropic viruses (HTLV) I and II.

REDUCTION OF TRANSFUSION-RELEVANT BACTERIA OR BACTERIAL SPORES DUE TO THE THERAFLEX MB-Plasma PROCEDURE FILTRATION STEPS

BACTERIA SPECIES	CUMULATIVE LOG10 REDUCTION FACTOR
Escherichia coli **(PEI-B-19)**	≥ 4.8
Staphylococcus epidermidis **(PEI-B-06)**	≥ 4.9
Staphylococcus aureus **(PEI-B-23)**	≥ 4.8 and ≥ 5.9
Bacillus cereus **(PEI-B-07)**	≥ 4.9
Klebsiella pneumoniae **(PEI-B-24)**	≥ 4.8
Bacillus subtilis spore preparation **(DSM 618)**	≥ 5.0
Brevundimonas diminuta **(DSM 1635)**	≥ 3.7 and 5.2



THERAFLEX MB-Plasma presents a HIGH SAFETY PROFILE EFFICACY ON:

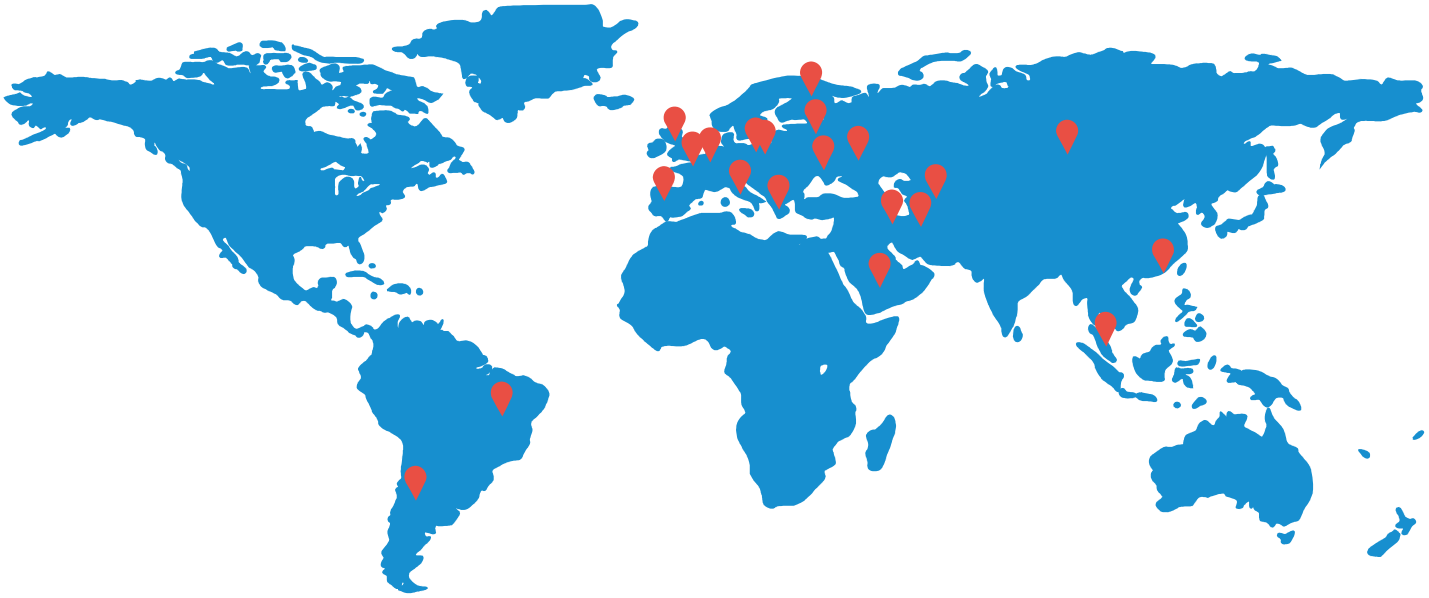
- **Enveloped and non-enveloped viruses**
- **Parasites such as *Trypanosoma cruzi***
- **Unknown or untested pathogens**
- **Cells (intracellular viruses), leucocytes, red cells and platelets**
- **Bacteria**

Bacterial reduction is achieved after both filtration steps (Plasma filtration with the **PLAS4 filter** and MB-treated plasma filtration with the **Blueflex filter**) in the treated plasma.
The overall reduction capacity of the THERAFLEX MB-Plasma system is sufficient to prevent transfusion-transmitted bacterial infections, taking into account the concentration of bacteria normally present in contaminated therapeutic plasma[25].

CLINICAL EXPERIENCE AND WORLDWIDE PRESENCE

Since 1992, over 7 million units of MB-FFP have been transfused in various clinical settings. Currently there is clinical experience with MB-treated plasma, produced with the THERAFLEX MB-Plasma system, for more than 20 years in more than 19 countries, with an excellent safety profile[26-32].

Clinical experience of THERAFLEX MB-Plasma:
Routine use in Europe, South America and Asia Pacific.



Countries:

Germany
Spain
Greece
Italy
United Kingdom
Belgium
Malaysia

Argentina
Russia
Belarus
Austria
Brazil
Singapore
Armenia

Kazakhstan
Turkmenistan
Hong Kong
Saudi Arabia
Poland
Ukraine

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Lead the way in blood SAFETY

THERAFLEX MB-Plasma

The THERAFLEX MB-Plasma is a CE marked medical device.
It is not available for sale in the United States.

Worldwide regulatory approvals:

Argentina: The National Administration of Drugs, Foodstuffs and Medical Technology (ANMAT)
Armenia: Ministry of Health of the Republic of Armenia
Austria: Austrian Medicines and Medical Devices Agency (AGES MEA)
Belarus: Ministry of Health
Belgium: Federal Agency for Medicines and Health Product (FAMHP)
Brazil: ANVISA
Canada: Health Canada
Croatia: Agency for Medicinal Products and Medical Devices
Czech Republic: Ministry of Health of Czech Republic
Germany: Paul-Ehrlich Institute (PEI)
Greece: National Organization for Medicines (EOF)
Hong-Kong: Medical Device Control Office (MDCO)
Italy: Ministry of Health
Kazakhstan: Ministry of Health
Malaysia: Medical Device Authority (MDA), Ministry of Health Malaysia
Mexico: Ministry of Health
Poland: Office for Registration of Medicinal Products, Medical Devices and Biocidal Products
Russia: Ministry of Health
Saudi Arabia: Saudi Food & Drug Authority (SFDA)
Singapore: Health Science Authority (HSA)
Spain: Agencia Española de Medicamentos y Productos Sanitarios (AEMPS)
Switzerland: Swissmedic
Turkmenistan: Ministry of Health and Medical Industry of Turkmenistan
Ukraine: Ministry of Health
United Kingdom: National Health Service (NHS)

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