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
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.
Key Locations

**Cologne, Germany**
- Cologne Technical Center (CTC)
  - Customer support
  - Training laboratory

**Brussels, Belgium**
- Regional head office
- Administration
- Logistics
- Customer support
- Warehouse for Europe and the Middle East

**Tokyo, Japan**
- Global HQ

**Glenview, IL, USA**
- Regional head office
- Administration
- Logistics
- Customer support
- Phage laboratory
- Equipment manufacturing

**Nobeoka & Oita, Japan**
- Virus removal filter manufacturing facilities
  - Hollow fiber spinning
  - Filter assembly

**Mumbai, India**
- Customer support office

**Singapore**
- Customer support office

**Shanghai, China**
- Customer support office

**Jamaica, NY, USA**
- Warehouse for North and South America
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2. Lineup of Planova Products
3. Planova as the robust virus removal step
2. Line up of Planova Products
## Line up of Planova Products

<table>
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<tr>
<th>Year</th>
<th>Planova 35N</th>
<th>Planova 15N</th>
<th>Planova 20N</th>
<th>BioEX</th>
</tr>
</thead>
<tbody>
<tr>
<td>1989</td>
<td>HIV, HBV, HCV</td>
<td>B-19, HAV</td>
<td>B-19, HAV</td>
<td>B-19, HAV</td>
</tr>
<tr>
<td>1991</td>
<td></td>
<td></td>
<td></td>
<td>PVDF</td>
</tr>
<tr>
<td>2001</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2009</td>
<td></td>
<td></td>
<td></td>
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</tr>
</tbody>
</table>
Planova filters

**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

15N
- Interleukin 12-35 kDa
- Factor IX 58 kDa
- Albumin 66 kDa
- IgG 160 kDa

20N BioEX
- IgG 160 kDa
- Factor VIII 300 kDa
- Fibrinogen 340 kDa

35N
- IgG 160 kDa
- Factor VIII 300 kDa
- Fibrinogen 340 kDa
- VWF >500 kDa
- IgM 800 kDa
3. Planova as the robust virus removal step
Potential for viral transmission

- 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

<table>
<thead>
<tr>
<th>Year</th>
<th>Virus</th>
<th>Product</th>
</tr>
</thead>
<tbody>
<tr>
<td>1989</td>
<td>HIV</td>
<td>PPSB</td>
</tr>
<tr>
<td>1992</td>
<td>B19</td>
<td>F-VIII</td>
</tr>
<tr>
<td>1992</td>
<td>HAV</td>
<td>F-VIII</td>
</tr>
<tr>
<td>1993</td>
<td>HCV</td>
<td>Ivlg</td>
</tr>
<tr>
<td>1994</td>
<td>HBV</td>
<td>PPSB</td>
</tr>
<tr>
<td>1995/96</td>
<td>HAV</td>
<td>F-VIII</td>
</tr>
<tr>
<td>1997</td>
<td>HAV</td>
<td>F-VIII</td>
</tr>
</tbody>
</table>
Safety Tripod

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

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

**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

Planova provides robust Virus Removal step

protein solution

Virus free protein solution

Easy!
The challenge
Planova filtration mechanism

Multi Layered Structure and Multi Step Filtration

Layer 1 Layer 2 Layer>100

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

Yoshiaki Hamamoto\textsuperscript{a}, Shinji Harada\textsuperscript{a}, Susumu Kobayashi\textsuperscript{a}, Kazuhito Yamaguchi\textsuperscript{b}, Hideki Iijima\textsuperscript{c}, Sei-ichi Manabe\textsuperscript{c}, Takashi Tsurumi\textsuperscript{c}, Hiizu Aizawa\textsuperscript{a}, Naoki Yamamoto\textsuperscript{a}

\textsuperscript{a}Department of Virology and Parasitology, \textsuperscript{b}Institute of Laboratory Animals, Yamaguchi University School of Medicine, Ube, Yamaguchi; \textsuperscript{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

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

<table>
<thead>
<tr>
<th>Filter</th>
<th>Virus</th>
<th>Size (nm)</th>
<th>LRV</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>F IX</td>
</tr>
<tr>
<td>Planova 15N</td>
<td>Polio Sabin Type 1</td>
<td>25-30</td>
<td>&gt;6.7</td>
</tr>
<tr>
<td></td>
<td>Bovine parvovirus</td>
<td>20-25</td>
<td>&gt;6.3</td>
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<tr>
<td>Planova 35N</td>
<td>HIV</td>
<td>80-100</td>
<td>7.8</td>
</tr>
<tr>
<td></td>
<td>BVDV</td>
<td>60-70</td>
<td>&gt;5.9</td>
</tr>
<tr>
<td></td>
<td>SV40</td>
<td>45</td>
<td>&gt;7.8</td>
</tr>
</tbody>
</table>
Prion removal by Planova 15N

*Biologicals* (2001) 29, 17-25

**Scrapie Removal using Planova® Virus Removal Filters**

Jun Tateishi¹, Tetsuyuki Kitamoto², Shirou Mohri³, Sakae Satoh⁴, Tetsuo Sato⁴, Ailsa Shepherd⁵ and Malcolm R. Macnaughton⁵

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

<table>
<thead>
<tr>
<th></th>
<th><strong>Scrapie agent dilution</strong></th>
<th><strong>No. of mice inoculated</strong></th>
<th><strong>No. of mice infected with Scrapie</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Control</strong></td>
<td>10⁻³</td>
<td>10</td>
<td>10</td>
</tr>
<tr>
<td></td>
<td>10⁻⁴</td>
<td>10</td>
<td>4</td>
</tr>
<tr>
<td></td>
<td>10⁻⁵</td>
<td>10</td>
<td>1</td>
</tr>
<tr>
<td><strong>Planova 35N</strong></td>
<td>10⁻¹</td>
<td>10</td>
<td>10</td>
</tr>
<tr>
<td></td>
<td>10⁻²</td>
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</tr>
<tr>
<td></td>
<td>10⁻³</td>
<td>10</td>
<td>3</td>
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<tr>
<td><strong>Planova 15N</strong></td>
<td>10⁻¹</td>
<td>10</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>10⁻²</td>
<td>10</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>10⁻³</td>
<td>10</td>
<td>0</td>
</tr>
</tbody>
</table>
Higher throughput: Planova 20N

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, (▲) 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.

Tolerant to Virus spiking

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

Plasma → Cryoprecipitate → Fibrinogen → VWF
Plasma → Cryosupernatant → DEAE → TII+III → TII
Plasma → DEAE → Albumin → α1 AT → ATIII
Plasma → DEAE → C1 Inh → FXI
Plasma fractionation at LFB
Plasma fractionation at Japan Blood Products Organization
BioEX: High capacity filter

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.

BioEX shows high LRV even for high protein concentration.
## Summary

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