Potential Contribution of Nanofiltration to the Virus Safety of Domestic Plasma Components

September 23 2021

Tomoko Hongo-Hirasaki,

Lead Expert, Bioprocess Division, Asahi Kasei Medical Co., Ltd.

Declaration of interest

Tomoko Hongo-Hirasaki is an employee: a lead expert of Bioprocess Division, Asahi Kasei Medical Co., Ltd., Tokyo, Japan.

Purpose of this presentation

- To provide an understanding of nanofiltration
- To reduce barriers to the use of nanofiltration
- To facilitate the use of nanofiltration as a virus removal process

Overview

1. Nanofiltration
2. Challenges for Implementation
3. Case Study of Implementation
4. Conclusion

1

Nanofiltration

Nanofiltration

- The most robust virus removal methods recognized by the plasma fractionation industry and in international regulatory guidance.
- Applicable to various types of plasma products.
- Can remove various known and emerging viruses based on a size-exclusion mechanism.
- Excellent scalability: straightforward process for implementation from mini-pools to large-scale batches of plasma fractions.

Nanofiltration

- The most robust virus removal methods are recognized by the plasma fractionation industry and in international regulatory guidance.
- Applicable to various types of plasma products
- Can remove various known and emerging viruses based on a size exclusion mechanism.
- Excellent scalability: straightforward process for implementation from mini-pools to large-scale batches of plasma fractions.

Viral Safety in Manufacturing Step

- Viral safety of bio-therapeutic products is required by regulatory agencies worldwide.
- Viral inactivation/ removal method(s) are necessary in production processes.
- “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”*

* EMEA/ CHMP/ BWP/ 398498, 2005

Recognition by Regulatory Guidance and Industry

AsahiKASEI BIOPROCESS

- Nanofiltration is a robust virus removal method

WHO Technical Report, Series No. 924, 2004

Annex 4

Guidelines on viral inactivation and removal procedures intended to assure the viral safety of human blood plasma products

The European Agency for the Evaluation of Medicinal Products
Evaluation of Medicines for Human Use

London, 28 March 2001
CPMP/BWP/BPWG/4080/00

EMEA WORKSHOP ON VIRAL SAFETY OF PLASMA-DERIVED MEDICINAL PRODUCTS WITH PARTICULAR FOCUS ON NON-ENVELOPED VIRUSES

13 September 2000
REPORT

Received: 20 November 2019 | Revised: 24 June 2020 | Accepted: 25 June 2020
DOI: 10.1111/trf.16022

BLOOD COMPONENTS

TRANSFUSION

Nanofiltration as a robust method contributing to viral safety of plasma-derived therapeutics: 20 years' experience of the plasma protein manufacturers

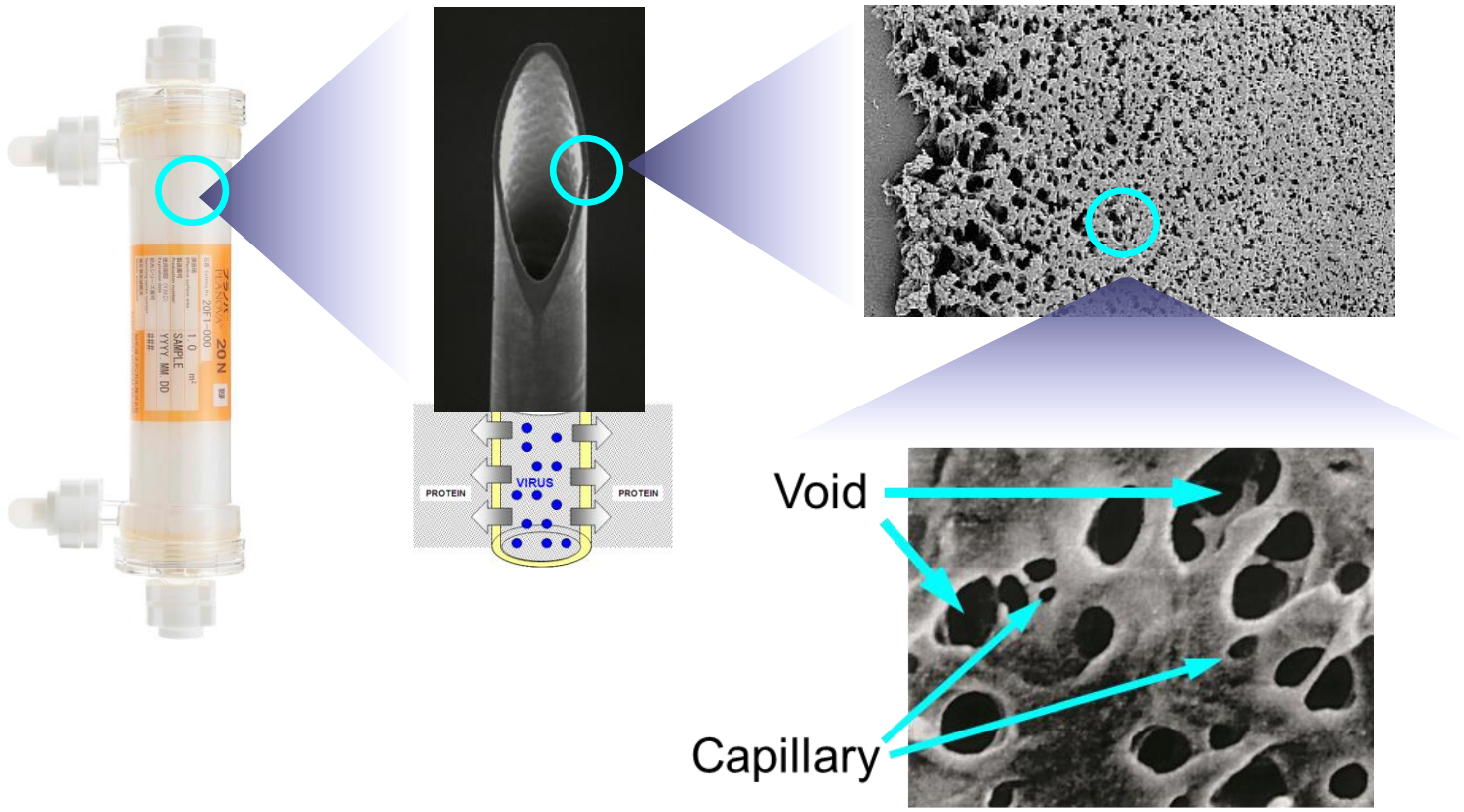
Nathan J. Roth[1] | Herbert O. Dichtelmüller[2†] | Fabrizio Fabbrizzi[3†] | Eckhard Flechsig[2] | Albrecht Gröner[4] | Mary Gustafson[5] | Juan I. Jorquera[6] | Thomas R. Kreil[7] | Dominika Misztela[8] | Elisa Moretti[3] | Mila Moscardini[3] | Gerhard Poelsler[2] | John More[9] | Peter Roberts[9] | Andreas Wieser[7] | Rodrigo Gajardo[6]

Nanofiltration

- The most robust virus removal methods are recognized by the plasma fractionation industry and in international regulatory guidance.
- Applicable to various types of plasma products.
- Can remove various known and emerging viruses based on a size-exclusion mechanism.
- Excellent scalability: straightforward process for implementation from mini-pools to large-scale batches of plasma fractions.

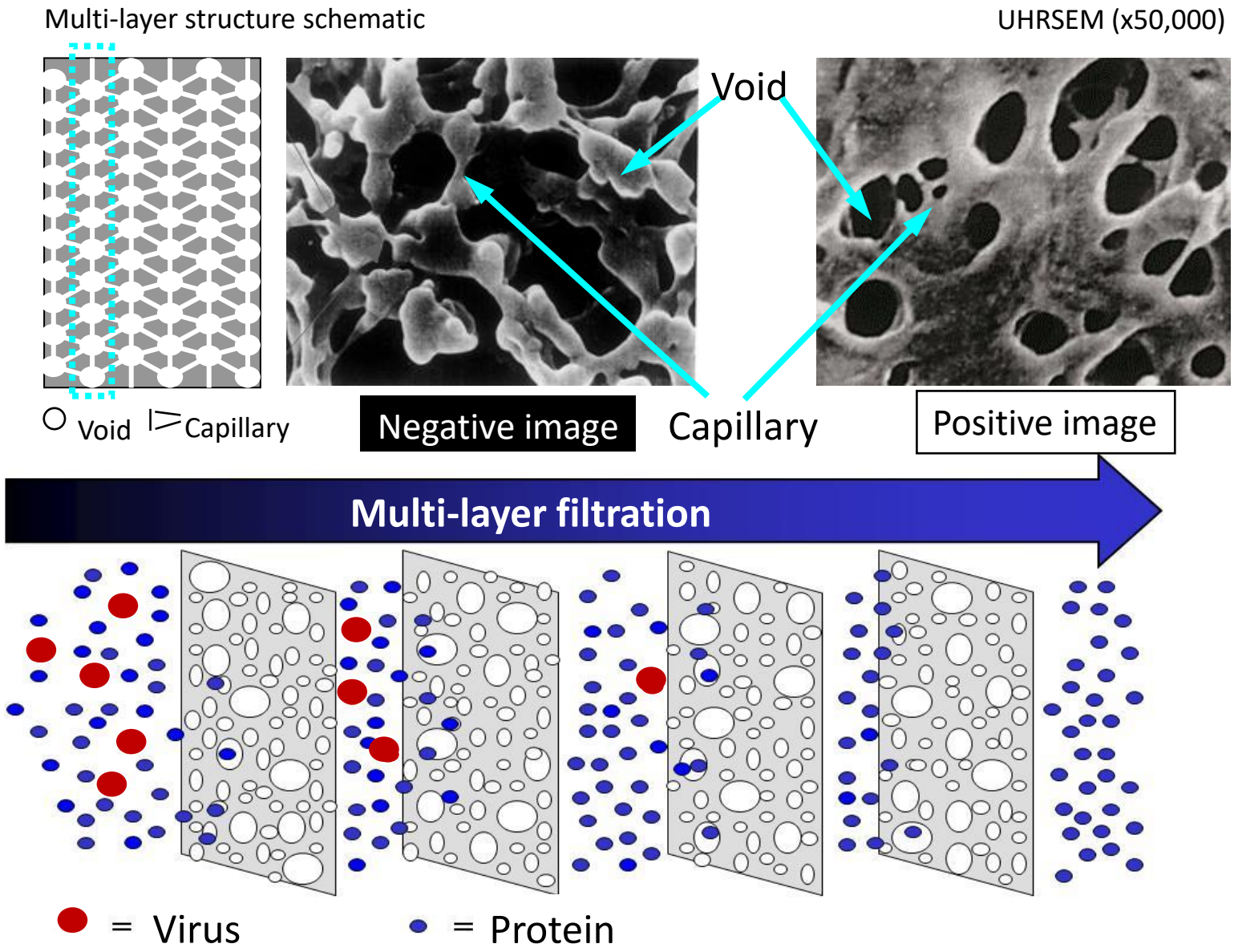
Planova Membrane Structure

Planova filter | Hollow fiber | Membrane cross-section



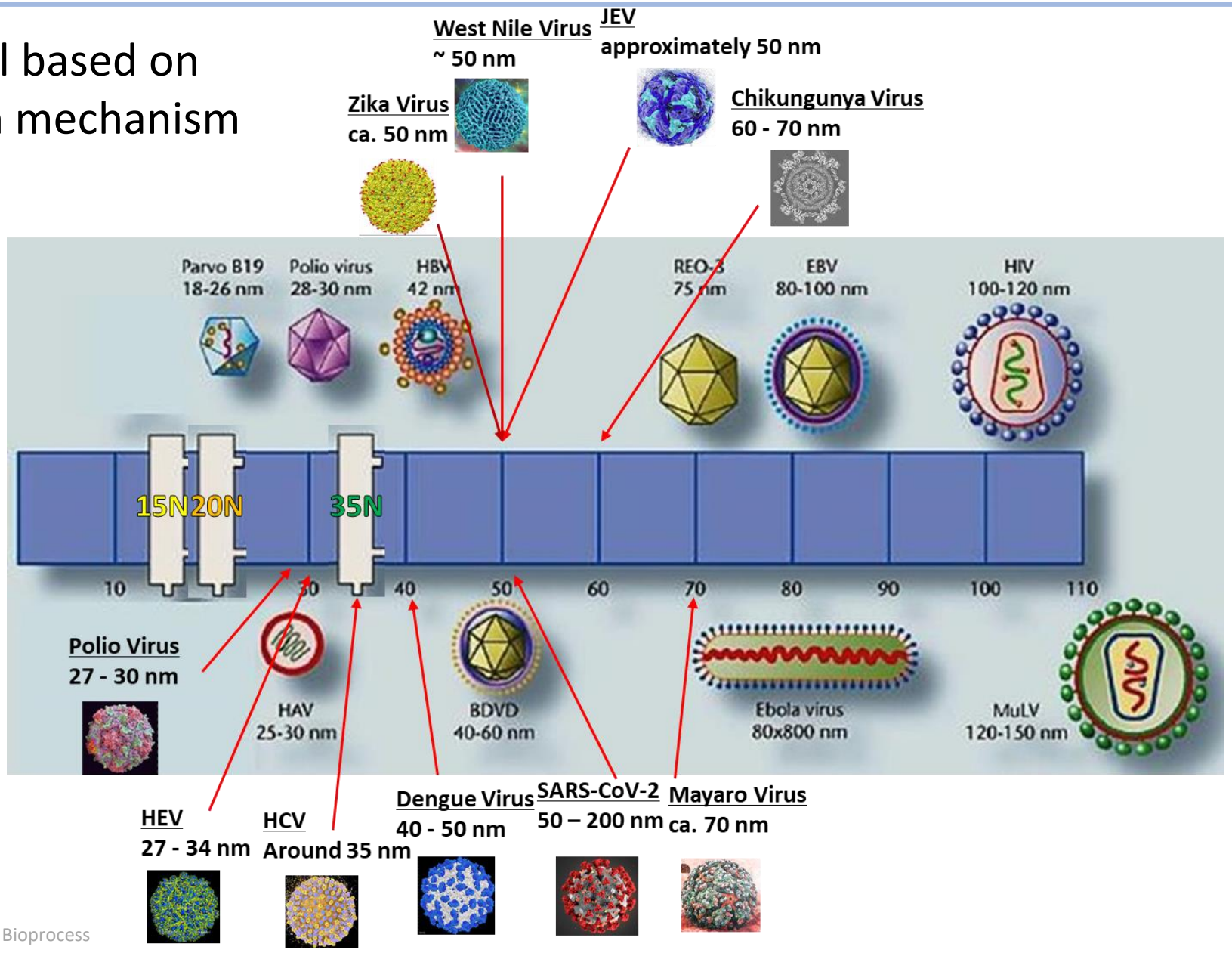
- Hollow fibers of Planova filters have a three-dimensional network structure consisting of voids connected by capillaries.

Filtration Mechanism: Size Exclusion



Planova Filters Against Emerging Viruses

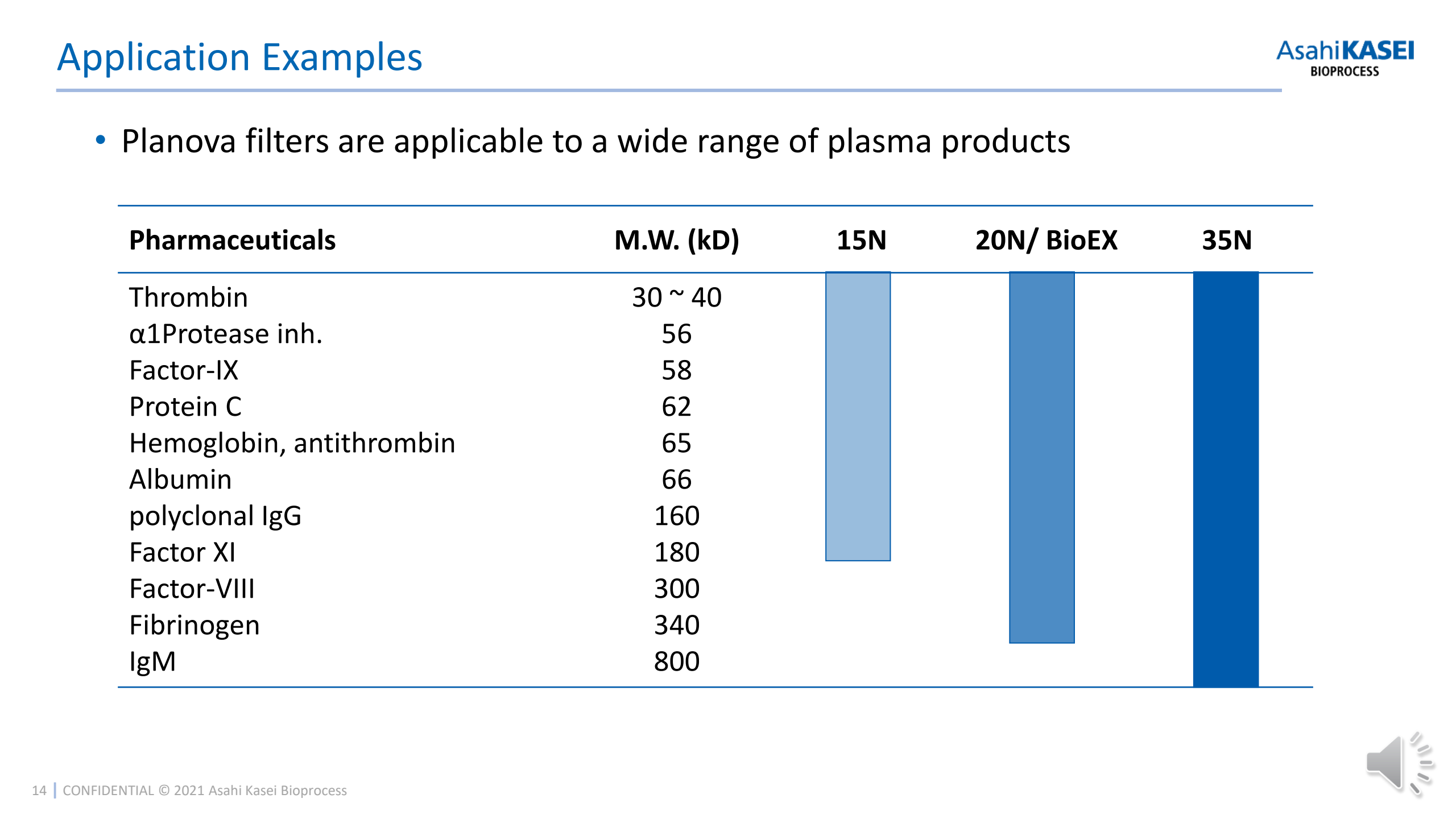
- Virus removal based on size exclusion mechanism



Application Examples

- Planova filters are applicable to a wide range of plasma products

Pharmaceuticals	M.W. (kD)	15N	20N/ BioEX	35N
Thrombin	30 ~ 40			
α1Protease inh.	56			
Factor-IX	58			
Protein C	62			
Hemoglobin, antithrombin	65			
Albumin	66			
polyclonal IgG	160			
Factor XI	180			
Factor-VIII	300			
Fibrinogen	340			
IgM	800			

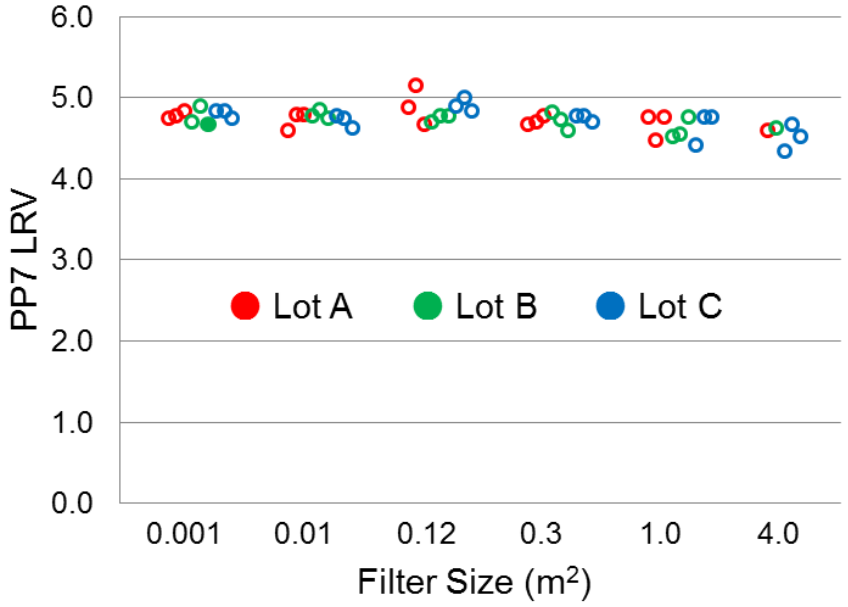


Nanofiltration

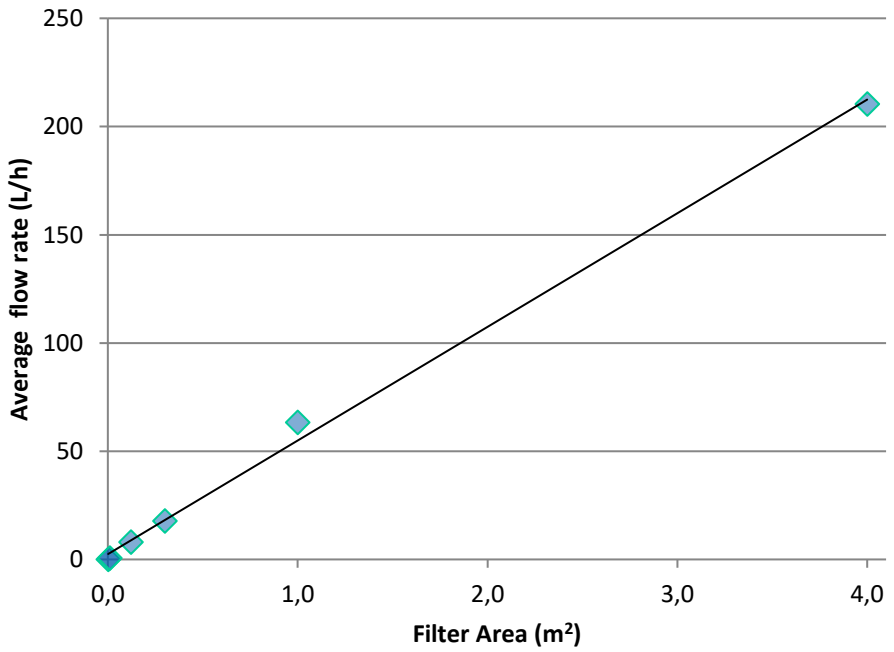
- The most robust virus removal methods are recognized by the plasma fractionation industry and in international regulatory guidance.
- Applicable to various types of plasma products.
- Can remove various known and emerging viruses based on a size exclusion mechanism.
- Excellent scalability: straightforward process for implementation from mini-pools to large-scale batches of plasma fractions.

Scalability

- Viral clearance and flow rate scalability data for Planova filters



Linear increase in flow rate for filtration



Brian Buesing, Asahi Kasei Bioprocess America, *Planova Workshop*, Athens, 2015 (excerpted)

- Robust viral clearance across both filter types and sizes
- Excellent filter: lot-to-lot consistency in virus removal
- The linear increase in flow rates shows uniform scalability of flux

2

Challenges for Implementation

Main Challenges and Proposed Solutions for LMIC

AsahiKASEI BIOPROCESS

Main Challenges

- ✓ Introducing nanofiltration in a process:
  -How to use it?

  -How to optimize the filtration conditions?

- ✓ How to meet regulatory requirements and technological trends regarding virus safety

Proposed Solutions

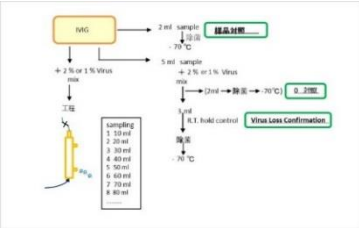
- ✓ Hands-on training to use Planova filter
- ✓ Providing in-depth technical advice and support services
- ✓ Providing regulatory information and updated scientific knowledge sharing
- ✓ On-site training on virus clearance study

Planova On-Site Technical Support

AsahiKASEI BIOPROCESS

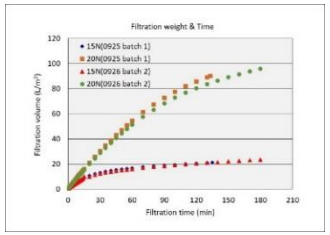
Lab test

Protocol design



Experimental support

Data analysis

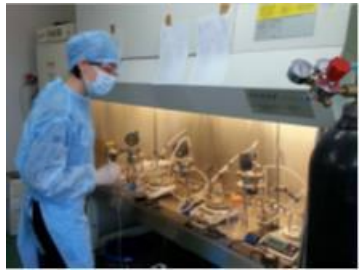


Proposal/ solution

Virus clearance study

Non-GLP

GLP (Validation)



Regulatory approval

Scale-up

Pilot test

Commercial production

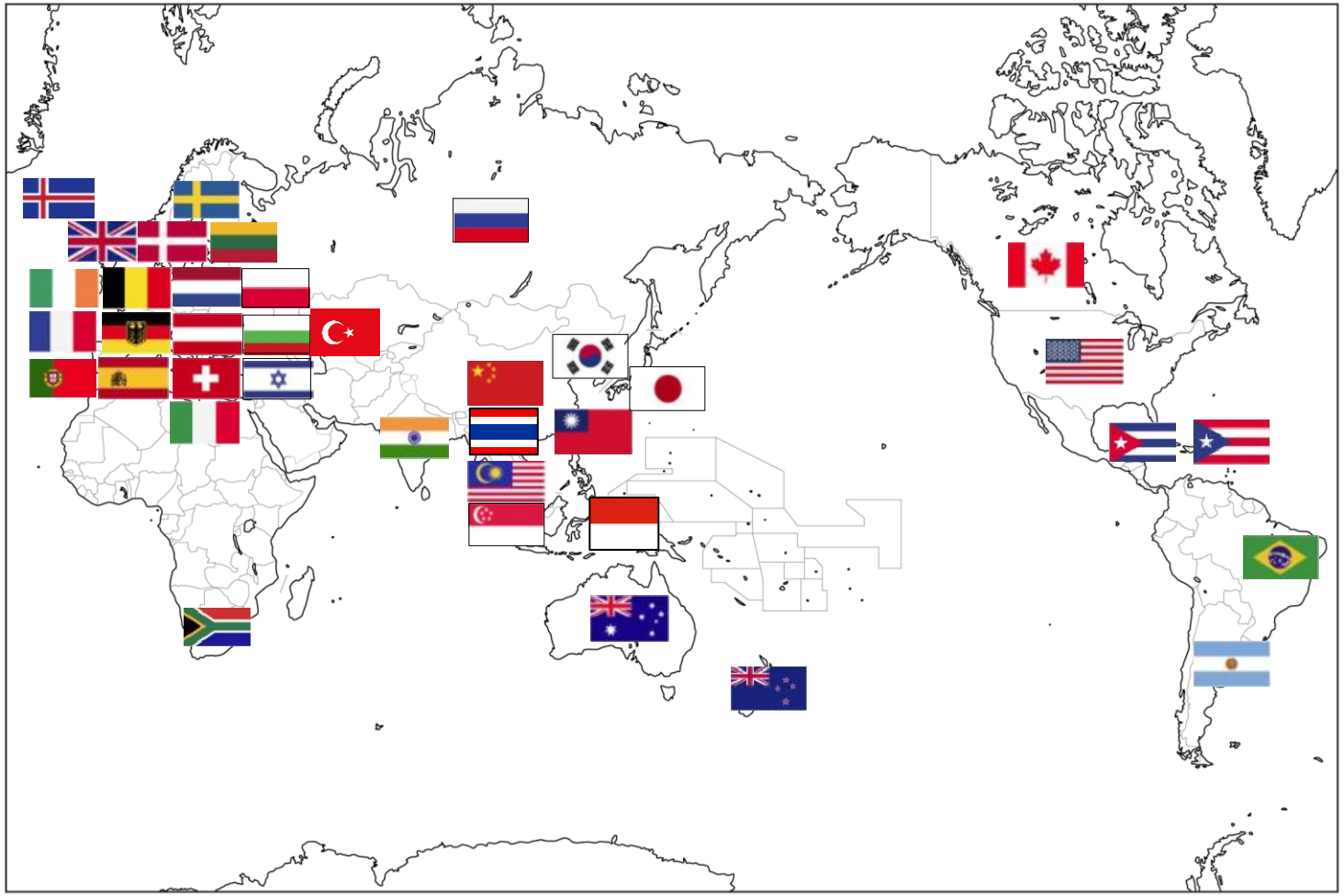
Scientific Knowledge Sharing: Planova Workshop

- Annual event where “Planova Family” gathers to exchange information
- Held since 1998, alternately in Europe and the United States
- Planova users, regulatory authorities and key opinion leaders present their experience of the regulation, downstream process development, pathogen safety and the manufacturing of biopharmaceuticals
- Asahi provides new data or other technical updates on nanofiltration

Planova Workshop, Rome, 2013

Planova Application in the Global Market

- Planova filters have been used for biological products for almost 30 years worldwide, including LMIC



3

Case Study of Implementation

China: IVIG

Optimal operating filtration conditions

Filter size: 0.001m^2
Operating Pressure, temperature, protein concentration,
Prefilter

Process scale up and product integrity

Filter size: 0.1m^2
Operating Pressure: 294 kPa
Temperature: 25℃
Protein concentration: 50 g/L
Prefilter: 0.1 µm

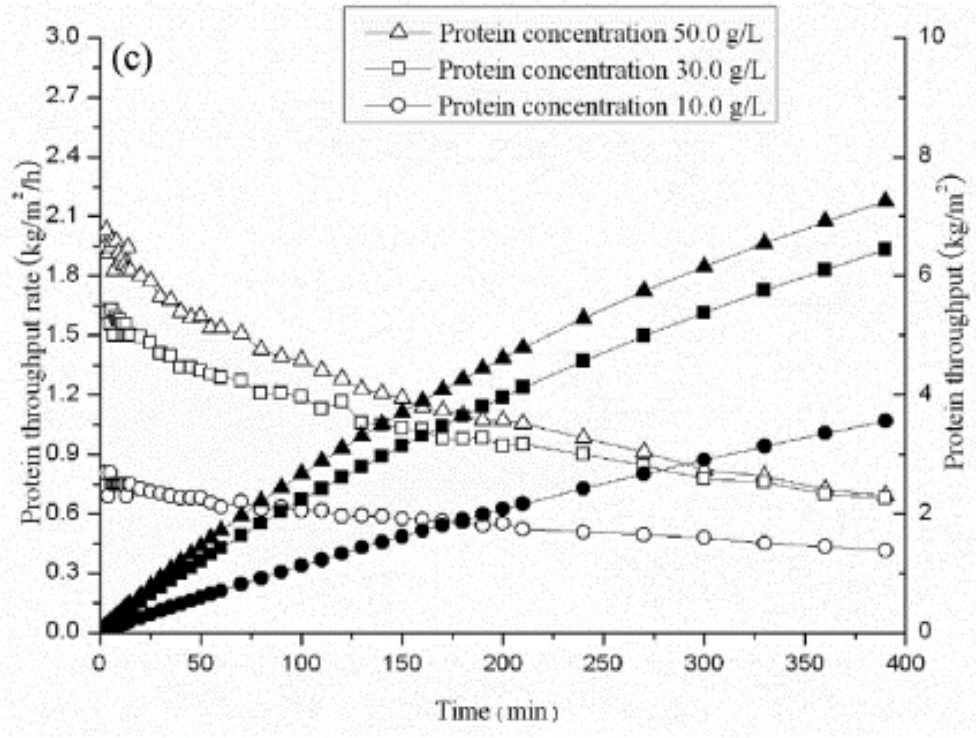
Preliminary viral clearance study

Filter size: 0.001m^2

Viral clearance validation study at NIFDC

Filter size: 0.001m^2

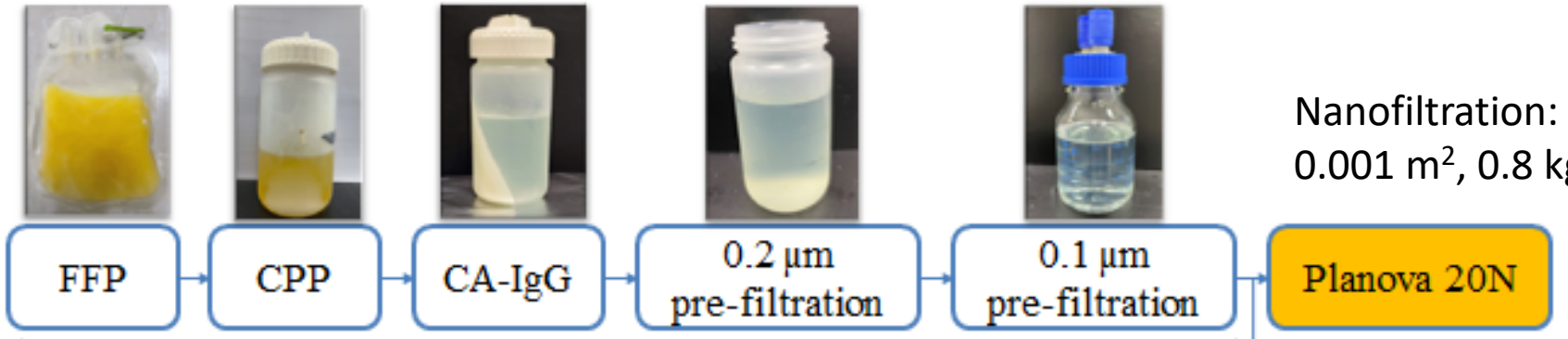
- This plasma derived IVIG product is the first to be certified for parvovirus safety by the NIFDC in China.



Sha Ma et.al., Biologicals 52(2018) 37-43 (adapted)

Nanofiltration test of mini-pool caprylic acid purified-IgG (CA-IgG) (1)

Flow chart of preliminary test: Experimental design



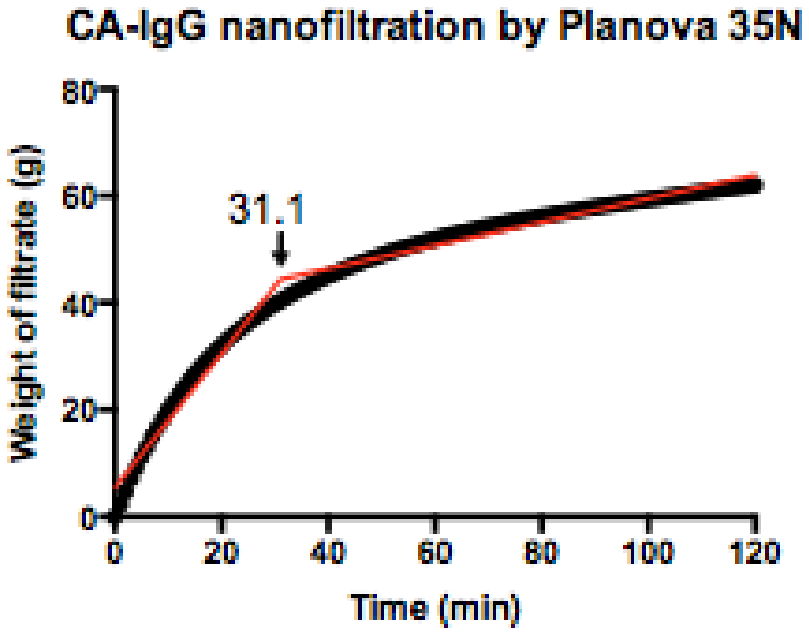
Nanofiltration:
0.001 m^2, 0.8 kgf/cm^2

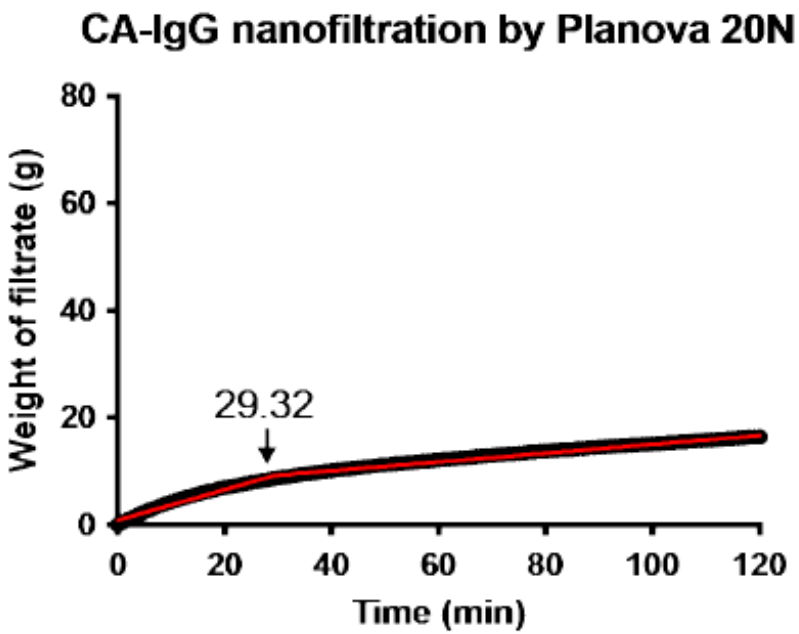
CA-IgG: protein content: 14 mg/ml, pH5.5

College of Biomedical Engineering

Unpublished data, Taipei Medical University (Prof. Thierry Burnouf)

Nanofiltration test of mini-pool CA-IgG (2)





✓ Planova 35N nanofiltration:

50-60 mL of CA-IgG could be readily nanofiltered on 0.001 m^2 Planova 35N within 2hrs at a constant pressure of 0.8 kgf/cm^2

✓ Planova 20N nanofiltration:

16 mL of CA-IgG could be nanofiltered on 0.001m^2 Planova 20N within 2hrs at a constant pressure of 0.8 kgf/cm^2

✓ Since CA is a virus inactivation step (enveloped viruses), nanofiltration of CA-IgG provides a second virus reduction step (enveloped and non-enveloped viruses) to consider when batch size increases

Unpublished data, Taipei Medical University (Prof. Thierry Burnouf)

4

Conclusion

Nanofiltration of domestic plasma components in LMIC

- Implementing nanofiltration is a straightforward process from mini-/small-pools domestic plasma components (e.g., immunoglobulins) to large-scale batches of plasma fractions (e.g., Factor VIII, Factor IX, immunoglobulins).
- Technical support and experienced/scientific knowledge sharing can be provided to LMIC to improve the virus safety of domestic plasma components.

AsahiKASEI
BIOPROCESS

감사합니다 Gracias Danke

Благодаря 谢谢 Tack धन्यवाद Dziękuję

Спасибо Thank You Obrigado

Děkuju Grazie Ευχαριστώ Merci Köszönöm

ありがとうございました Teşekkür ederim