

Regarding plasma-derived von Willebrand factor concentrates: what about viral safety?

A propósito de los concentrados de factor von Willebrand de origen plasmático: ¿qué decir de la seguridad viral?

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Abstract

We present a brief report on the status of viral safety of plasma derived factor concentrates (pd-FC), especially von Willebrand factor (VWF), in the 21st century. We also present the results of the efforts of the manufacturers and the close observation of guidelines to produce plasma factor concentrates. These efforts and continuous monitoring of these processes allow us to reach a level of safety never achieved before. We remark that this continuous process is necessary to guarantee the safety of a product such as plasma, increasingly necessary in different areas of medicine, focusing on plasma concentrates of VWF (pdVWF). This control is need for products obtained by biotechnology, for which there is less experience.

Keywords: Biotechnology. Guidelines. Plasma-derived concentrate von Willebrand factor. Recombinant von Willebrand factor. Viral safety.

Resumen

Presentamos un breve informe sobre el estado de la seguridad viral de los concentrados de factor derivados del plasma, especialmente del factor de von Willebrand, en el siglo XXI. Asimismo, comentamos los resultados en cuanto a cómo los esfuerzos de los fabricantes y la estrecha observación de las directrices para la producción de concentrados plasmáticos de factores, así como la monitorización continua de estos procesos, permiten alcanzar un nivel de seguridad nunca logrado anteriormente. Resaltamos que este es un proceso continuo, necesario para garantizar la seguridad de un producto como el plasma, cada vez más necesario en diferentes áreas de la medicina, centrándonos en los concentrados plasmáticos de factor de Von Willebrand y también en la necesidad de control de los productos obtenidos por biotecnología, con los que existe menos experiencia.

Palabras clave: Biotecnología. Guías clínicas. Concentrados de factor von Willebrand de origen plasmático. Factor von Willebrand recombinante. Seguridad viral.

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Introduction

von Willebrand disease (VWD) is the most common hemorrhagic disease in the world, affecting men and women equally,¹ affecting up to 1% of the population according to epidemiological data, although figures based on clinical presentation are close to 0.1%.² In milder types of VWD (type 1 and low von Willebrand factor [VWF]), 70–90% of patients are women. In recent years, there have been great advances in terms of improvements in diagnostic techniques, for example, molecular biology techniques or the binding of VWF to collagen or glycoprotein IIb/IIIa. The treatment of bleeding episodes is still basically an on-demand treatment, that is, replacement therapy of the deficient protein (in this case, VWF) for the cessation of bleeding when it occurs. For this purpose, until not so long ago, we used desmopressin (DDAVP) to patient responders, namely Type 1 and some of the Type 2 VWD patients. Other options are VWF of plasma-derived (pd-VWF) origin, with differences in both the content of VWF, the VWF/FVIII ratio, and the structural integrity of the VWF. Itself is reserved to patients not responders to DDAVP or not candidates to DDAVP. The option of recombinant VWF is more recent and has less experience of use. It has important differences in relation to pd concentrates.

Methods

We searched PubMed and Google Scholar with the words viral safety, VWD, and treatment. We have selected those studies with the largest number of patients. We also reviewed the state of the art regarding the infectious risk. This includes measures to minimize it of products obtained from human plasma and those obtained from recombinant technology. Finally, we proceeded to review what has been published by different national and supranational hemovigilance systems and review the concerns about recombinant factor concentrate (FC), especially recombinant VWF.

Discussion

The epidemic derived from the transmission of viral infections by contaminated blood products in the 70 s and 80 s of the last century forced a great effort to improve the process of obtaining the different therapeutic products derived from human plasma on the part of the different companies. This is very important in view of the expected further increase in the volume of plasma

required to fractionate and cover clinical needs. This effort has resulted in a very high level of viral safety. On the other hand, extreme vigilance has been exercised to maintain this margin of safety and avoid infectious risks. These risks could be associated with any possible emerging pathogen that enters the plasma reserve in the future. This improvement begins with the appropriate selection of donors, driven by knowledge of viral epidemiology. It continues with the development of blood tests based on molecular diagnosis by polymerase chain reaction techniques. This test, together with viral inactivation techniques in the manufacturing process, is the main measures that contribute to the safety of pathogen transmission.^{3,4}

In 2012, Franchini et al.⁵ carried out a systematic review, this review included prospective studies published in the preceding 20 years on adverse events (AEs) related to the infusion of FC, of plasma or recombinant origin, on behalf of the European Hemophilia Safety Surveillance System (EUHASS). In his introduction, he points out the high viral safety achieved by FC in the previous 25 years. The greatest safety concern since then had been the development of neutralizing inhibitors to FVIII. In this publication, they consulted electronic databases and article references. AEs related to treatment with plasma and recombinant FC from 1990 to 2011 were collected, excluding inhibitors and thrombotic events on which the main focus had been placed. They reported 946 patients treated with pdFC: 445 Hemophilia A patients, 127 Hemophilia B, and 374 VWD patients. No viral transmissions were reported, which confirms the high degree of safety in this type of concentrate.

In this process of manufacturing pdFC, the inactivation or elimination of viruses⁶ occurs during their purification and formulation. Cryoprecipitation, chromatographic separation (particularly immunoaffinity chromatography), and lyophilization remove significant amounts of viruses. Further, it is a key to subject these concentrates to a double viral inactivation process in accordance with EMA standards. These recommend two distinct viral inactivation steps with different modes of action. These steps help to ensure that any virus that survives Step 1 is inactivated and/or eliminated in Step 2. At least 1 of the steps should inactivate or eliminate viruses without a lipid envelope. The guidelines further state that if a manufacturing process contains a step that reliably inactivates and/or removes a wide range of enveloped and non-enveloped viruses, and additional manufacturing steps reliably contribute

Table 1. Purification and viral inactivation methods applied in plasma-derived von Willebrand factor approved in Europe¹⁰

Product	Manufacturer	Purification	Viral inactivation
Alphanate	Grifols	Heparin ligand chromatography	S/D + dry heat (80°C, 72 h)
Factor 8Y	BioProducts laboratory	Heparin/glycine precipitation	Dry heat (80°C, 72 h)
Fanhdi	Grifols	Heparin ligand chromatography	S/D + dry heat (80°C, 72 h)
Hemate P	CSL Behring	Multiple precipitation	Pasteurization (60°C, 10 h)
Immunate	Baxter	Ion exchange chromatography	S/D + vapor heat (60°C, 10 h)
Wilate	Octapharma	Ion exchange + size exclusion chromatography	S/D + dry heat (100°C, 2 h)
Wilfactin	LFB	Ion exchange + affinity	S/D, 35 nm filtration, dry heat (80°, 72 h)

LFB: Laboratoire Français du Fractionnement et des Biotechnologies; S/D: solvent/detergent.

to the inactivation and/or elimination of the viruses, the second step may not be necessary.⁷ A reduction of at least 10 log¹⁰ is required for viruses with lipid envelope – a reduction that involves the presence of < 1 viral particle per 1000 L of the plasma pool – and which is considered safe – and of 6 log¹⁰ in viruses without this envelope.⁸

A previous publication⁹ in 2006 had already highlighted the differences between 12 pd-VWF. The difference is in terms of the number and nature of specific viral safety measures incorporated into the manufacturing processes. Some of these concentrates did not comply with the recommendations of the EMA's Committee for Proprietary Medicinal Products. It was claimed that the viral safety required should be the same for all of them. [Tables 1 and 2](#)^{10,11} show the different methods used for different pd-VWF approved for use in Europe. [Table 3](#)¹¹, for example, shows the reduction achieved in a widely used pdVWF, such as Wilate® (Lab, Octapharma).¹² This pd-VWF applies two very effective and robust viral inactivation procedures for lipid-enveloped viruses. These procedures are a solvent/detergent treatment (S/D) and prolonged terminal dry heat (called PermaHeat) of the lyophilized product at residual moisture (MR) as recommended. Indeed, it includes one step for non-enveloped viruses, ion exchange chromatography. These steps are aggressive enough to effectively inactivate viruses, above the World Health Organization (WHO)¹³ standards ([Table 4](#)).¹¹ The WHO considers that a robust, efficient, and reliable process will be capable of removing or inactivating substantial amounts of viruses, typically four logs or more, being relatively insensitive to changes in process conditions. At the same time, it must be gentle enough to

maintain the structural integrity and function of the VWF and FVIII molecules. Emphasis is placed on the need for both physicians and recipients of these concentrates, the patients, to be properly informed about the viral safety of existing products on the market. Finally, potential batch-to-batch contamination is avoided by strict cleaning and disinfection methods as part of the manufacturing process.¹⁴ For this reason, some authors affirm that the experience acquired in recent decades has resulted in the absence of transmission of pathogens by the current generation of blood products.³ In fact, no case of transmission of viral infection has been reported in the past 30 years or more.

For blood-borne viruses (e.g., human immunodeficiency virus [HIV], hepatitis C virus [HCV], and hepatitis B virus [HBV]), the uninterrupted safety record of solvent-detergent-treated factor (S/D)¹⁵ concentrates makes a strong case to choose it as the method of choice in the manufacture of these products. For pd-VWF, the large molecular size of VWF makes separation by the size of viral particles (by nanofiltration, for example) less feasible. In this case, one step in the manufacturing process should be effective for hepatitis A virus (HAV) at least. Heat inactivation procedures, such as pasteurization or Permaheat, have proven to be effective against HAV. These methods are effective even for other more resistant viruses such as parvovirus B19.⁶ There are no transmissions of human transmissible spongiform encephalopathies (TSE) agents by plasma derivatives. The problem is that analytical methods capable of detecting the prion in affected human brains or in other tissues are not capable of detecting the agent in blood or plasma.¹⁵ This suggests that, if present, the amount found would be very low and the

Table 2. Virus inactivation and/or removal methods for plasma-derived vWF concentrates¹¹

Brand name (manufacturer)	Precipitation	Chromatography*	Pasteurization	S/D	Dry heat	Lyophilization
Alphanate/Fanhdia (Grifols)	x	x*	x	x	x	x
Biostate (CSL)	x	x†	x	x	x	x
Humate-P/Hemate-P (CSL Behring)	x		x			x
Koate DVI (Talecris Biotherapeutics)	x			x		x
Wilate octapharma	x‡			x	x	x

*Immunoaffinity chromatography.

†Size-exclusion chromatography.

‡Ion-exchange chromatography.

vWF: von Willebrand factor; S/D: solvent/detergent.

Table 3. Pathogen inactivation/elimination by Wilate® manufacturing process¹¹

Pathogen	HIV	HBV	HCV	WNV	HAV	B19	vCJD
Model used	HIV-1	PRV	SBV	SBV	HAV	PPV	HAS 263 K
Step	Logarithmic reduction factor [log ₁₀]						
Sequential precipitations							1.8
Ion exchange chromatography					1.9	3.3	
Sequential chromatography purifications							2.4
S/D treatment	≥ 7.5	≥ 8.5	≥ 8.6	≥ 8.6			
PermaHeat treatment*	≥ 5.8	4.9	≥ 5.5	≥ 5.5	≥ 5.7	4.1	
Total	≥ 13.3	≥ 13.4	≥ 14.1	≥ 14.1	≥ 7.6	7.4	4.2

*100°C 2 h.

HIV: human immunodeficiency virus; HBV: hepatitis B virus; HCV: hepatitis C virus; WNV: West Nile virus; HAV: hepatitis A virus; B19: human parvovirus B19; vCJD: variant Creutzfeldt–Jakob disease; PRV: pseudorabies virus; SBV: sindbis virus; PPV: porcine parvovirus; HAS: hamster adapted scrapie; S/D: solvent/detergent.

capacity of plasma fractionation. The purification processes applied to coagulation products to eliminate TSE agents are based on the physicochemical change of properties caused by the conversion of the natural form of prion protein (PrP^c; rich in α -helix) to pathological form (PrP^{Sc}; rich in β -sheets).¹⁶ This implicates new different properties such as insolubility or hydrophobicity providing the basis for its elimination during manufacturing steps. Besides, the production of plasma products includes many steps with a capacity to eliminate impurities and other different pathogens.

Heat treatment is a widely used method.⁷ Viruses have a variable sensitivity to heat. The efficacy of heat in viral inactivation depends on variables such as time, physical state (dry or in solution), saline content, the reason for the temperature change, or the nature and concentration of the stabilizers. The temperature is important; if < 80°C is relatively ineffective against some

viruses in lyophilized products. Heat can be applied to freeze-dried concentrates at higher temperatures (80–100°C), from half an hour to 72 h. Other stages, such as pasteurization, apply heat treatment to the product in aqueous solution at 60° for 10 h. Both types of stages have been shown to be effective against enveloped and non-enveloped viruses,¹⁴ as can be seen in table 4. Here showed the logarithmic reductions for each virus model of different stages of viral inactivation and purification.

As previously discussed, the EMA⁷ requires pd-FC to have several stages of viral inactivation/reduction. These must be aggressive enough to guarantee the viral safety of the product. At the same time, they must be respectful of the structural integrity of the proteins of interest.⁸ To meet these two premises, each manufacturer designs or chooses these stages of viral inactivation and purification to achieve the greatest safety and

Table 4. Virus reduction factors (log) for relevant viruses reported for individual process steps¹¹

Process step evaluated	Virus reduction factors (log)									
	Enveloped viruses					Non-enveloped viruses				
	HIV	HCV model	HBV model		HAV and model		B19V and model			
	HIV-1	BVDV	BHV	PRV	HAV	POL	B19V	PPV	CPV	MMV
Lyophilization	1.2	1.7	1.3	-	2.1	3.4	-	< 1.0	-	-
Cryoprecipitation	-	-	-	1.6	1.5	-	-	1.5	-	-
3.5% PEG precipitation	< 1.0	< 1.0	< 1.0	-	-	3.3	-	1.2	-	-
Al (OH) 3 adsorption/glycine precipitation/NaCl precipitation	3.6	2.4	-	3.7	2.4	-	-	3.4	-	-
S/D	≥ 11.1	≥ 4.5	≥ 8.0	≥ 8.5	NA	NA	NA	NA	NA	NA
Dry heat	5.2 [†]	≥ 4.9 [†]	2.1 [†]	4.9 [§]	≥ 5.8 [*]	≥ 2.5 [*]	4.1 [‡]	4.1 [‡]	-	-
Pasteurization [§]	≥ 6.4	≥ 8.9	-	4.6	4.2	-	≥ 3.9	1.1	-	-
Chromatography	≥ 2.0	< 1.0	7.6	-	-	< 1.0	-	< 1.0	-	-
Virus filtration	> 6.4 [¶]	6.6 ^{**}	-	> 6.0 [¶]	6.8 ^{**}	-	-	-	≤ 1.0 [¶]	-
Vapor heat	> 6.8	> 7.1	-	> 7.4	> 4.5	-	≥ 3.5 ^{††}	-	≤ 1.0	-

Hyphens indicate that no data are available.

^{*}100°C for 30 min.[†]80°C for 72 h.[‡]100°C for 120 min.[§]In aqueous solution at 60°C for 10 h.[¶]35-nm filtration.^{**}35- to 15-nm sequential filtration applicable.^{††}60°C for 500 min, followed by 80°C for 60 min.

BHV: bovine herpes virus (a nonspecific model virus for HBV); CPV: canine parvovirus (a model virus for B19V); MMV: mice minute virus (a model virus for B19V); NA: not applicable; PEG: polyethylene glycol; POL: poliovirus Sabin type 2; human parvovirus B19.

efficacy of its products, depending on the pathology for which they were designed, as can be seen in [table 3](#).¹¹

In relation to the viral transmission associated with the use of pd-VWF, no cases are reported in this publication by Kouides et al.¹⁷ in the period from 1982 to 2015. A total of 670 AEs were reported. 343 AEs corresponded to adverse reactions considered clinically relevant risks adverse drug reactions (ADRs) and 103 suspected virus transmission. None of the suspected cases was confirmed as associated with the infusion of the pd-VWF in question. The analyzed concentrate was subjected to viral inactivation by pasteurization at 60°C for 10 h in the presence of stabilizers before a second precipitation with sodium chloride.¹⁸ Escuriola-Ettingshausen et al.¹⁹ in a systematic review of the literature evaluated the existing evidence on, among others, the safety of a pd-VWF in the treatment of VWD. They incorporated an analysis of pharmacovigilance data collected over more than 40 years. They identified a total of 1296 ADRs in the database from June 1982 to June 2022, but any confirmed cases of viral transmission.

A retrospective study by Jiménez-Yuste et al.²⁰ in 2022 also evaluated the safety, among other items, of a pd-VWF in the management of VWD in Spain. This product is subjected to two viral inactivation steps: S/D (using a combination of TNBP and polysorbate 80) and terminal heat at 80°C for 72 h after lyophilization. The time period runs from July 2019 to February 2020. 15 AEs were reported in eight of 72 patients. None was related to possible transfusion transmission of viral infections.

Federici et al.,²¹ reported the results of a retrospective analysis of the efficacy and safety of a pd-VWF in 10 centers in Italy. The data were collected from the medical records of 57 patients. The time period runs from January 2017 to December 2019. They did not reported significant AEs, including the transmission of viral infections. Rugeri et al.²² conducted a systematic review on efficacy and safety of the same product for the treatment of VWD patients. They selected 11 publications from eight study cohorts, all from multicenter trials with pediatric and adult patients. They included pharmacovigilance data reported from clinical trials and on

246 patients receiving the pd-VWF. The authors reported 34 AEs in 24 patients, but no cases of viral transmission related to use of these concentrates. In addition, pharmacovigilance data from 23 years were included in relation to 5877 patients, reporting 150 cases. These cases corresponded to 378 ADRs, but the transmission of any viral infection with the use of this pd-VWF was also not reported.

In 2020, the results of a prospective, observational, post-marketing study of another pd-VWF in relation to the treatment of VWD were reported. They evaluated, among other items, the safety in 158 of the included patients. These patients belonged to 31 centers in France. AEs were reported in 21.5% of patients. None were considered related to the treatment itself. No safety alerts were reported from an infectious point of view.²³

In 2021, it was reported the results of WIL-20 study. This is a prospective, observational, phase 4, and post-marketing study. It was designed to evaluate safety, tolerability, and efficacy of a pd-VWF in routine clinical practice. It included patients of all ages with all types of VWD in various settings.²⁴ Over a 2-year period (2015-2017), out of 120 included patients, only 111 were selected for safety evaluation. No cases of transmission of viral infections were reported in 7024 infusions of this product. In addition, in the latest Food and Drug Administration (FDA) report²⁵ evaluating the safety of this pd-VWF from September 2019 to April 2022, no seroconversion was reported in the USA.

The latest data reported from EUHASS²⁶ to 2022 include 4641 AEs since 2008. No cases of viral infection transmitted by the use of pd-FC were reported, included pd-VWF. This safety is reinforced, for example, by the dates reported from different registries: in the United Kingdom alone, between 2022 and 2023, 68,892,532 international units of VWF were transfused, in 1034 patients. No incidence was reported from an infectious point of view.²⁷

These data effectively contrast with the infectious risks of other blood products used daily in our hospitals, such as apheresis platelets or red blood cell concentrates. These are not subjected to viral inactivation processes used in pd-FC. An US publication retrospectively analyzed the transmission of viral infections by transfusion of contaminated blood products in the hospital. The time period runs between 2013 and 2018. It reported an infection rate of 1/225,440 units transfused.²⁸ Spanish hemovigilance system reports no viral infections associated with transfusion of blood components in 2021. In 2020, transmission was confirmed in one case of West Nile virus

(WNV), without clinical consequences, or in 2019, one case of cytomegalovirus and one case of HEV.²⁹

Cases of positive antibodies to some viruses are reported^{17,22,24,25} as is the case in the general population, especially those that are easier to transmit such as parvovirus B19. The batches involved were certified to be virus free after comparing and analyzing. It is ruled out that these few reported viral infections can be attributed to treatment with the product in question. The lower requirements demanded by the WHO¹³ or EMA⁷ for viruses such as HAV or parvovirus B19 are based in two facts: first, on their lower risk to humans as they do not generally lead to chronicity of symptoms and second, on the potential presence of neutralizing antibodies in the plasma pool of untransfused infection.⁸

Conclusion

With all that said, from the point of view of viral safety, it can be said that pd-FC, including pd-VWF, is safer than ever before.³ At the present time, the possibility of infection by HBV, HCV, and HIV, combined with general and universal case vaccination against HAV and HBV, especially in first-world countries, is rather theoretical.³⁰ Thanks to these improved and comprehensive steps for the reduction of pathogens, doctors and patients should be confident in the efficacy and safety of these FC¹⁴ for, among others, the treatment of VWD. As a result of the work carried out, no case of transmission of any viral infection by transfusion of pd-FC has been reported over the past 30–40 years. Further, and unlike what has happened in hemophilia, efforts to obtain a recombinant VWF (rVWF) have been less successful. At present, only one approved rVWF has been obtained.³¹ In the past 35 years, the transmission of viral infections with the use of products obtained by recombinant technology not reported. It is known that these concentrates could theoretically transmit human or non-human mammalian viruses. These viruses would be introduced through the stem cell lines or by human or animal proteins contained in the liquid medium used for freezing or culturing the cells.^{5,6} This risk is considered real,⁶ more so for products obtained from human cell lines than those from animal cell lines (such as, Chinese hamster ovary [CHO] cells). They must be subjected to the same viral inactivation processes as pd-FC. Barone et al.⁴ underline the importance of the choice of cell line once the reported contaminations have been detected. Four of five viruses identified in human and primate cell lines are human and primate pathogens. Only one (the Cache Valley virus) that caused contamination of CHO cell

cultures is known to cause infection in humans.⁵ Manufacturers are aware of these differences in risk associated with the cell line used. Testing is critical to determining viral safety in biotech products but this alone does not guarantee safety. It is important to adopt an holistic and multifaceted approach. This fact was highlighted by severe acute respiratory syndrome coronavirus 2 pandemic, whose ability to infect production cell lines or to be detected with existing assays was not initially known. Therefore, the viral safety of some biotechnological products, today, depends almost exclusively on the prevention of contamination through rigorous controls of the manufacturing process. As previously stated, recombinant FC must be subjected to the same viral inactivation processes as products of plasma origin.^{4,5,7} Transmission of viral infections with rVWF has not been reported so far.

The appearance of the first rVWF is one more therapeutic element to add to the current arsenal. Its appearance does not respond in any way to a question of viral safety. It leaves open questions such as superiority in terms of clinical efficacy or potential immunogenic risk. Other questions are related to cost and how it can impact the sustainability of health systems, at least, those financed with public resources. Given the clinical efficacy of current pd-VWF, and with the accumulated experience of use, other issues, especially inhibitor development in hemophilic patients, are a much more real concern, not viral safety. The effort continues to prevent the entry of any emerging pathogens into the much-needed plasma reserves. In our opinion, until we find a test, and only depending on the plasma source not languishing, we can and should ensure that our patients are being treated with safe and effective pd-FC as they have done so far. We cannot forget that not even the recombinant FC, even though it avoids the use of proteins in its composition, excludes 100% of the possibility of contamination of cell lines. However, no cases of viral transmission have been reported with these recombinant concentrates. Therefore, the no possibility of transmitting infections of viral or other origin to humans should not be the only valid argument to justify its use. It should demonstrate efficacy and efficiency at least similar to that of the products currently used to treat VWD. Admittedly, this can be complicated and beyond the scope of this report. Leebeek et al.³¹ recognize that rVWF prophylaxis maintained a similar level of hemostatic control in patients switching from pdVWF prophylaxis to rVWF prophylaxis, not better. In fact, on pd-VWF prophylaxis, 37.5% of patients had more than two BEs

and 25% had no BEs. After switch to rVWF, 62.5% had more than two BEs and 37.5% had no BEs. As said Dr Klamroth¹¹, 10 years ago, and especially when it is not clear that these new recombinant products bring any real net benefit, certainly not in terms of effectiveness and probably, efficiency, all of us should rely not only on the proven efficacy but also on the safety of this pd-VWF for treatment of VWD. Although some cases of positivity have been described, for example, to parvovirus B19, it has been highlighted that the current requirements for this virus by regulatory agencies are adequate. No alarm situation should be generated for our patients. Therefore, zero risk is never guaranteed, but even so, pd-FC never had a wider safety margin than today, comparable to any existing biologically derived therapeutic product, in terms of theoretical risks of biological agent transmission. This is amply covered by millions and millions of units transfused to patients in the past 25–30 years. Any incidence has been reported as derived from the reports of EUHASS, British surveillance systems or the FDA itself, regardless of the manufacturer and/or product. In our opinion, in the light of the data, we believe that viral safety, at least as far as known pathogens are concerned, is fully guaranteed. This cannot be an excuse to reduce the efforts made by the industry, in all phases of the process of obtaining plasma derivatives. They are carried out to ensure both the safety and efficacy of the final product.

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Conflicts of interest

None.

Ethical considerations

Protection of human subjects and animals. The authors declare to have followed the ethical standards of the relevant experimentation committee, according to the World Medical Association and the Declaration of Helsinki. The procedures were approved by the institutional Ethics Committee.

Confidentiality, informed consent, and ethical approval. This study does not involve personal patient data, medical records, or biological samples, and does not require ethical approval. SAGER guidelines do not apply.

Declaration on the use of artificial intelligence.

The authors declare that no generative artificial intelligence was used in the writing or creation of the content of this manuscript.

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