Planova as a Virus Barrier for Biopharmaceutical Plasma Products



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Technical Marketing
Bioprocess Division
Asahi Kasei Medical Co., Ltd

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IPFA ASIA PACIFIC WORKSHOP
Taipei Medical University, Taipei, Taiwan

Asahi Kasei's Core Operating Companies

Holding company

Asahi Kasei Corporation

Core operating companies

- Asahi Kasei Chemicals
- Asahi Kasei Fibers
- Asahi Kasei Homes
- Asahi Kasei Construction Materials
- Asahi Kasei Microdevices
- Asahi Kasei E-materials
- Asahi Kasei Pharma
- Asahi Kasei Medical
- ZOLL Medical

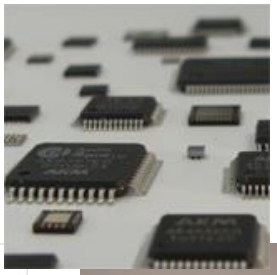
Operating segments

- Chemicals
- Fibers
- Homes
- Construction Materials
- Electronics
- Health Care
- Critical Care

Business sectors

- Chemicals & Fibers
- Homes & Construction Materials
- Electronics
- Health Care











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About Asahi Kasei Medical



Hemodialysis

Developed based on the Asahi Kasei core technology of hollow-fiber membrane separation, our polysulfone-membrane dialyzers (artificial kidneys) feature superior biocompatibility and permeability. With distribution extending to more than 70 countries and growing, we continue to help more diabetes patients around the world enjoy a better quality of life.



Therapeutic apheresis

Our innovative therapeutic apheresis devices enable new possibilities for the treatment of autoimmune and intractable diseases for which drugs are ineffective or unsuitable. Therapeutic apheresis is used to treat a wide range of intractable diseases such as neurological diseases, ulcerative colitis, and hepatic insufficiency. Blood is drawn from a patient and circulated through the device which removes pathogenic substances by separation or adsorption; the treated blood is then returned to the patient. We are the world's leading producer of devices and systems for therapeutic apheresis, based on our core technologies of membrane separation and selective adsorption.



Leukocyte reduction

We are the world's leading manufacturer of filters for reduction of leukocytes from blood components for transfusion. By adsorbing leukocytes in an ultrafine fiber membrane, Sepacell™ leukocyte reduction filters help to prevent adverse reactions to blood transfusion such as headache, chills, or fever.



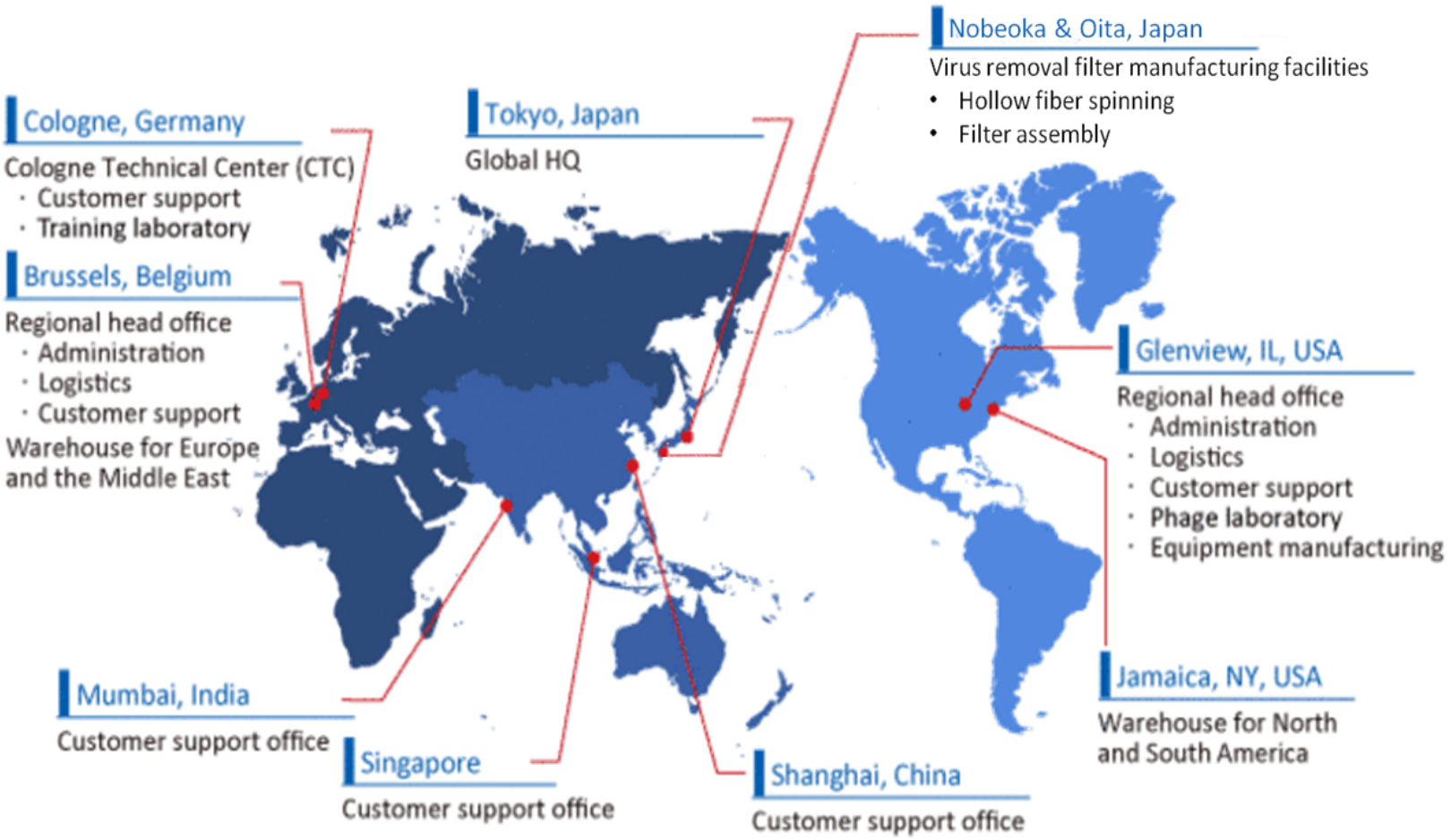
Bioprocess products

We manufacture a range of filters and equipment for the production of biotherapeutics and plasma derivatives. Our Planova™ virus removal filters contribute to enhanced safety in the production of plasma derivatives and biopharmaceuticals throughout the world.

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Key Locations

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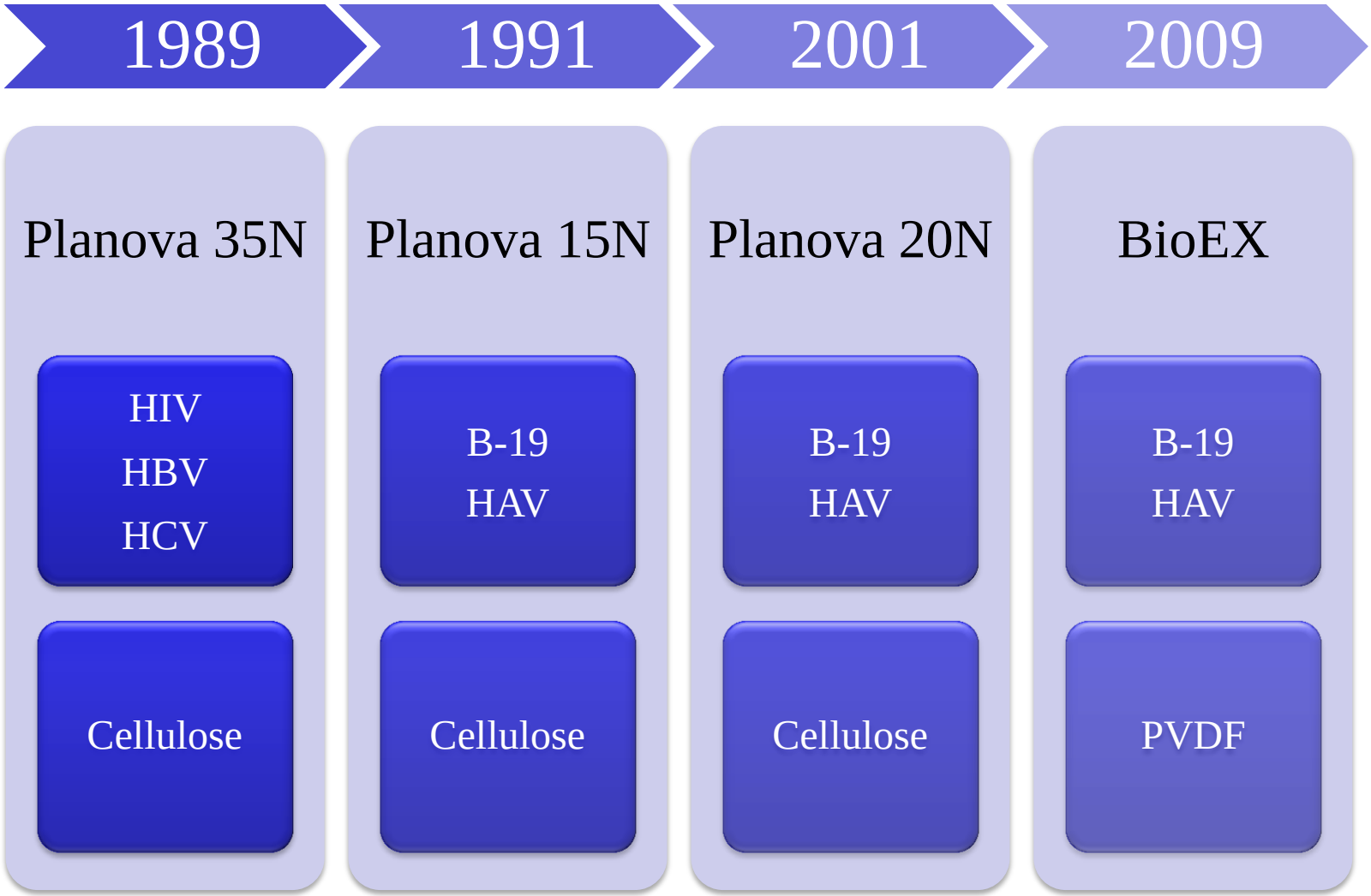
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1. Introduction of Asahi Kasei
2. Lineup of Planova Products
3. Planova as the robust virus removal step

2. Line up of Planova Products

Line up of Planova Products

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Planova filters

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Planova 15N, 20N, 35N

- Membrane material: Cuprammonium regenerated cellulose
- Max pressure: 98 kPa

Planova BioEX

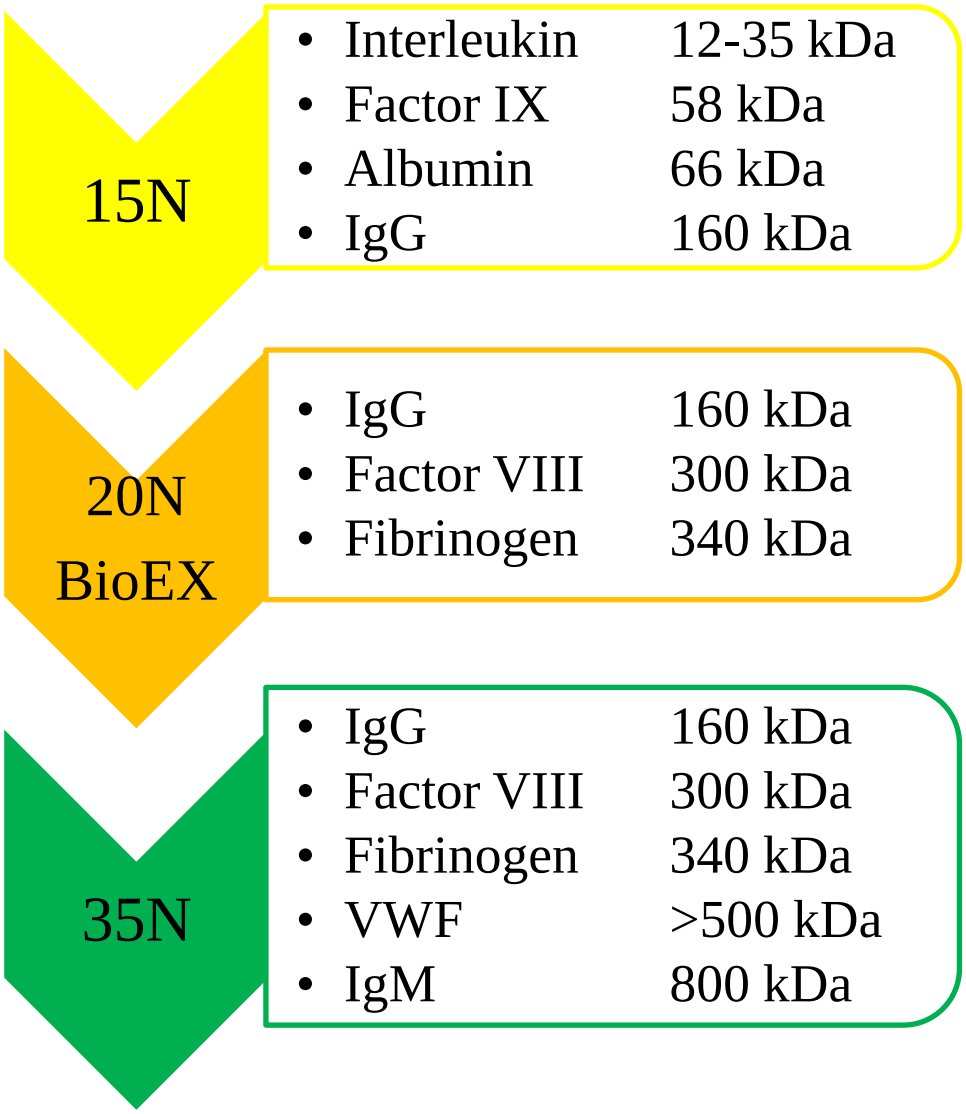
- Membrane material: Hydrophilized polyvinylidene Difluoride (PVDF)
- Max pressure: 343 kPa





Application Examples

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3. Planova as the robust virus removal step

Potential for viral transmission

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- -1990's: Non-virally inactivated Coagulation factor concentrates have caused widespread transmission of HIV, HCV and HBV.

- 1990’s - early 2000’s: Infectious non-enveloped viruses were detected in certain plasma-derived medicinal products virally-inactivated by technologies not affecting non-enveloped viruses

PPSB	**1989**	**HIV**
F-VIII	**1992**	**B19**
F-VIII	**1992**	**HAV**
Ivlg	**1993**	**HCV**
PPSB	**1994**	**HBV**
F-VIII	**1995/96**	**HAV**
F-VIII	**1997**	**HAV**

Safety Tripod

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I. Sourcing Careful Raw Material Selection
Biologic Raw Materials => inherent Risk of Virus contamination

II. Clearance
Validation of virus inactivation or removal (**clearance**) by the manufacturing process

III. Testing
Testing of donations including testing of plasma pool



Guideline on Plasma-derived products

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It is desirable in most cases to incorporate two distinct effective steps which complement each other in their mode of action such that any virus surviving the first step would be effectively inactivated/removed by the second; at least one of the steps should be effective against non-enveloped viruses.

(EMA/CHMP/BWP/706271/2010)

It is desirable to investigate the contribution of more than one production step for virus reduction and at least two orthogonal steps should be assessed. Orthogonal steps are defined as process steps where different mechanisms are responsible for virus inactivation/**removal**. The criteria for an effective step have been outlined in Note for Guidance on Virus Validation Studies .

(CPMP/BWP/268/95)

Virus removal/inactivation procedures of plasma products

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Virus removal

Chromatography：AEX, CEX, Affinity

Virus removal filter: Planova, Ultipore, Viresolve, Virosart

Virus inactivation

Pasteurisation

Solvent/Detergent (SD)：TNBP/Triton X-100

Low pH：～pH4

Dry-heat treatment

Caprylic acid treatment

Virus removal filter

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protein solution

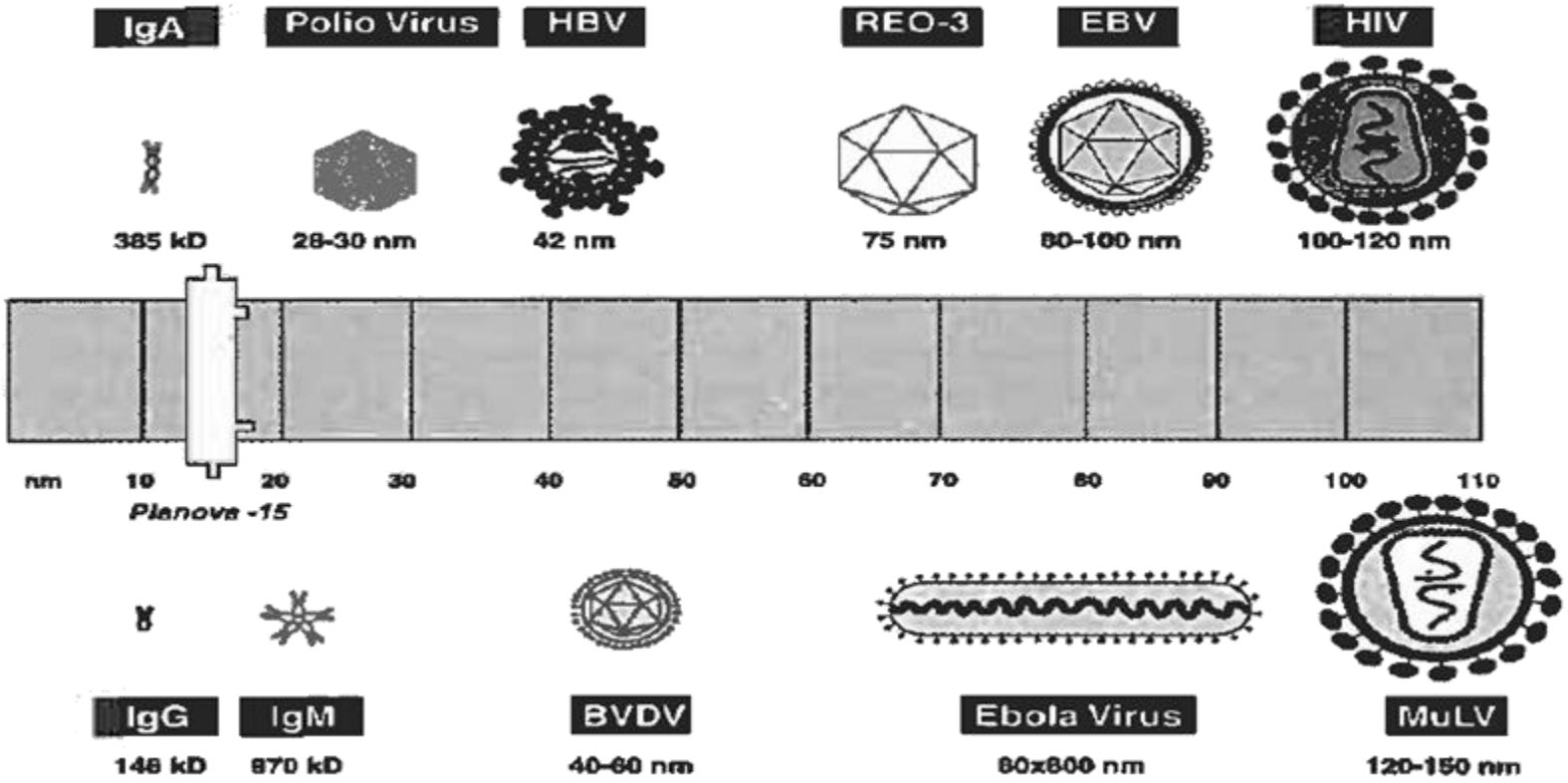
Planova provides robust
Virus Removal step

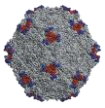
Easy!

Virus free
protein solution

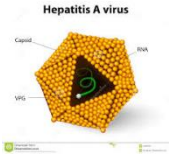
The challenge

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B19



HAV

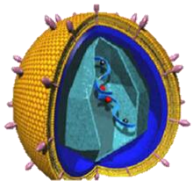


Image: Retrovirus

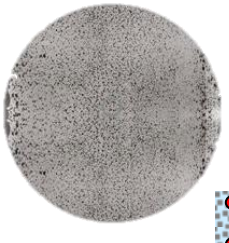
Marx, Nature Biotechnology Vol14, 1996

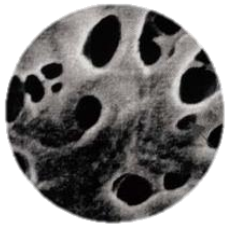
Planova filtration mechanism

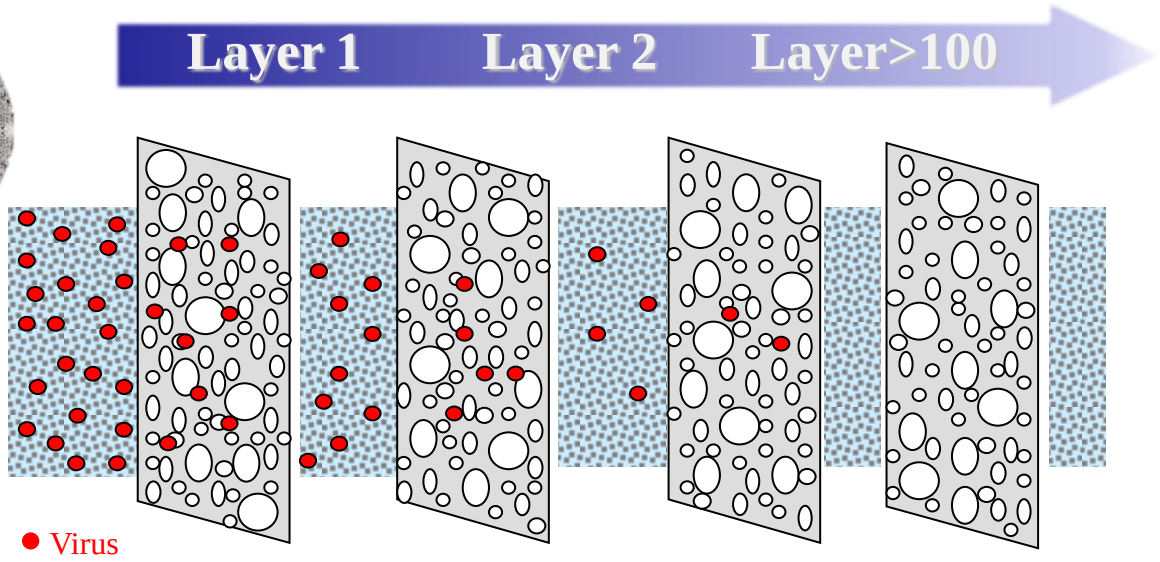
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Multi Layered Structure and Multi Step Filtration

Proof of HIV removal by Planova filter

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Vox Sang 1989; 56, 230-236

© 1989 S. Karger AG, Basel
0042–9007/89/0564–0230 $ 2.75/0

A Novel Method for Removal of Human Immunodeficiency Virus: Filtration with Porous Polymeric Membranes

Yoshiaki Hamamoto[a], *Shinji Harada*[a], *Susumu Kobayashi*[a], *Kazuhito Yamaguchi*[b], *Hideki Iijima*[c], *Sei-ichi Manabe*[c], *Takashi Tsurumi*[c], *Hiizu Aizawa*[c], *Naoki Yamamoto*[a]

[a]Department of Virology and Parasitology, [b]Institute of Laboratory Animals, Yamaguchi University School of Medicine, Ube, Yamaguchi; [c]Asahi Chemical, Osaka, Japan

Abstract. We propose a new method to rid solutions of a virus by using a novel regenerated multilayered structured cellulose membrane (BMM). When the filtrate of human immunodeficiency virus (HIV) preparation was obtained through BMM it showed no infectivity. Electron microscopic observation revealed that HIV was completely caught by the multilayers of the BMM. Conveniently, BMM was seldomly found to adsorb protein molecules and also to have a high filtration rate. These characteristics may have a use in the removal of other variously sized pathogenic agents from plasma.

Virus removal from Factor IX and XI

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Original Paper

Vox Sang 1994; 67: 132-138

Nanofiltration, a New Specific Virus Elimination Method Applied to High-Purity Factor IX and Factor XI Concentrates

M. Burnouf-Radosevich
P. Appourchaux
J. J. Huart
T. Burnouf

Centre Régional de Transfusion Sanguine, Lille, France

Filter	Virus	Size (nm)	LRV	
			F IX	F XI
Planova 15N	Polio Sabin Type 1	25-30	>6.7	>6.9
	Bovine parvovirus	20-25	>6.3	>6.4
Planova 35N	HIV	80-100	7.8	7.4
	BVDV	60-70	>5.9	>5.7
	SV40	45	>7.8	>7.0

Prion removal by Planova 15N

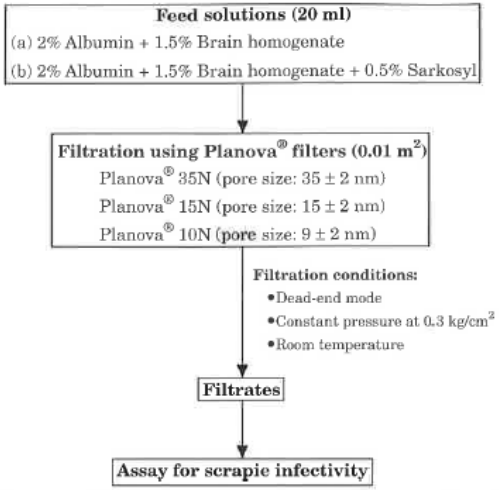
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Biologicals (2001) **29,** 17-25

Scrapie Removal using Planova® Virus Removal Filters

Jun Tateishi[1], Tetsuyuki Kitamoto[2], Shirou Mohri[3], Sakae Satoh[4]*, Tetsuo Sato[4], Ailsa Shepherd[5] and Malcolm R. Macnaughton[5]

[1]Dept. of Neuropathology and [3]Laboratory Animal Center, Kyushu University, Japan; [2]Dept. of Neurological Science, Tohoku University, Japan; [4]Planova Division, Asahi Kasei Corporation, Japan; [5]Biotechnology Dept., Inveresk Research, Tranent, U.K.



	Scrapie agent dilution	No. of mice inoculated	No. of mice infected with Scrapie
Control	10^{-3}	10	10
	10^{-4}	10	4
	10^{-5}	10	1
Planova 35N	10^{-1}	10	10
	10^{-2}	10	8
	10^{-3}	10	3
Planova 15N	10^{-1}	10	**0**
	10^{-2}	10	**0**
	10^{-3}	10	**0**

Higher throughput: Planova 20N

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1. Planova 20N is designed to remove B-19 for Plasma derived products
2. Planova 20N is also designed to achieve higher flux and throughput than Planova 15N

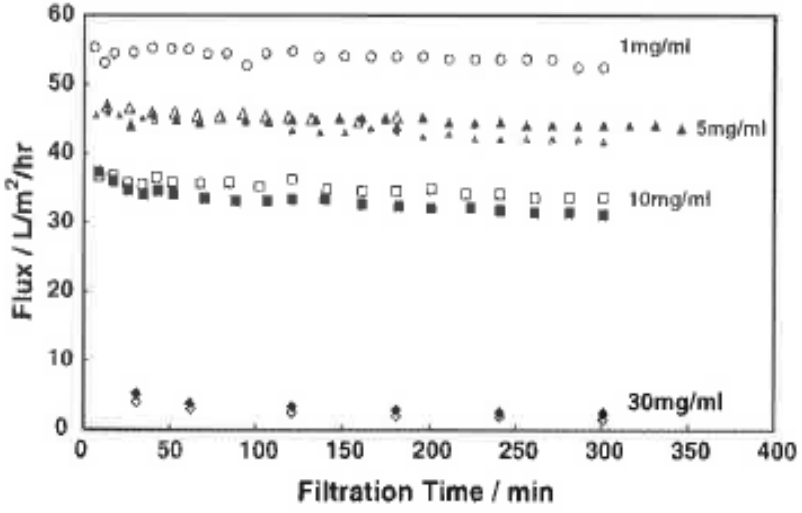


Fig. 5. Relationship between the flux and filtration time on different concentrations of IgG solutions (1, 5, 10 and 30 mg/ml) with different PPV spiking conditions (with purified/supernatant PPV and without PPV). (◯) 1 mg/ml IgG with purified PPV, (△) 5 mg/ml IgG without PPV, (▲) 5 mg/ml IgG with purified PPV, (Δ) 5 mg/ml IgG with supernatant PPV, (□) 10 mg/ml IgG with purified PPV, (■) 10 mg/ml IgG with supernatant PPV, (◊) 30 mg/ml IgG with purified PPV and (♦) 30 mg/ml IgG with supernatant PPV.

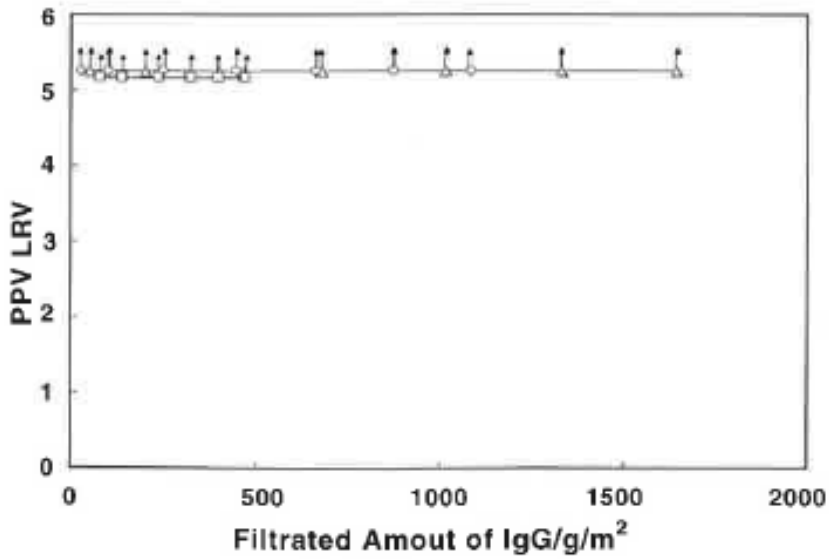


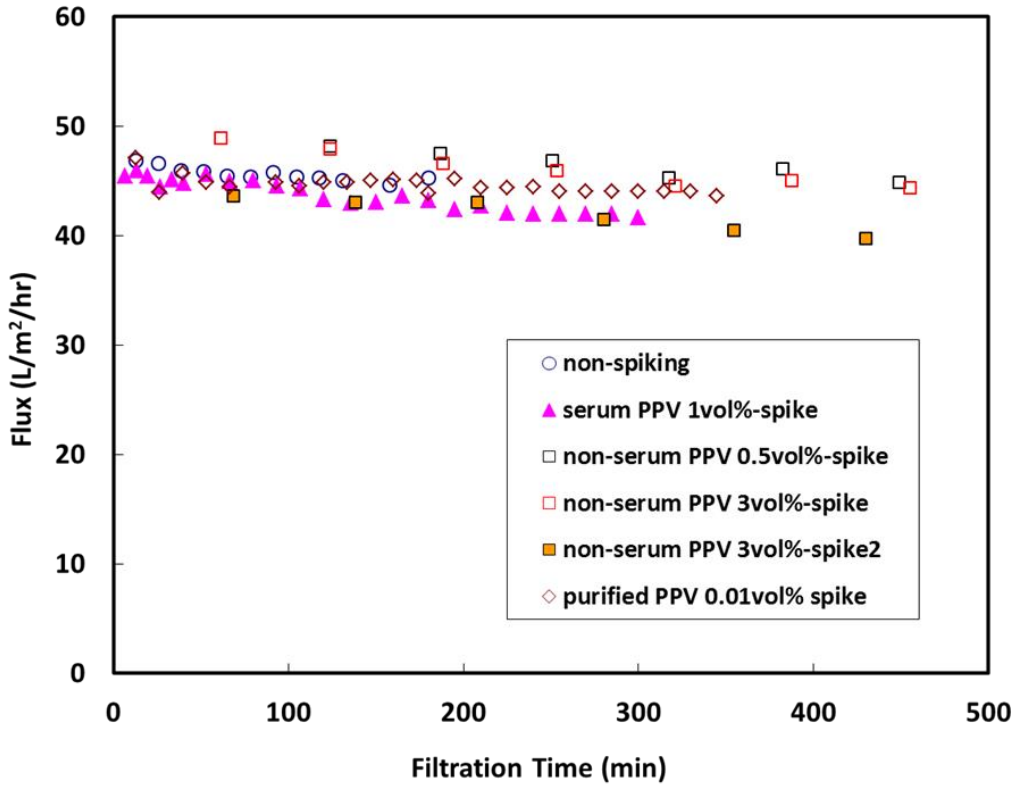
Fig. 6. Dependency of PPV LRV on the amount of IgG solution filtered on different concentrations of IgG solutions (5, 10 and 30 mg/ml) with supernatant PPV. The arrow shows the concentration of virus is under the detectable level. (◯) 5 mg/ml, (△) 10 mg/ml and (□) 30 mg/ml.

Tomoko Hongo Hirasaki et. Al, Journal of Membrane Science (2006) 278

Tolerant to Virus spiking

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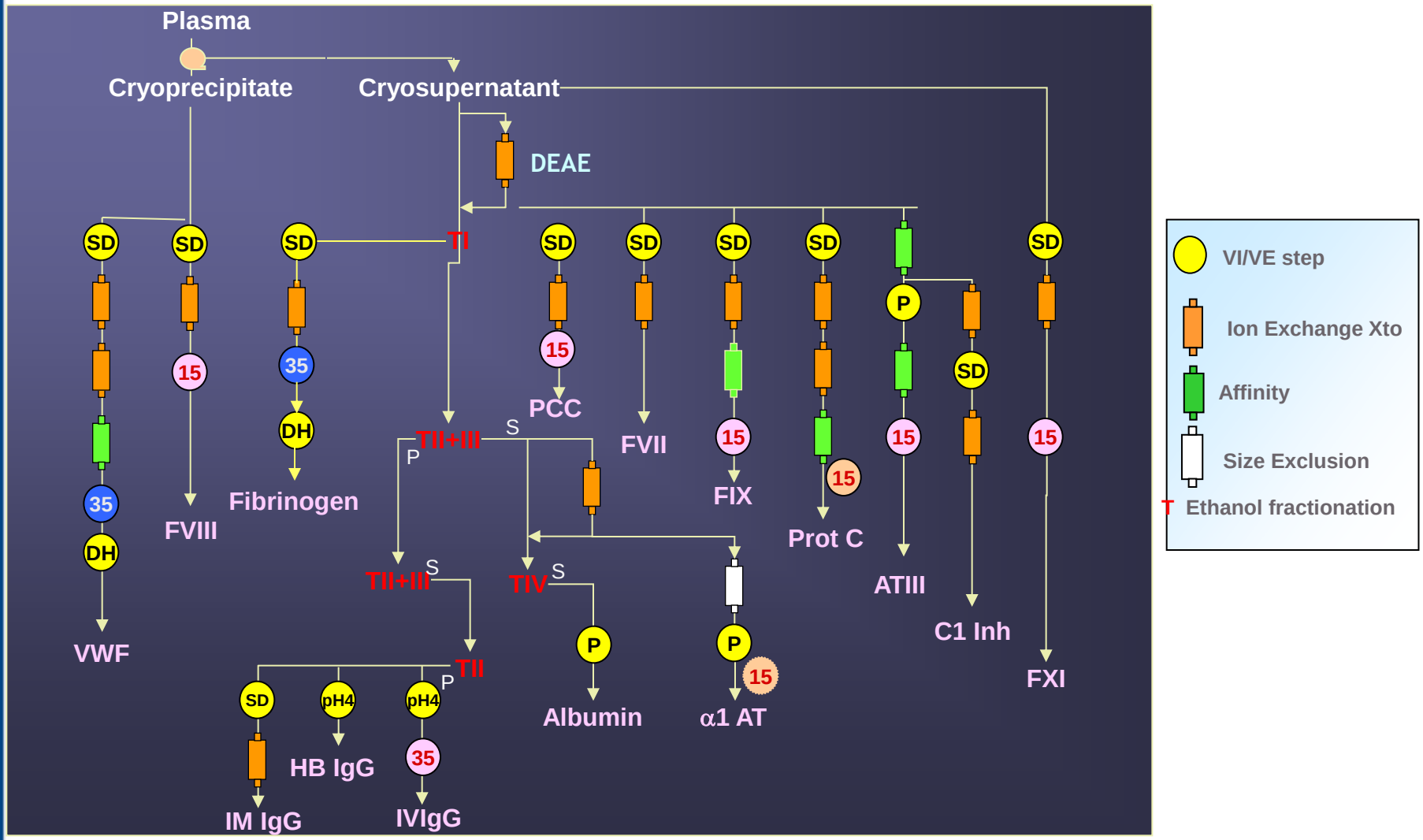
Virus spiking does not affect the flux and protein throughput of Planova 20N.



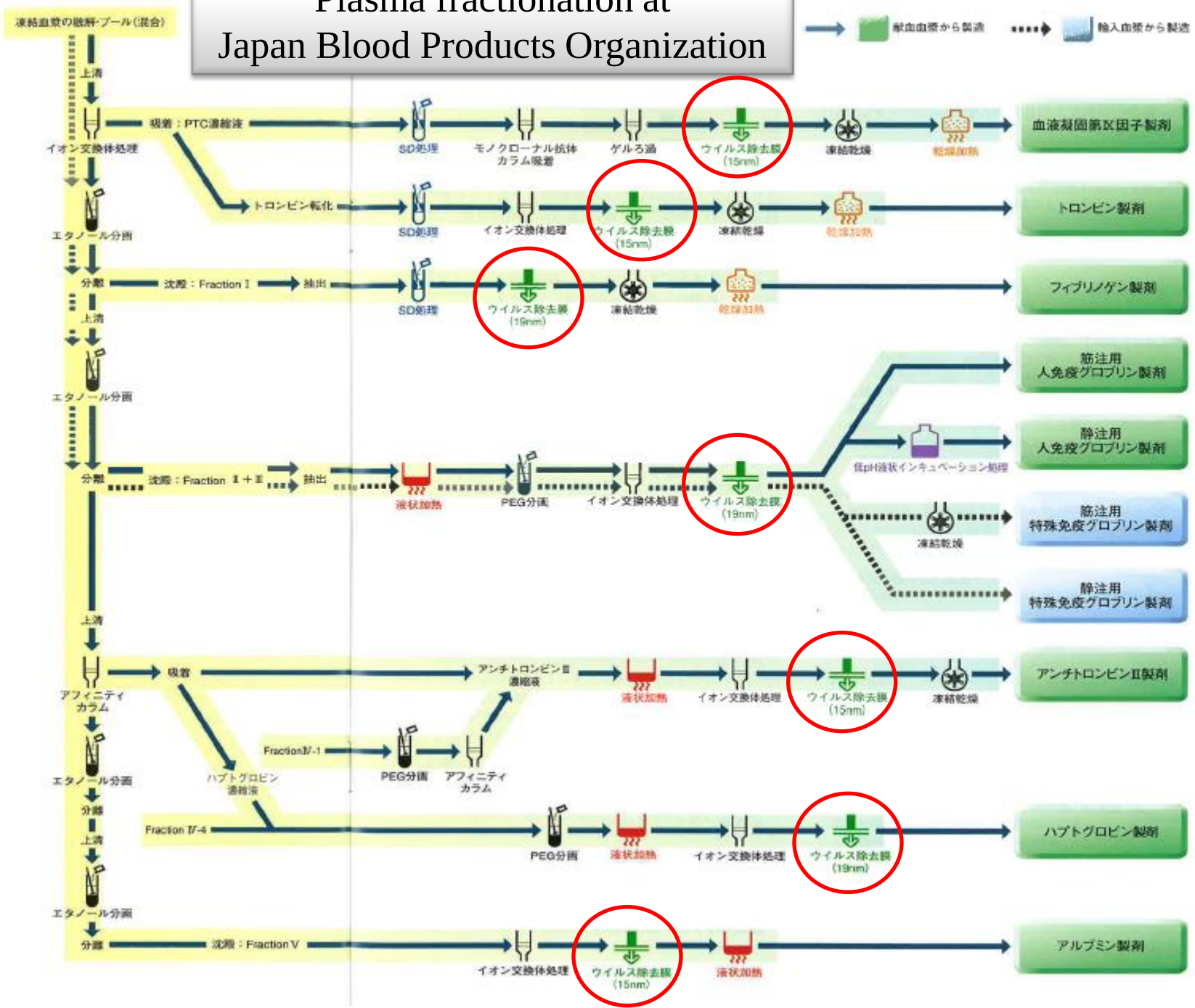
5 mg/ml IgG/D-MEM
Serum PPV; 1 vol%
Serum free PPV; 0.5, 3 vol%
Purified PPV; 0.01 vol%
0.8 bar filtration

Plasma fractionation at LFB

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Plasma fractionation at Japan Blood Products Organization

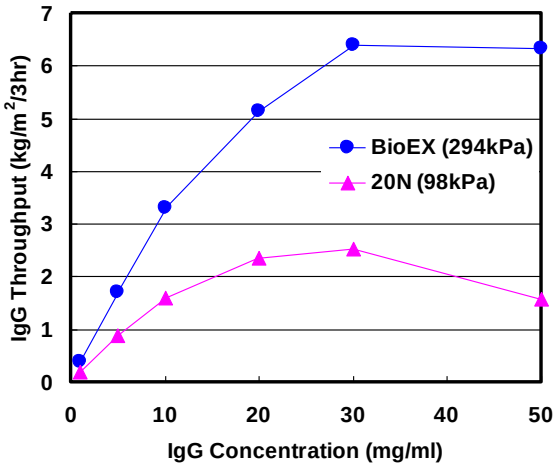


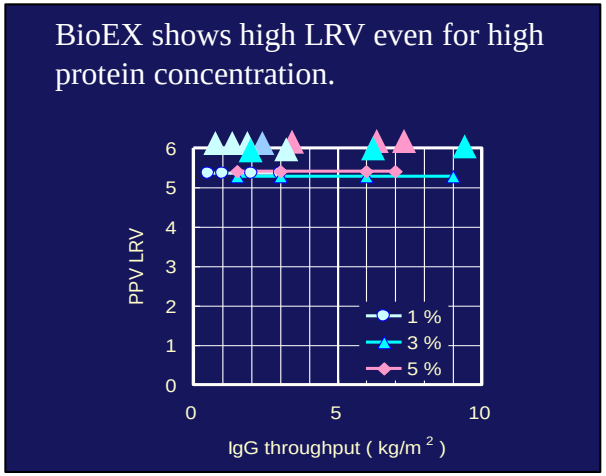
BioEX : High capacity filter

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BioEX is the small virus removal filter made from PVDF with hydrophilic modification.

- PVDF enables BioEX to be SIP capable.
- Higher operating pressure enable BioEX to have higher flux.
- BioEX has an advantage over 20N in the protein throughput at the highly concentrated protein filtration.





Summary

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Physical Property

Suitable Protein

	15N	20N	BioEX
Material	Re-generated Cellulose	Re-generated Cellulose	PVDF
Capillary Size	Very Small	Small	Relatively Large
Trapping Capacity	Small	Large	Very Large
Small Virus LRV	Excellent	Good	Good
Tolerance for Clogging	Not Good	Good	Good
Molecular Weight	Small	Small – Large	Small – Large
Concentration	Low	0-3% (IvIG)	1->3% IvIG
Application	F-IX, AT-III, PCC	F-VIII, IvIG, AT-III, Fibrinogen, PCC	IvIG (5, 7%)

Planova has been used for over 20 years for increasing the safety of plasma products.

It is an established and robust procedure that is recognized by the main regulatory authorities in the world and used by essentially all plasma fractionators .

Thank you for your attention