


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

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Abstract

Background: Nanofiltration entails the filtering of protein solutions through membranes with pores of nanometric sizes that have the capability to effectively retain a wide range of viruses.

Study Design and Methods: Data were collected from 754 virus validation studies (individual data points) by Plasma Protein Therapeutics Association member companies and analyzed for the capacity of a range of nanofilters to remove viruses with different physicochemical properties and sizes. Different plasma product intermediates were spiked with viruses and filtered through nanofilters with different pore sizes using either tangential or dead-end mode under constant pressure or constant flow. Filtration was performed according to validated scaled-down laboratory conditions reflecting manufacturing processes. Effectiveness of viral removal was assessed using cell culture infectivity assays or polymerase chain reaction (PCR).

Results: The nanofiltration process demonstrated a high efficacy and robustness for virus removal. The main factors affecting nanofiltration efficacy are nanofilter pore size and virus size. The capacity of nanofilters to remove smaller, nonenveloped viruses was dependent on filter pore size and whether the nanofiltration process was integrated and designed with the intention to provide effective parvovirus retention. Volume filtered, operating pressure,

Abbreviations: LRF, log₁₀ Virus Reduction Factor; PDMP(s), plasma-derived medicinal product(s); PPTA, Plasma Protein Therapeutics Association; TT, transfusion-transmitted.

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and total protein concentration did not have a significant impact on the effectiveness of virus removal capacity within the investigated ranges.

Conclusions: The largest and most diverse nanofiltration data collection to date substantiates the effectiveness and robustness of nanofiltration in virus removal under manufacturing conditions of different plasma-derived proteins. Nanofiltration can enhance product safety by providing very high removal capacity of viruses including small non-enveloped viruses.

KEYWORDS

plasma derivatives

Plasma-derived medicinal products (PDMPs) have never been safer than today. Multiple complementary safety measures required by regulations^{1,2} or implemented voluntarily by Plasma Protein Therapeutics Association (PPTA) member companies³ as well as those used by other plasma fractionators⁴⁻⁸ contributed to the current safety profiles.

Only healthy donors are accepted to donate after passing medical screenings and testing negative for human immunodeficiency virus (HIV) and hepatitis B and C viruses (HBV and HCV); all plasma donations are tested by serologic and nucleic acid amplification techniques (NAT) assays; plasma pools for fractionation are only released for further manufacturing when tested non-reactive in serologic and NAT assays; and manufacturing steps that have a high virus inactivation and/or removal capacity are included in each manufacturing process. As a result of the introduction of these complementary measures, there have not been any documented transmissions of HIV, HBV, and HCV through products manufactured by PPTA member companies and other recognized plasma fractionators in the past two decades with over 35 million doses of various products administered.^{9,10}

Dedicated manufacturing steps introduced into the manufacturing processes with a high robust virus inactivation and removal capacity for the production of PDMPs represent an essential part of highly complex safety measures aimed to assure the safety of these products. Steps with virus inactivation capacity include heat treatment,¹¹ solvent/detergent (S/D) treatment,¹²⁻¹⁴ low-pH treatment,¹⁵ and caprylate inactivation.¹⁶ Nanofiltration was integrated into the manufacturing process in the 1990s as a complementary step with virus removal capacity based on size exclusion.^{8,17,18,19}

The first available nanofilters with pore sizes of 75 nm and 35 nm were developed by the Japanese manufacturer Asahi Kasei. Later, a range of nanofilters with pore sizes of 15 nm, 20 nm and 50 nm produced by several manufacturers became available and were incorporated into production processes of PDMPs.²⁰⁻²³ Over the course of the

following years, nanofiltration was introduced also into the manufacturing of cell-derived biologics, including recombinant proteins, derived from mammalian cells or mammalian origin.²⁴⁻²⁹ Today, nanofiltration is standardly used in the manufacturing processes of PDMPs, such as immunoglobulins (IgG),³⁰⁻³² coagulation factors such as von Willebrand Factor (vWF),³³ Factor VIII (FVIII),^{34,35} Factor IX (FIX), and prothrombin complex,^{18,36} and inhibitors such as alpha1-protease inhibitor (A₁PI),^{37,38} anti-thrombin (ATIII),³⁹ and C1-esterase inhibitor.⁴⁰⁻⁴²

PPTA member companies performed a retrospective data collection and analysis of the virus removal capacity validation data for nanofiltration steps for variety of commercial PDMPs using 15 to 20 nm and 35 to 50 nm nanofiltration platforms. This data set represents the largest and most diverse studies of conditions ever analyzed for factors that could influence robustness or the efficacy of nanofiltration across the ranges of industrial scale operations.

1 | MATERIALS AND METHODS

1.1 | Data collection

Data from 754 virus validation studies from PPTA member companies (BioProducts Laboratory, Biotest, CSL Behring, Grifols, Kedrion, and Takeda) detailing filter brand, filter pore size, mode of filtration (dead-end or tangential), operating pressure, test materials (plasma product intermediate), test virus, and virus removal capacity were collected, anonymized, and analyzed. Virus removal capacity, expressed as the log₁₀ Virus Reduction Factor (LRF), was determined by quantifying either virus titer by cytopathic effect in cell culture infectivity assays or, in a small number of studies, by detection of virus nucleic acid by PCR. Volume filtered per m², protein concentration, pH, temperature, interruption of filtration, and conductivity of the intermediate to be filtered were also provided.

Nanofiltration steps that were intentionally designed to provide effective virus removal (4 log₁₀ or higher of virus removal capacity) for all viruses (HIV, HBV, HCV, etc.), including parvovirus B19, were also specified as such within the data sets.

1.2 | Scaled-down validation

Studies were performed using validated scaled-down nanofiltration models^{43–45} according to manufacturing conditions and at the edge of manufacturing specifications to assess robustness. Virus validation studies were performed according to laboratory-specific standard operating procedures in compliance with established safety guidelines and quality assurance standards. All studies were performed by intentionally spiking product intermediates with virus. Filtration was performed using constant pressure or constant flow in a dead-end filtration or tangential flow mode.

1.3 | Nanofilters

The studies used filters made by Asahi Kasei Corp. (Tokyo, Japan; 536 studies), Pall Corp. (Port Washington, NY, USA; 150 studies), Merck Millipore Corp. (Darmstadt, Germany; 52 studies), and Sartorius (Göttingen, Germany; 16 studies). The nominal pore sizes of the filters ranged from 15 to 50 nm. Filters were assigned into groups according to pore sizes (Table S1): nominal pore size 15 to 20 nm (Planova 15N, Planova 20N, Planova BioEx, Pall DV20, Virosart HC, Viresolve NFP, Viresolve VPro) and nominal pore size 35 to 50 nm (Planova 35N, Pall DV50, Viresolve NFR).

1.4 | Product classes

For analyses, studies were grouped according to product class: inhibitors (total of 138 studies), immunoglobulins (total of 295 studies), coagulation factors (total of 299 studies), and others (total of 22 studies). The number of studies per product subclass within each product class is shown in Table 1.

1.5 | Viruses studied

The main relevant transfusion-transmitted (TT) viruses are HIV (80–100 nm), HCV (55–65 nm), and HBV (42 nm). Other viruses also implicated in TT diseases are HAV (25–30 nm) and B19V (18–24 nm). Studies were performed using viruses relevant for blood transfusion, where

TABLE 1 Plasma product intermediates (test material) and number of studies performed

Product class	Product	Number of studies
Inhibitors	Antithrombin	75
	A ₁ PI	50
	C1-inhibitor	13
Immunoglobulins	IVIG	280
	IgM	15
Coagulation factors	FIX	143
	FVIII/vWF-FVIII	52
	FX	30
	PCC	24
	Partly activated coagulation factor	14
	Fibrinogen	13
	FXIII	13
Others	Thrombin	10
	Protein X	12
	Plasminogen	10

Note: Number of plasma products studied and number of studies conducted. Protein X is a developmental protein and does not belong to any of the plasma products described.

Abbreviations: A₁PI, alpha1-protease inhibitor; PCC, prothrombin complex concentrate or Factor IX complex.

technically possible (HIV, HAV, and B19V), and model viruses covering a wide range of physicochemical properties and sizes (Table 2). Viruses were grouped according to their size, i.e., from smaller to larger, parvoviruses (B19V, BPV, CPV, MVM, PPV; total of 225 studies), picornaviruses (HAV, BEV, EMCV, PEV, HPV-1, TMEV; total of 170 studies), caliciviruses (FCV; two studies), papovaviruses (SV40; total of nine studies), flaviviruses (BVDV, WNV; total of 159 studies), togaviruses (SINV, SFV; total of nine studies), reovirus 3 (Reo3; seven studies), retroviruses (HIV; 82 studies), rhabdoviruses (VSV; three studies), and herpesviruses (PRV, HSV, IBRV; total of 88 studies).

1.6 | Viral assays

Virus infectivity was assayed by measuring the virus titer (TCID₅₀) through the cytopathic effect in susceptible cell cultures (end-point dilution assays or plaque-forming assays) or other equivalent state-of-the-art methods. In some cases (primarily for parvovirus B19V) the virus concentration (load) was measured by cell culture infectivity assays^{46–52} or through detection of replicated virus

TABLE 2 Characteristics of viruses studied and number of studies performed

Size (shape)	Family	Virus	Blood borne virus	Number of studies
18-24 nm (icosahedral)	<i>Parvoviridae</i>	Parvovirus B19 (B19V)	Yes	14
		Bovine parvovirus (BPV)	No (model virus)	8
		Canine parvovirus (CPV)	No (model virus)	52
		Minute virus of mice (MVM)	No (model virus)	84
		Porcine parvovirus (PPV)	No (model virus)	67
25-30 nm (icosahedral)	<i>Picornaviridae</i>	Hepatitis A virus (HAV)	Yes	99
		Bovine enterovirus (BEV)	No (model virus)	2
		Encephalomyocarditis virus (EMCV)	No (model virus)	39
		Porcine enterovirus (PEV)	No (model virus)	4
		Human poliovirus 1 (HPV-1)	No (model virus)	17
		Theiler's murine encephalomyelitis virus (TMEV)	No (model virus)	9
27-40 nm (icosahedral)	<i>Caliciviridae</i>	Feline calicivirus (FCV)	No (model virus)	2
40-50 nm (icosahedral)	<i>Papovaviridae</i>	SV40	No (model virus)	9
50-70 nm (pleo-spherical)	<i>Flaviviridae</i>	Bovine viral diarrhea virus (BVDV)	No (model virus)	131
		West Nile virus (WNV)	Yes	28
60-70 nm (spherical)	<i>Togaviridae</i>	Sindbis virus (SINV)	No (model virus)	7
		Semliki Forest virus (SFV)	No (model virus)	2
60-80 nm (spherical)	<i>Reoviridae</i>	Reovirus 3 (Reo3)	No (model virus)	7
80-100 nm (spherical)	<i>Retroviridae</i>	Human immunodeficiency virus (HIV)	Yes	82
70 × 175 nm (bullet)	<i>Rhabdoviridae</i>	Vesicular stomatitis virus (VSV)	No (model virus)	3
120-200 nm (spherical)	<i>Herpesviridae</i>	Pseudorabies virus (PRV)	No (model virus)	85
		Human herpesvirus 1 (herpes simplex virus [HSV-1])	No (model virus)	2
		Bovine herpesvirus 1 (Infectious bovine rhinotracheitis virus [IBRV])	No (model virus)	1

Note: Physicochemical properties and sizes of viruses relevant for blood transfusion and model viruses and number of studies performed. The viruses were grouped according to their sizes and each test was performed in validated down scaled version of the production process.

nucleic acid by PCR. Virus reduction factors, expressed as the \log_{10} (LRF), were calculated according to current guidelines.^{1,53}

1.7 | Statistical analysis

1.7.1 | Data analysis

The data were grouped according to virus type, product class, presence of residual infectivity in the filtrate, and whether the filtration step was designed as an effective removal step (LRF of 4 \log_{10} or higher^{34,54} of virus removal capacity) for the smallest virus, parvovirus

(B19V or relevant model viruses), and for all other relevant viruses assessed (HIV, HBV, HCV, etc.).

1.7.2 | Robustness

A statistical analysis (t test) of the virus LRF achieved by tangential flow filtration versus (vs.) dead-end filtration was performed for all studies employing nanofilters with pore sizes of 15 to 20 and 35 to 50 nm (Planova 15N, Planova 20N, and Planova 35N filters); a proportion of studies with Planova 15N, Planova 20N, and Planova 35N filters were performed using dead-end mode.

1.7.3 | Pearson's correlation coefficient (Pearson's r) calculation

LFR (\log_{10}) vs. volume filtered (L/m^2), operating pressure (bar), and total protein concentration (g/L) was expressed using a scatter plot to determine a functional relationship between the different variables. The

Pearson's r was calculated using SAS/JMP (Version 13.1.0) as a measure of association between the variables LFR vs. volume filtered (L/m^2), operating pressure (bar), and total protein concentration (g/L). No linear relationship of the two continuous variables exists at a Pearson's r of near 0, and a strong linear relationship exists at ± 0.8 or higher.

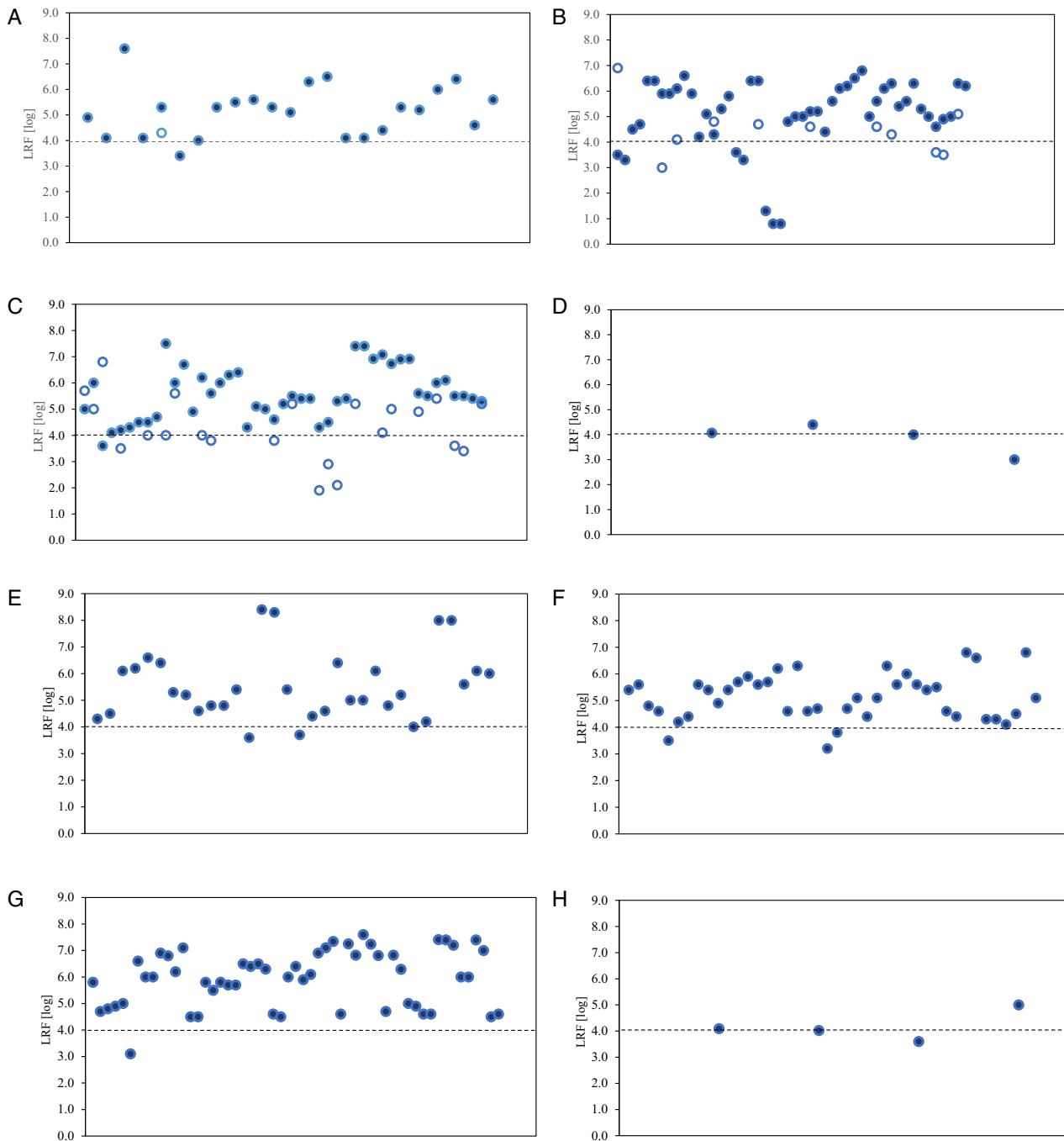


FIGURE 1 Virus retention capacity (LRF [\log_{10}]) of viruses larger than approximately 25 nm by 15 to 20 nm pore-size nanofilters for different product classes (A,E,I,M, inhibitors; B,F,J,N, immunoglobulins; C,G,K,O, coagulation factors; D,H,L,P, other product intermediates) and size of the virus tested (A-D, approx. 25-40 nm; E-H, approx. 50-70 nm; I-L, approx. 70-120 nm; M-P, >120 nm). ●, \geq values for which the detection limit of the titration method was reached. ○, Values for which the detection limit of the titration method was not reached. Each circle is representative of one study [Color figure can be viewed at wileyonlinelibrary.com]

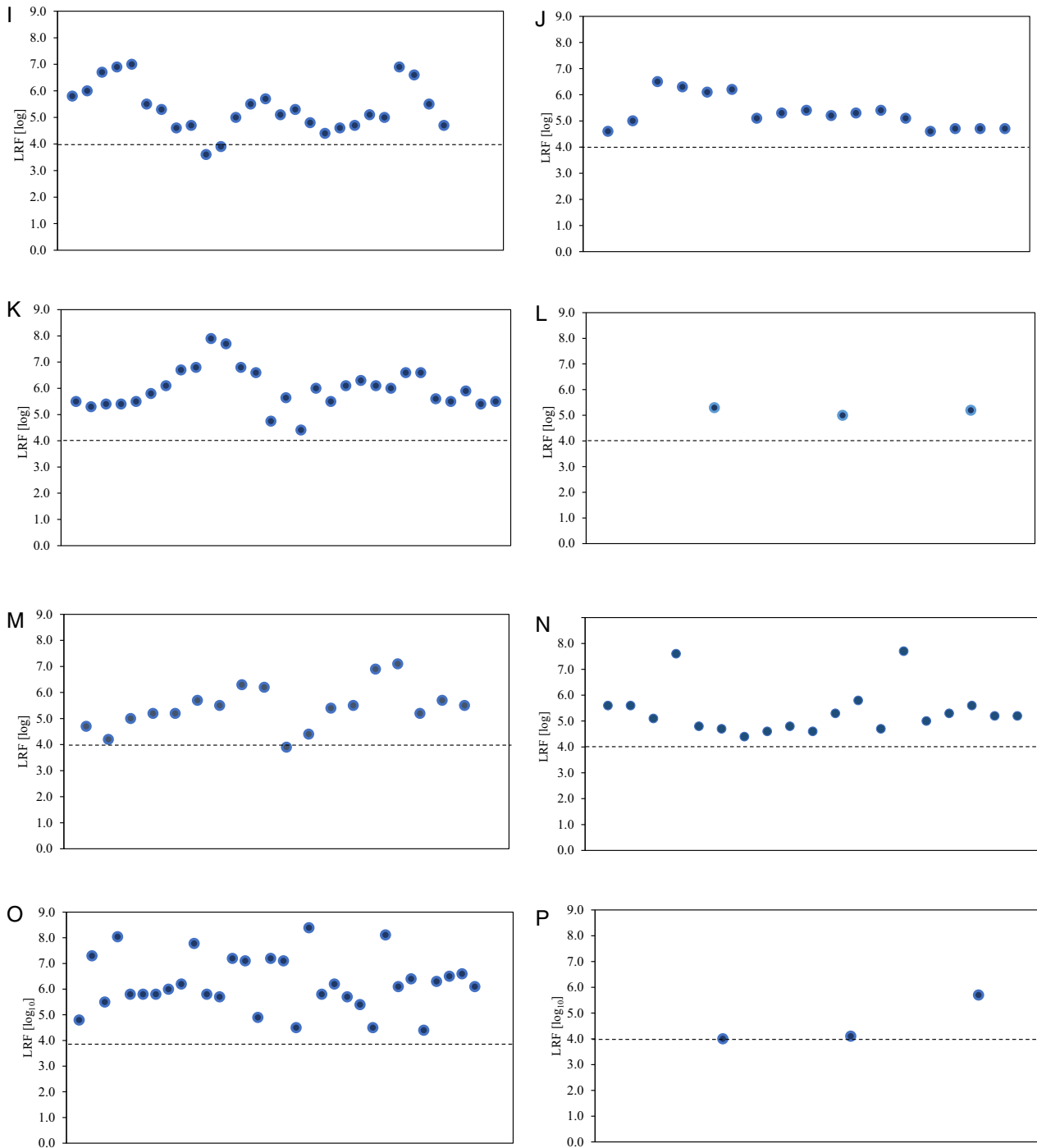


FIGURE 1 (Continued)

2 | RESULTS

2.1 | Virus removal capacity of nanofilters

The virus removal capacity of nanofilters for different product classes and different sized viruses was evaluated under scaled-down manufacturing conditions. The

individual LRFs for each study performed with viruses larger than 25 nm using 15 to 20 nm nanofilters are shown in Figure 1. Complete virus retention to the limit of detection for all viruses was almost always observed with a few exceptions. In general, viruses of the size range 25 to 40 nm (picornaviruses, caliciviruses, and SV40) were effectively removed by 15 to 20 nm pore-size filters (Figure 1A-D), regardless of

whether the filters were introduced with the intention to enhance viral safety or implemented to achieve effective removal of small parvoviruses. In some cases where less virus retention and incomplete retention were observed (Figure 1C), these results were always associated with conditions under which the nanofiltration step was performed to improve viral safety, mainly for larger blood-borne enveloped viruses without intentionally optimizing the process for effective removal of small parvoviruses. Certain studies

performed with immunoglobulin and HAV resulted in low LRFs of approximately 1 yet reached the limit of detection by cell culture assays (Figure 1B). For all larger viruses (>50 nm), no residual infectivity in the filtrate was ever observed, independent of the filter brands employed (Figure 1E-P). The few studies with LRFs below 4 (but also without residual infectivity in the filtrate) were due to the moderate virus load in the spiked starting material or virus neutralization due to presence of virus-specific antibodies.

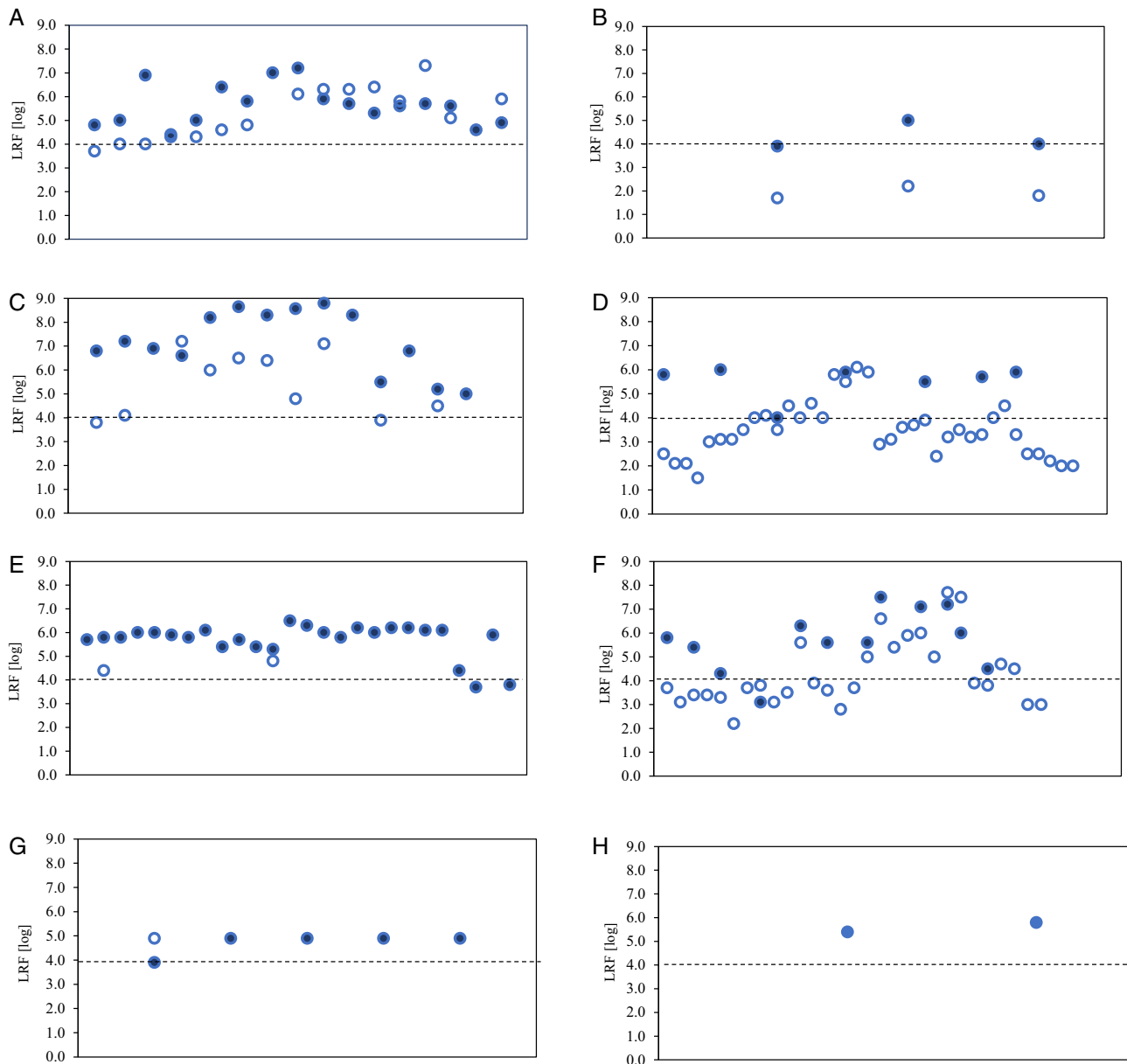


FIGURE 2 Virus retention capacity (LRF [\log_{10}]) for different product classes (A, B, inhibitors; C, D, coagulation factors, E, F, immunoglobulins; G, H, other product intermediates) using 15 to 20 nm nanofilters with filtration step designed to enhance virus safety, including effective parvovirus removal (A, C, E, G) or implemented to enhance virus safety for viruses larger than parvovirus (18–24 nm; B, D, F, H). ●, \geq values for which the detection limit of the titration method was reached. ○, Values for which the detection limit of the titration method was not reached. Each circle is representative of one study

The individual LFRs for each study performed with the smallest parvoviruses (18-24 nm) using 15 to 20 nm pore virus filters are shown in Figure 2. Parvovirus retention (LFRs) was for all classes ranging from 4 \log_{10} or greater, and therefore showed a remarkable removal capacity, when the intention of the nanofiltration was to improve viral safety mainly for blood-borne enveloped viruses while the step was specifically targeted to achieve a comparably effective removal of parvoviruses (Figure 2A,C,E,G). When the

intent of nanofiltration was to primarily enhance virus safety in general, but not specifically targeted toward retention of small parvoviruses then the parvovirus LFR values were lower and variable (Figure 2B, D,F,H).

The retention of smaller viruses by 35 to 50 nm nanofilters was variable and depended on product class (Figure 3A-D). Higher LFRs were observed with some viruses spiked into immunoglobulins (Figure 3A) probably due to retention of antibody-virus complexes.^{32,55}

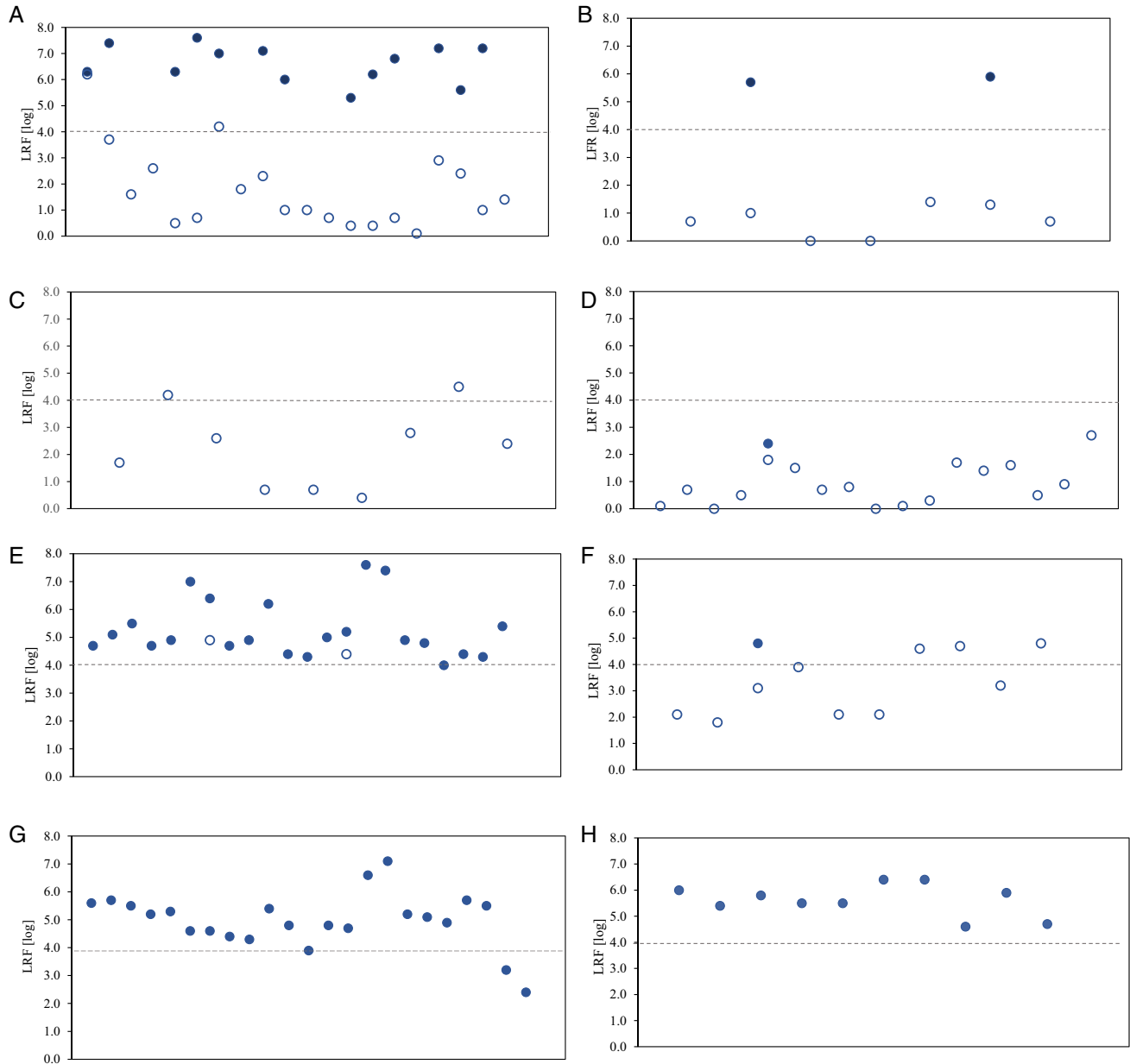


FIGURE 3 Virus retention capacity (LRF [\log_{10}]) demonstrated for different viruses and product classes for 35 to 50 nm pore nanofilters. A,B, viruses studied with sizes of approximately 18 to 24 nm included parvoviruses. C,D, viruses of sizes of approximately 25 to 50 nm included picorna- and caliciviruses and SV40. E,F, viruses of sizes of approximately 50 to 70 nm included flavi- and togaviruses. G,H, viruses of sizes greater than 70 nm included retro-, rhabdo-, and herpesviruses. A,C,E,G, immunoglobulins; B,D,F,H, coagulation factors. ●, \geq values for which the detection limit of the titration method was reached. ○, Values for which the detection limit of the titration method was not reached. Each circle is representative of one study

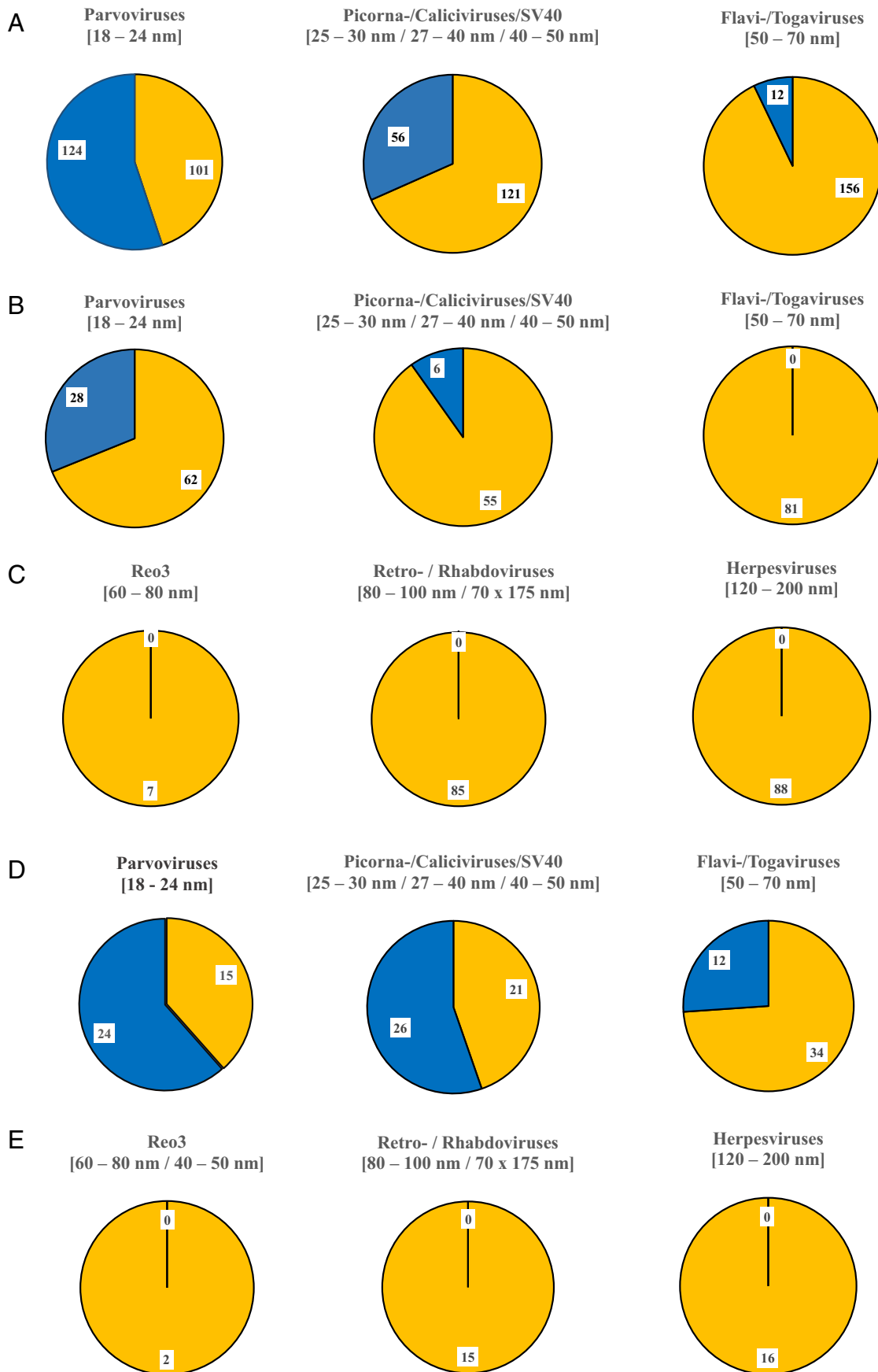


FIGURE 4 Legend on next page.

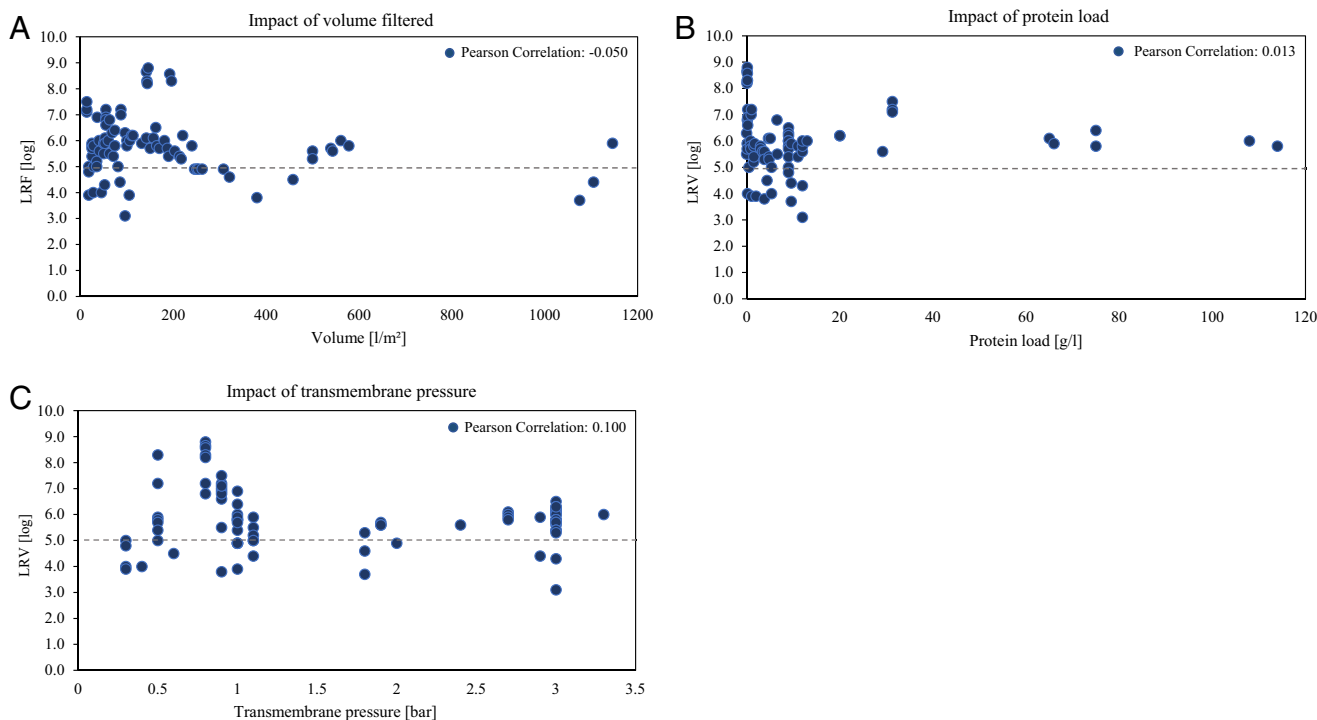


FIGURE 5 Impact of distinctive robustness parameters on small virus (parvovirus, 18-24 nm) removal using 15 to 20 nm nanofilters. Impact of volume filtered (A), protein load (B), and transmembrane pressure (C) on virus removal (LRV [\log_{10}]) of 15 to 20 nm nanofilters for different product classes. ●, \geq values for filters implemented to provide effective virus retention, including effective parvovirus removal

Effective (or complete) removal was always observed for viruses larger than 70 nm (Figure 3G,H) and almost always observed for flavi- and togaviruses (\sim 50-70 nm) when immunoglobulins were filtered (only two studies did not demonstrate complete removal of virus 50-70 nm for immunoglobulins; also Figure 3E). The 35 to 50 nm nanofilters were not tested or reported to be implemented for inhibitors and “others.”

2.2 | Virus retention based on size

The proportion of studies with the presence or absence of residual infectivity in the filtrate is shown in Figure 4. As virus size increased the proportion of studies where complete (to the limit of infectivity detection) virus retention was achieved also increased. This was observed for both 15 to 20 nm (Figure 4A-C) and 35 to 50 nm pore-size

nanofilters (Figure 4D,E). For small- and medium-sized viruses, the proportion of studies with complete virus retention increased when the step was designed to enhance virus safety primarily for retention of blood-borne enveloped viruses and, at the same time, specifically targeted to provide effective parvovirus removal (Figure 4A vs. Figure 4B). For nanofilters with pore sizes of 15 to 20 and 35 to 50 nm, complete removal of large viruses (Reo3, Retroviruses, and Herpesviruses) was achieved (Figure 4C,E).

2.3 | Robustness

The experimental data set encompassed a wide range of physicochemical process variables, such as pH (4.1-8.4), conductivity (0.48-48 mS/cm), and temperature—below room temperature (2°C-10°C), at room temperature (18°C-25°C), and above room temperature (>25°C).

FIGURE 4 Number of studies in which residual infectivity was detected (■) or not (□) in the filtrate. A, nanofiltration step designed to enhance virus safety (4 \log_{10} or higher of virus removal capacity for viruses larger than approx. 25 nm) in studies covering 15 to 20 nm pore nanofilters. B, nanofiltration step designed to enhance virus safety, including effective removal of the smallest viruses (parvovirus) in studies covering 15 to 20 nm pore nanofilters. C, all studies covering 15/20 nm pore nanofilters using Reo3/SV40, retro-/rhabdoviruses, and herpesviruses. D,E, number of studies with and without residual infectivity or NAT signal in the filtrate for 35/50 nm pore nanofilters covering all studies for all viruses. Number in brackets denotes virus size

Comparing the LRF for all viruses in dead-end vs. tangential-mode nanofiltration, no significant difference in removal could be shown (t test) for nanofilters with pore sizes of 15 to 20 nm and 35 to 50 nm [15 to 20 nm pore sizes—mean of LRF 5.3 (\pm 1.3) vs. 4.6 (\pm 0.7), calculated t value 2.01 vs. t value of 2.36 for $P = 0.05$; 35 to 50 nm pore sizes—mean LRF 3.5 (\pm 2.1) vs. 4.0 (\pm 2.2), calculated t value 1.28 vs. t value of 2.36 for $P = 0.05$]. Robustness of nanofiltration was assessed based on the smallest virus (parvovirus) removal as a function of volume filtered, total protein load, or transmembrane pressure (Figure 5). LRFs for parvovirus were on the order of four or higher, when the process was designed to provide effective virus retention including effective parvovirus removal. Variability in LRFs was observed in cases where the nanofiltration step was introduced to increase virus safety primarily for enveloped blood-borne viruses but not specifically intended to produce comparably effective parvovirus removal (data not shown). Comparison of two variables, namely, volume and protein load (Figure 5A,B, respectively) resulted in Pearson's r close to 0, indicating that these variables were not deterministic for the level of effectiveness of parvovirus removal. However, an increase in operating pressure (Figure 5C) resulted in a moderate positive effect on virus removal (Pearson's $r \sim 0.34$ - 0.49).

3 | DISCUSSION

This analysis represents the largest historic retrospective evaluation of nanofiltration use to assess removal of viruses in manufacturing of PDMPs to date, covering 754 studies from six companies. The studies evaluated the nanofiltration step of 17 different classes of PDMPs ranging from highly purified proteins to intermediate purity complex multiprotein mixtures filtered under a wide range of physicochemical process variables, such as pH, temperature, conductivity, filter load, protein concentration, and transmembrane pressure. Retention of 16 different viruses with a wide range of physicochemical properties and sizes, ranging from approximately 18 to 200 nm, were used. Seven types of 15 to 20 nm pore and three types of 35 to 50 nm pore nanofilters from four different manufacturers were assessed. This range of variable conditions is broader and more extensive than those evaluated previously for PDMPs and recombinant products.⁵⁶

The results convincingly show that nanofiltration is an effective and robust method with high virus removal capacity of targeted viruses based on their size. The data show that the most relevant TT viruses, i.e., HIV, HCV, and HBV (42 to 100 nm) would be effectively removed

during the manufacturing process in the rare case they would escape detection during the extensive donor and plasma screening process applied before donations are released for manufacturing. Other viruses of similar size that are not specifically tested for in plasma screening (e.g., WNV, Zika) would also be effectively removed.⁵⁷ In addition, when the nanofiltration step is optimized to also intentionally provide effective removal of parvoviruses there is a greater likelihood of complete parvovirus and another small virus retention by 15 to 20 nm pore nanofilters. Optimization variables may include the use of prefilters to maintain product flow or limiting the volumetric or protein load of the nanofilter. Robustness of nanofiltration was specifically assessed for three variables where data were available across all data points, namely, volume filtered (L/m^2), operating pressure (bar), and total protein (g/L; Figure 5). These three data set groupings also included a wide range of other robustness variable, such as pH, temperature, process interruption, and conductivity, which could potentially impact virus retention. Because the data sets were limited to manufacturing ranges, it was not unexpected that statistical analysis showed that processes were robust to these variables, and these variables were not deterministic for the level of effectiveness of the parvovirus removal. Therefore, the analyses confirm that the nanofiltration steps introduced by plasma protein manufacturers have been implemented with appropriately defined manufacturing ranges to ensure robustness. Overall, nanofiltration steps implemented into the production processes are highly robust.

In all studies using viruses of 70 nm or larger (189 nm), complete retention of infectivity was achieved by all nanofilters. These results provide strong evidence that the use of large viruses in virus validation studies, at least for well-established nanofiltration platforms, is not warranted. Since the virus removal capacity of nanofiltration is based primarily on size exclusion, the LRFs of studies with smaller viruses can be applied to estimate the minimum removal capacity of larger viruses.

Nanofiltration has become one of the most important steps with pathogen removal capacity in assuring the safety of both plasma-derived and recombinant products. Because efficiency of nanofiltration is based on retention of viruses by size exclusion, it is highly complementary to other established and highly robust steps with pathogen inactivation capacity. The significance of implementation of nanofiltration in the production of PDMPs is comparable to the initial introduction of S/D treatment, dry heat treatment, and pasteurization. Its routine application in manufacturing processes, in combination with an effective and robust inactivation methods, has substantially increased the final product safety regarding all viruses.

In conclusion, the large variety of products and process conditions assessed in this data compilation show that a nanofiltration step can be developed and optimized to provide effective virus removal capacity to almost any plasma-derived biologic intermediate. The main factors affecting nanofiltration efficacy are filter pore size and virus size. The data presented here substantiate the effectiveness and robustness of nanofiltration during manufacturing of different plasma-derived proteins.


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CONFLICT OF INTEREST

The authors are employees of plasma protein manufacturers or trade associations and some also hold shares within the companies. The authors declare no conflicts of interest.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of this article.

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