plasma-derived impurities, such as proteases. Therefore, other manufacturing steps were added for the further purification of IgG and removal of aggregates [7]. Until the 1980s, IVIG preparations were thought not to transmit viral infections. However, reports of the transmission of hepatitis C virus (HCV) by a variety of IVIG preparations, which were not subjected to dedicated virus inactivation, led to serious concern about the safety of IVIG with respect to virus transmission [8–10]. This necessitated the addition of specific virus-inactivation steps to the manufacturing process.

The addition of multiple steps to the manufacturing process of IVIG lowers the yield of IgG and raises the manufacturing costs. At the same time, an increasing demand for IVIG has made the yield even more important. Therefore, the emphasis has lately been to develop completely new IVIG manufacturing processes. Recently, Lebing *et al.* [11] described a novel process for IVIG manufacture, which starts from Cohn fraction II+III paste and utilizes caprylic acid treatment and chromatography for purification of IgG. Caprylic acid precipitation serves both as an effective virus inactivation and purification step. This approach resulted in a simplified process with a much improved yield of IgG.

The introduction of sensitive screening assays for viral markers in donated blood and plasma, and the implementation of effective virus-inactivation methods, has greatly improved the safety of current IVIG products. However, a risk of viral transmission may still exist with physico-chemically resistant agents, which are not effectively inactivated by current chemical virus-inactivation methods [3]. Parvovirus B19 is an example of a physico-chemically resistant virus transmitted by plasma products [12]. Parvovirus B19 antibodies present in IVIG are useful in the treatment of severe complications of parvovirus infection [13]. However, the virus itself was detectable, by polymerase chain reaction (PCR), in IVIG preparations and could theoretically pose a threat of infection to recipients [12]. A case of parvovirus B19 infection, transmitted by a heat-treated IVIG preparation, that led to pure red blood cell (RBC) aplasia has recently been reported [14], as well as a possible superinfection with a new strain of parvovirus B19 in an IVIG recipient already infected with B19 [15].

Considering additional reduction steps for physico-chemically resistant viruses, nanofiltration is efficient at removing non-enveloped viruses from solutions of biologically active proteins [16]. However, efficacious nanofiltration of IVIG preparations with filters, which would remove even small viruses, such as parvovirus, has been difficult because of a tendency for the filters to clog. This reduces the filtration capacity, decreases the yield of IgG and increases the filtration costs. In the present study we describe a modified caprylic acid process for the high-yield purification of IgG from human plasma. Owing to the optimization of filtration conditions and lack of polymeric proteins, the product can be efficiently filtered through a small pore-size virus filter. The described process has a very high capacity to remove non-enveloped viruses.

Materials and methods

Purification of IgG from Cohn fraction II+III

Fraction II+III paste was fractionated by the Cohn method from human plasma (Krijnen's modification). The filter aid free fraction II+III was collected by centrifugation. All experiments were carried out on a laboratory scale using up to 0·5 kg of fraction II+III paste per batch. A flow scheme of the developed process is shown in Fig. 1. The paste was suspended in eight volumes of purified water below 5 °C and the pH was adjusted to pH 4·8 with 0·2 M acetic acid. The solution was brought to room temperature (≈ 22 °C) and caprylic acid was added to a concentration of 50 mM over a 1-h time-period. The suspension was mixed for 2 h and the precipitate was removed by centrifugation. During the development phase, polyethylene glycol (PEG) and caprylic acid were compared as precipitating agents, and different caprylic acid concentrations were tested (10–60 mM). The final conditions were chosen based on IgG recovery and virus-inactivation efficacy of the caprylic acid treatment. The pH of the solution was raised to pH 5·4 with 0·2 M NaOH, PEG 4000 was added and the solution was mixed for 2 h; 2% of diatomaceous earth was then added and the mixture was filtered. Different concentrations of PEG were compared and 3% was chosen for the final process based on clearance of polymers and parvovirus and IgG recovery. The solution conductivity was adjusted to 2·0 mS/cm using sodium acetate buffer. The filtrate was applied to a column (5·0 cm × 15 cm) of ANX Sepharose FF gel (GE Healthcare, Uppsala, Sweden) equilibrated with 20 mM sodium acetate buffer, pH 5·4. The flow rate was 70 cm/h. The flow-through fraction containing IgG was recovered, and the pH of the solution was adjusted to pH 4·4 with 0·5 M acetic acid. After filtration through a 0·1-μm prefilter (AcroCap; Pall Life Sciences, Ann Arbor, MI), the solution was filtered through a Millipore V-NFP virus filter (Millipore Corp., Mosheim, France) at 35 °C with a pressure of 3·5 bar. The protein concentration was ≈ 8 g/l, and a load of ≈ 11 kg of IgG/m^2 of filter area was used. The filtrate was concentrated by ultrafiltration, diafiltered with water for injection to remove PEG, and finally concentrated. The concentrated solution was formulated to 100 g/l IgG, 0·2 M glycine was added and the pH was adjusted to either 4·4 or 5·3. Alternatively, trehalose was tested as a stabiliser. The formulated solution was sterile filtered and transferred aseptically into containers.

Analytical methods

IgG was determined by immunoturbidimetry using a kit from ThermoClinical Labsystems (Helsinki, Finland). Immunoglobulin

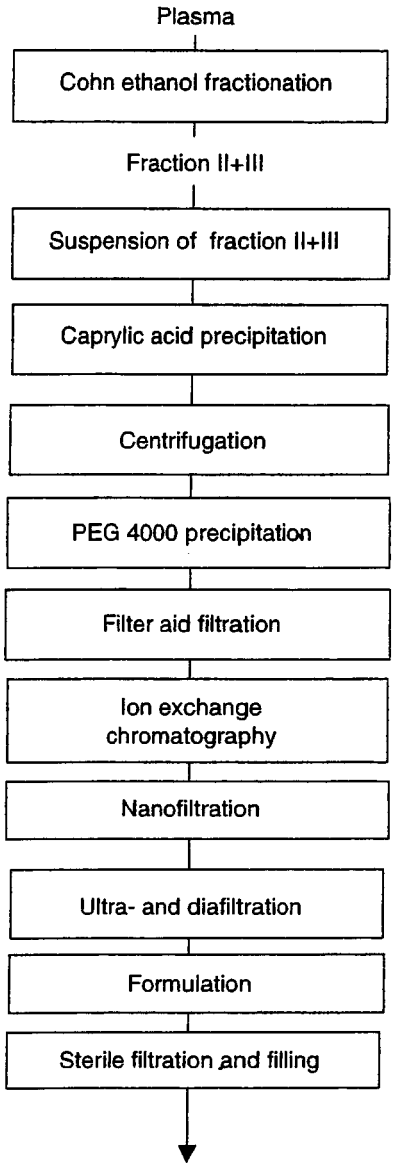

Fig. 1 Flow scheme of the new manufacturing process for intravenous immunoglobulin (IVIG).

A (IgA) was determined by an enzyme immunoassay, as described previously [17], and IgG subclasses were determined using PeliClass enzyme-linked immunosorbent assay (ELISA) kits (Sanquin Reagents, Amsterdam, the Netherlands). Purity was established by zone electrophoresis on agarose, and molecular size distribution was determined by size-exclusion liquid chromatography according to Ph. Eur [18]. Albumin and immunoglobulin M (IgM) were quantified by radial immunodiffusion, using LC Partigen immunoplates (Dade Behring, Marburg, Germany). Prekallikrein activator (PKA) was determined using purified prekallikrein and S-2302 (Chromogenix AB, Mölndal, Sweden) as the chromogenic substrate, according to Ph. Eur [18]. Direct kallikrein (KAL) activity was measured as hydrolysis of S-2302 without the addition of prekallikrein. Anticomplementary activity (ACA) was determined as consumption of complement and measured by haemolysis of red cells, according to Ph. Eur [18]. Caprylic acid was determined by gas chromatography [18], and PEG as described by Skoog [19].

Virus-reduction studies

Inactivation of bovine viral diarrhoea virus (BVDV, strain NADL; ATCC VR-534, Manassas, VA) was studied at Sanquin Viral Safety Services (Amsterdam, the Netherlands). The virus was propagated and assayed as described by Terpstra *et al.* [20]. The virus inoculum contained $10^{7.7}$ tissue culture infective dose 50% ($TCID_{50}$)/ml and the spiked starting material contained $10^{6.4}$ $TCID_{50}$/ml. Parvovirus reduction was studied by spiking the starting solution with high-titre parvovirus B19-positive plasma containing $3{\cdot}6 \times 10^{12}$ genome equivalents (geq)/ml of parvovirus DNA (a generous gift from Dr Hideki Abe, Hokkaido Red Cross BTS, Sapporo, Japan). The spiked starting materials contained 10^{8}–10^{10} geq/ml in different experiments. To remove free viral DNA, samples were treated with DNAse (RQ1 RNAse-Free DNAse; Promega, Madison, WI). Nucleic acids were isolated from the starting solution and processed samples were diluted in parvovirus-negative plasma using the MagNA Pure method (Roche, Mannheim, Germany). Parvovirus B19 DNA was determined by real-time PCR using the LightCycler and the Parvovirus B19 Quantification Kit (Roche Diagnostics, Basel, Switzerland).

Results

We compared PEG and caprylic acid precipitation as a first step in the preparation of polymer-free immunoglobulin solution from suspended Cohn fraction II+III. A relatively high concentration of PEG (≈ 6%) was needed for clarification of the crude immunoglobulin solution, which compromised immunoglobulin yield. Using caprylic acid precipitation combined with anion exchange chromatography, pure IgG could be obtained with a good yield. However, some polymeric IgG remained in the product, and nanofiltration downstream in the process was not efficacious owing to a tendency of the filter to clog. We therefore tested different ways to improve the removal of polymeric proteins in the caprylic acid process.

When the supernatant solution, after caprylic acid treatment, was subjected to precipitation with a low concentration of PEG, effective removal of polymers was achieved, while monomeric IgG was recovered with a good yield in the supernatant solution (Fig. 2). Furthermore, the immunoglobulin solution could be effectively filtered through a small pore-size virus filter. Optimal PEG concentration was found to be ≈ 3%, which enabled high flux and filtration capacity in nanofiltration

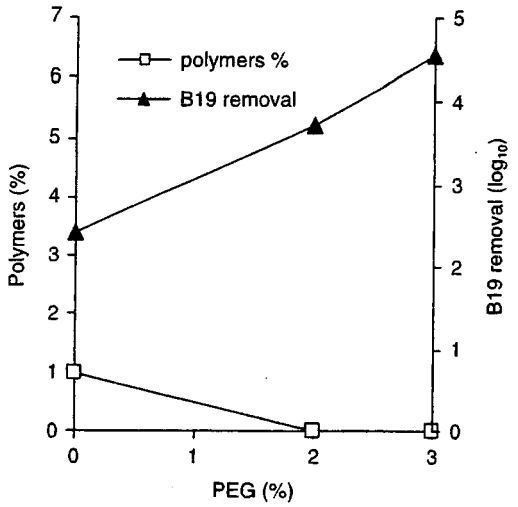

Fig. 2 Influence of polyethylene glycol (PEG) concentration on the removal of immunoglobulin G (IgG) polymers and parvovirus B19 in the PEG precipitation step. B19 removal was measured by polymerase chain reaction (PCR) in spiked process samples before the addition of PEG 4000 and after removal of PEG precipitate by filter aid filtration. Polymers were determined after the anion exchange chromatography step.

(Fig. 3a). The use of higher PEG concentrations decreased the yield of IgG.

Caprylic acid was added as free acid for the inactivation of enveloped viruses and the precipitation of contaminating proteins and lipids. Addition of caprylic acid to a concentration of 50 mM in 1 h resulted in the complete inactivation of BVDV (Fig. 4), which was previously identified as a resistant model virus in caprylic acid inactivation [11]. Immunoglobulin was recovered in the supernatant solution, which was treated with PEG and clarified by filtration in the presence of filter aids.

A combination of PEG precipitation with caprylic acid treatment was found to be beneficial, not only for the removal of polymers but also for the removal of non-enveloped viruses. When the human parvovirus B19 was used as a model virus, almost 4 log_{10} of the virus was removed, even with 2% PEG, and with 3% PEG the reduction was ≈ 4·7 log_{10} (Fig. 2). The effective clearance of parvovirus apparently was a combined effect of residual caprylate remaining after the caprylic acid treatment and the relatively low PEG concentrations, as without caprylate a higher PEG concentration was needed for effective virus clearance (data not shown).

The final purification of IgG was achieved in a single anion-exchange chromatography column using the ANX Sepharose FF gel. Pure IgG was recovered in the flow-through fraction, whereas albumin and other contaminating proteins bound to the column. When the behaviour of parvovirus B19 in the ANX Sepharose column was studied by spiking the starting solution with high-titre parvovirus-positive plasma, the ANX gel bound most of the parvovirus, resulting in an average reduction of $10^{3\cdot1}$ in the IgG fraction. About 30% of the parvovirus B19 was recovered in the wash fraction eluted with 1 M NaCl. The column was cleaned and sanitized with 0·5 M NaOH at room temperature to destroy and remove potential residual viruses from the column.

During the optimization of the nanofiltration step, it was found that the pH of the IgG solution had a major effect on the flux and filtration capacity. The optimal pH was found to be ≈ 4·4–4·8, whereas the filtration capacity was clearly lower, at pH 4·2, 5·0 and 5·2 (Fig. 3b). At optimal pH, the PEG-treated pure IgG solution could be filtered with high efficacy, yielding ≈ 11 kg of IgG/m^2 of filter area, with a decrease in flux of < 50%. When different virus filters were compared, the best flux with the process intermediate was achieved by using a composite membrane filter (Millipore V-NVP).

Reduction of parvovirus B19 by the nanofiltration step was studied by PCR. As the PCR assay detects not only DNA in virus particles but also free virus DNA occurring in high-titre plasma, we treated the samples of the spiked starting solution and filtrate with DNAse, which destroys free DNA. The reduction factor calculated for the removal of total virus DNA was 3·8 log_{10}, and 4·1 log_{10} when calculated from the

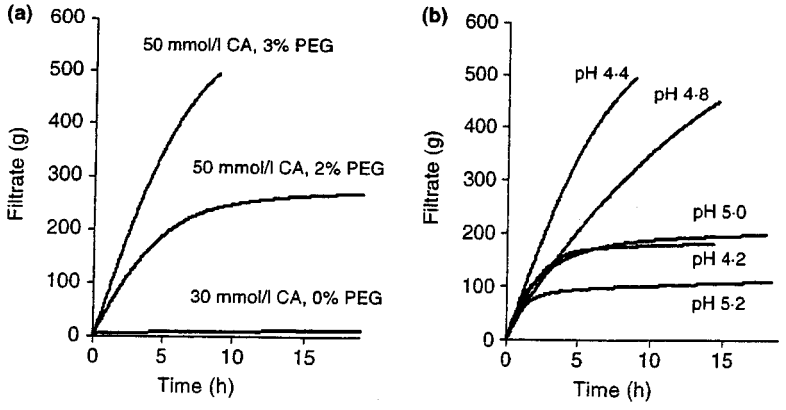

Fig. 3 Influence of (a) polyethylene glycol (PEG) treatment and (b) pH on the flow rate in nanofiltration. Five-hundred millilitres of the pure immunoglobulin G (IgG) solution (≈ 8 g/l), recovered after the anion-exchange chromatography, was filtered through a 0·1-μm prefilter and a Millipore V-NFP filter (3·5 cm^2) at 35 °C at a constant pressure of 3·5 bar. (a) The starting material treated with the different concentrations of caprylic acid (CA) and PEG indicated was adjusted to pH 4·4. (b) The starting solution that had been treated with 3% PEG was adjusted to the different pH values indicated.

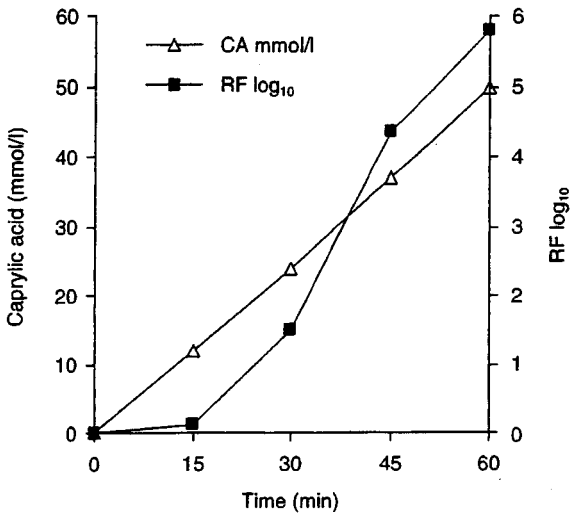

Fig. 4 Reduction of bovine viral diarrhoea virus (BVDV) during caprylic acid precipitation. At 60 min the BVDV was completely inactivated (RF > 5·8 $\log_{10}$). CA, caprylic acid; RF, reduction factor.

Table 1 Reduction of parvovirus B19 DNA in the different process steps

Process step	Log_{10} reduction factor
Caprylic acid precipitation	1·7
Polyethylene glycol precipitation	4·6
ANX chromatography	3·1
Nanofiltration	4·1
Total reduction factor	13·5

Table 2 Yield of immunoglobulin G (IgG) in the purification process starting from recovered plasma

	IgG yield	
Process step	Plasma (g/kg)	%
Suspended II+III paste	7·5	100
After caprylic acid treatment	6·8	91
After polyethylene glycol precipitation	5·7	76
After chromatography	5·1	68
After nanofiltration	5·0	67
Final product	4·8	64

DNAse-treated samples. The cumulative reduction of parvovirus in the different process steps was ≈ 14 $\log_{10}$ (Table 1).

The overall yield of IgG from dissolved fraction II+III paste to final product was ≈ 64%, corresponding to ≈ 4·8 g/l from recovered plasma. The final product had high purity and did not contain detectable polymers (Table 2). Four batches of pure IgG solution were manufactured at a laboratory scale for the stability studies. The process proved reproducible within reasonable tolerance limits of the process parameters. The IgG subclass distribution was similar to that of the starting plasma, with somewhat lowered proportions of IgG3 and IgG4. Some IgG3 was lost in the removal of immunoglobulin polymers, and IgG4 was lowered in the anion-exchange chromatography when removal of IgA was optimized (Table 3).

We studied the stability of the final product as a 100 g/l IgG solution at pH 4·4 and 5·3, and compared trehalose, a non-reducing disaccharide, with glycine as a stabiliser. No polymer formation took place in any of the formulations during 12 months at room (25 ± 2 °C) or refrigerator (2–8 °C) temperatures. Interestingly, the formation of polymers at an elevated temperature (37 ± 2 °C) was more effectively prevented by trehalose than by glycine. However, an increase in pH from 4·4 to 5·3 was even more effective than replacement of glycine with trehalose in preventing polymer formation at this temperature (Fig. 5). No fragmentation was detected at the refrigerator temperature during 12 months. At room temperature, slight fragmentation could be detected, and fragmentation was clearer at the elevated temperature, but again, to a lower extent, in the formulations at pH 5·3 than at pH 4·4 (Fig. 5).

Discussion

The new method described here makes it possible to purify IgG, at a high yield, from human plasma in a few process steps.

Table 3 Characteristics of intravenous immunoglobulin (IVIG) manufactured by the new process

Analysis	Result
Monomers %	92·9
Dimers %	7·1
Polymers %	0·0
Fragments %	0·0
IgG 1% (in plasma %)	59·0 (55–57)
IgG 2% (in plasma %)	36·0 (32–35)
IgG 3% (in plasma %)	2·4 (3·5–4·1)
IgG 4% (in plasma %)	2·6 (6·0–6·4)
IgG g/l	100
IgA mg/l	14·6
ACA CH50/mg	0·47
IgM mg/l	< 17
PKA IU/ml	< 5
KAL IU/ml	< 5
Albumin mg/l	< 13
PEG g/l	0·16
Caprylate g/l	< 0·17

ACA, anticomplementary activity; IgA, immunoglobulin A; IgG, immunoglobulin G; IgM, immunoglobulin M; KAL, kallikrein; PEG, polyethylene glycol; PKA, prekallikrein activator.

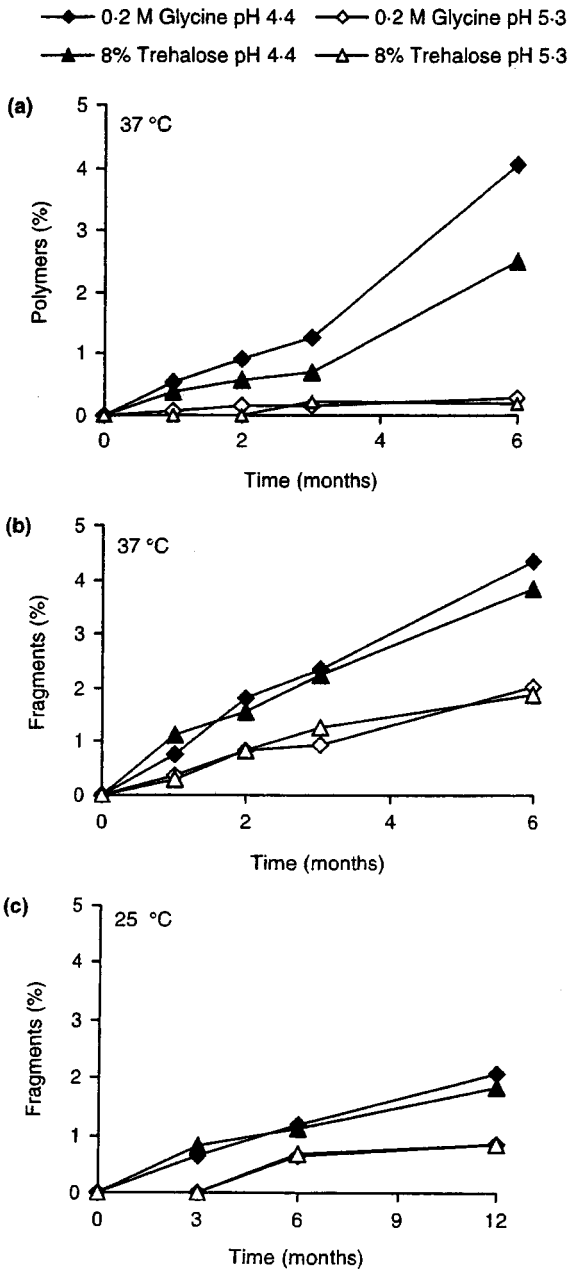

Fig. 5 Polymer formation (a) and fragmentation (b,c) during the storage of immunoglobulin G (IgG) purified by the new process and formulated to 100 g/l solutions at different pH values and with different stabilisers indicated. No polymer formation took place at 2–8 °C or 25 °C, and no fragmentation took place at 2–8 °C.

The main benefit of the new method is its exceptionally high capacity to remove physico-chemically resistant viruses, such as parvovirus. This is based on the efficient precipitation with PEG, which removes both viruses and polymeric proteins and enables efficient nanofiltration downstream in the process. The pure, essentially polymer-free IgG obtained after a single anion-exchange chromatography can be filtered with high flux and low clogging tendency through a small pore-size virus-removal filter. After concentration and diafiltration, the purified IgG proved stable as a 10% solution.

Caprylic acid was found, by Steinbuch & Audran, to be beneficial in the isolation of IgG [21]. Later, Lundblad & Seng [22] showed that it effectively inactivates enveloped viruses. The caprylic acid concentration used in the current process is similar to the concentration used by Steinbuch & Audran [21] and later shown to be effective in the inactivation of various enveloped viruses by Dichtelmüller *et al.* [23]. In the caprylic acid process developed by Lebing *et al.* [11], sodium caprylate is added in two consecutive steps, and somewhat lower concentrations were found to be effective in virus inactivation at those conditions [24].

PEG precipitation has been used since the 1980s for the removal of polymeric immunoglobulin and so-called ACA of IVIG [25,26]. It has typically been used at concentrations of 4% or higher. In the process described in the present study, excellent removal of polymers was obtained with 2–3% PEG, which evidently was a combined effect of PEG and caprylate. This allowed the recovery of IgG, at a good yield, in the supernatant. Even though no polymers could be detected by size-exclusion liquid chromatography in the purified IgG treated with 2% PEG, the flux and capacity in nanofiltration were clearly increased when the PEG concentration was increased to 3%.

The clogging of small pore-size virus filters with protein aggregates is well known. Hirasaki *et al.* [27] showed that clogging of filter pores with protein aggregates results in decreasing flux and impairs virus removal, probably by shifting the residual flux to larger pores. In the present study we found that in addition to the freedom of polymers, pH had a profound effect on IgG throughput in the nanofiltration. The optimal pH range at 35 °C was surprisingly narrow, at ≈ 4·4–4·8. It has been shown that IgG changes its conformation reversibly at acid pH and elevated temperatures close to 35 °C [28,29]. A conformational change could explain the remarkable improvement in filtrate flux and disappearance of clogging tendency observed in the present study.

Previously, filtration of IVIG products with virus-removal filters, which are capable of effectively removing even small viruses such as parvovirus, has been relatively expensive. This is because of the limited amount of IgG that could be filtered before the filters became clogged. The current method makes it possible to filter even close to 10 kg of IgG with high yield through 1-m^2 of a virus-removal filter, which lowers manufacturing costs. Effective removal (≈ 4 $\log_{10}$) of parvovirus B19 was observed under the optimized filtration conditions. It is possible that parvovirus antibodies, which are always present in large plasma pools, bound to the viruses (despite the relatively low pH) and contributed to virus removal during

the filtration. The contributing effect of virus antibodies in nanofiltration has been demonstrated previously [30].

The combination of an effective virus-inactivation step with two effective virus-removal steps increases the safety margin of the IVIG purified by the new process. Although the risk of parvovirus transmission with current IVIG products is already very low, based on the presence of protecting antibodies in plasma pools, and limitation of virus load by PCR testing [31], other non-enveloped viruses, with less commonly occurring neutralizing antibodies, may still pose a threat. On the other hand, the original Cohn process has proved effective in removing prions, which are far more resistant to physio-chemical agents than non-enveloped viruses. In particular, the precipitation of fraction III effectively removes prions [32,33] and when this step is omitted from IgG manufacturing when aiming at a higher yield, other process steps with corresponding efficacy should be considered for the new process to maintain the same level of safety. Both PEG precipitation and nanofiltration have proved effective in removal of prion infectivity and provide a beneficial combination also in this respect [16,33]. Additionally, caprylic acid precipitation and the subsequent depth filtration have been shown to effectively remove prions [34].

The concentrated pure IgG solution obtained after ultrafiltration proved stable during long-term storage. Interestingly, trehalose prevented, more effectively than glycine, polymer formation of IgG at an elevated temperature. Trehalose is known to be an excellent cryoprotectant but less is known about its ability to protect proteins in solutions [35]. However, an increase of pH to > 5 was even more effective than trehalose in preventing IgG polymerization. This is in accordance with the increase in thermal stability of concentrated IgG solutions when the pH is raised above 5·0, which has been shown by differential scanning calorimetry [36]. The slight fragmentation of IgG found at room temperature was similar to that reported for other liquid IVIG products [37]. Similarly to polymer formation at the elevated temperature, fragmentation was also less pronounced during storage at pH 5·3 than at 4·4.

In conclusion, our results indicate that it is possible to manufacture, with high yield from Cohn fraction II+III, stable, polymer-free IgG that can be filtered with high capacity through a small pore-size virus-removal filter. The polymer removal step also serves as an effective virus-reduction step and, as a whole, the process has very high capacity to remove even physico-chemically stable viruses.

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医薬品　研究報告 調査報告書

識別番号・報告回数			報告日	第一報入手日	新医薬品等の区分	総合機構処理欄
一般的名称	－		研究報告の公表状況	http://www.bloodservices.ca/CentreApps/Internet/UW_V502_MainEngine.nsf/web/C2364AA876DBB6998525705E0052854F?OpenDocument	公表国：カナダ	
販売名（企業名）	－					

研究報告の概要

英国およびフランスでBSEの流行がピークとなった1980年1月から1996年12月という期間を反映し、1999年9月30日に開始された、変異型クロイツフェルトヤコブ病(vCJD)伝播のリスクから供血システムを保護するための予防措置が変更された。

1. 1980年1月1日以降、英国、フランスおよび西ヨーロッパで、輸血または血液製剤の投与を受けたことのあるドナーは、無期限に供血停止とする(これまでは英国に限定)。
2. 1980年1月1日から1996年12月31日の間に、フランスまたは英国に累積合計3ヵ月滞在以上したドナーについては、無期限に供血停止とする(これまでは1997年1月1日以降も対象期間に含まれていた)。
3. 英国またはフランスでの累積3ヵ月間の滞在期間が1980年1月1日から1996年12月31日の間に入らないドナーについては、供血適格者とする。

また、抗体検査法の改良やC型肝炎およびHIVの核酸検査法(NAT)の実施により、輸血伝播性疾患の検査法が著しく進歩していることから、一時的な供血停止措置に対する変更として、刺青、ピアス、針治療、電気治療を受けている人、性的背景が不明のパートナーと性的接触を行っている人、針刺し事故を受けたことのある人、他人の血液と接触したことのある人の供血停止期間を12ヵ月から6ヵ月に短縮する。48時間(これまでは3日間)以上投獄されていた人は、釈放から12ヵ月間は、供血停止とする。

使用上の注意記載状況・その他参考事項等

報告企業の意見	今後の対応
vCJDに対する献血除外基準の緩和、HCV、HIVに対する短期的な供血停止期間変更に関する情報である。vCJDについては日本の献血制限は英国への滞在が1980年～1996年の間に1日以上等、本報告の内容よりも厳しいものとなっている。	今後ともvCJDに関する安全性情報、規制情報等に留意していく。

Canadian Blood Services Makes Changes to Donor Deferral Criteria
Welcomes back donors who travelled to U.K. and France since 1996

Ottawa, August 15, 2005 – Canadian Blood Services is implementing changes to its donor deferral criteria in order to reflect the most up-to-date scientific research regarding risks to the blood supply. As a result, some donors will be subject to new deferrals while deferral periods for others will be reduced or eliminated.

"Safety and adequacy are two essential components of the blood system," said Dr. Graham Sher, Chief Executive Officer for Canadian Blood Services. "These changes will allow us to keep our commitment to Canadians on both counts."

Changes to Indefinite Deferrals – vCJD
Since September 30, 1999 safeguards have been in place to protect the blood system from the risk of transmission of variant Creutzfeldt Jakob Disease (vCJD). Donors who meet certain criteria under this policy are indefinitely deferred from donating. The following changes directly reflect the most recent information on the safeguards the United Kingdom, France and Western Europe have in place to protect the bovine and human populations:

1. Donors who have received a blood transfusion or received medical treatment with a product made from blood in the United Kingdom, France or Western Europe since January 1, 1980 will now be deferred indefinitely. Previously, this deferral was limited to the United Kingdom.

2. Donors who have spent a cumulative total of three months or more in France or in the United Kingdom between January 1, 1980 and December 31, 1996 will be deferred indefinitely. In the past, donors who had spent a cumulative total of three months or more in France or the United Kingdom since January 1, 1980 were deferred.

3. Donors whose cumulative three month travel period to the UK or France did not occur between January 1, 1980 and December 31, 1996, will once again be eligible to donate.

Since 1992, confirmed BSE cases in the UK and France have been steadily declining. The 1996 cut-off date is reflective of the period between January 1980 and December 1996 when the BSE epidemic was at its peak in the United Kingdom and France. Since that time, cases have continued to decline and BSE monitoring and control mechanisms have been implemented to stop the spread of the disease in the bovine population and thereby decreasing the risk of transmission of vCJD to humans.

For more information on indefinite deferrals (vCJD), click here.

Changes to Temporary Deferrals
Some prospective blood and/or bone marrow donors may be unable to donate for a period of time for reasons of their own health or the safety of the blood supply or marrow product. The following changes are being made to the temporary deferral criteria policies:

1. The following deferral periods will be reduced from 12 months to six months:

   - Persons who have a tattoo, ear or body piercing, or who have undergone acupuncture or electrolysis procedures;
   - Individuals who have had sexual contact with a partner whose sexual background is unknown; and
   - Individuals who have been injured by a needle or who have had contact with

blood from another person.

Reducing the deferral period reflects the latest available medical research on the "window period" – the brief period after the onset of a viral infection during which early signs of a virus cannot be detected by existing tests. Additionally, significant advances in transfusion transmissible disease testing has occurred in recent years, such as improved antibody assays and more recently, the implementation of nucleic acid testing (NAT) for hepatitis C (HCV) and HIV.

2. In order to comply with the Canadian Standards Association standard on Blood and Blood components, persons who have been incarcerated for 48 hours (rather than three days – Canadian Blood Services previous standard) or more will now be deferred from donating blood for 12 months following the date of release from incarceration.

For more information on temporary deferrals, click here.

Message to Donors
If you believe that you may now be eligible to donate or would like more information, please call 1-888-2-DONATE to speak to a Canadian Blood Services representative who will be able to provide more details and/or book an appointment.

About Canadian Blood Services
Canadian Blood Services is a national, not-for-profit charitable organization that manages the blood supply in all provinces and territories outside of Quebec and oversees the country's Unrelated Bone Marrow Donor Registry. Canadian Blood Services operates 41 permanent collection sites and more than 19,000 donor clinics annually. The Provincial and Territorial Ministers of Health provide operational funding to Canadian Blood Services. The federal government, through Health Canada, is responsible for regulating the blood system. For more information, please visit the website at www.bloodservices.ca.

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For further information, please contact:
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CANADIAN BLOOD SERVICES SOCIÉTÉ CANADIENNE DU SANG

別紙様式第 2-1

別紙 3-3

医薬品
医薬部外品　研究報告　調査報告書
化粧品

識別番号・報告回数		回	報告日 年　月　日	第一報入手日 2005 年 9 月 26 日	新医薬品等の区分 該当なし	厚生労働省処理欄
一般的名称			研究報告の公表状況	EU GUIDELINE-AS ADOPTED IN AUSTRALIA BY THE TGA-WITH AMENDMENT- NOTE FOR GUIDANCE ON MINIMISING THE RISK OF TRANSMITTING ANIMAL SPONGIFORM ENCEPHALOPATHY AGENTS VIA HUMAN AND VETERINARY MEDICAL PRODUCTS (EMEA/410/01 REV 2) Australian Government 21 September 2005	公表国 オーストラリア	
販売名（企業名）						

研究報告の概要	使用上の注意記載状況・その他参考事項等
伝染性海綿状脳症(TSE)がヒト由来または動物由来の医薬品を介して伝播するリスクを最小限にするためにEUが発行したガイドラインの改訂版である。本ガイドラインはオーストラリアで採択されている。医薬品を介したTSEの伝播を完全に防ぐことは不可能であるため、当局では厳密なリスク評価を実施に関する指針を示している。本ガイダンスが包含するのは、TSEが報告されている動物種、原料、セルバンクや培養産物である。リスクを最小限にするための原則としては、1. 原料動物および産地、2. 全ての製造工程に使用される動物由来原料の性質、3. 製品の均一性およびトレーサビリティに関する品質保証システムを含む製造工程、である。また、動物由来原料については、ウシ由来原料、ヒツジおよびヤギ由来原料のリスク管理について記載されている。さらに各原料の部位ごとの危険度によって分類し規制を設けている。法遵守に関連した医薬品の製造における原料および物質のリスク評価の項では、製造業者は本ガイダンスに記載されている全てのリスク評価を実施しなければならない旨が記載されている。リスク/ベネフィットについても言及されている。TSEが伝播し得る動物種由来の材料を含む医薬品が許容可能であるかどうかは、1. 医薬品の投与経路、2. 医薬品に使用された動物由来原料の量、3. その医薬品の最大使用量、4. 使用目的および治療効果を考慮して検討すべきであるとされている。	BYL-2005-0198

報告企業の意見	今後の対応
EUが発行したBSE対策のガイドラインをオーストラリア政府が採択し公布した。BSE、CWDなどのプリオン病があらゆる生物由来の医薬品を介して伝染することを防ぐことを目的とした規制等について記載されている。	現時点で弊社において新たな安全対策上の措置を講じる必要はないと考える。

Australian Government

Department of Health and Ageing
Therapeutic Goods Administration

EU GUIDELINE
- AS ADOPTED IN AUSTRALIA BY THE TGA -
- WITH AMENDMENT -

NOTE FOR GUIDANCE ON MINIMISING THE RISK OF TRANSMITTING ANIMAL SPONGIFORM ENCEPHALOPATHY AGENTS VIA HUMAN AND VETERINARY MEDICINAL PRODUCTS

(EMEA/410/01 REV 2)

This EU guideline has been adopted in Australia by the TGA, with the following notation:

This EU Guideline replaces EMEA/410/01 REV 1 (adopted by the TGA 20 December 2002).

This EU Guideline should be interpreted in the context of the TGA Policy Document - *Supplementary Requirements for Therapeutic Goods for Minimising the Risk of Transmitting Transmissible Spongiform Encephalopathies (TSE's).*

Effective: 21 September 2005
Published: TGA Internet Site

Note for guidance on minimising the risk of transmitting animal spongiform encephalopathy agents via human and veterinary medicinal products (EMEA/410/01 Rev. 2 — October 2003) adopted by the Committee for Proprietary Medicinal Products (CPMP) and by the Committee for Veterinary Medicinal products (CVMP)

(2004/C 24/03)

This revision of the TSE (Transmissible Spongiform Encephalopathy) note for guidance has been undertaken to introduce, *inter alia*, risk assessment into the regulatory compliance process, to provide clarification on a variety of terms and classifications, and to take into account advances in scientific knowledge, Community legislation and rules affecting the authorisation of medicinal products for human or veterinary use. It replaces the previous revision of the note for guidance (EMEA/410/01 Rev. 1 published in the *Official Journal of the European Communities* C 286, 12.10.2001, p. 4). The date of application of this note for guidance is 1 July 2004.

1. INTRODUCTION

1.1. *SCIENTIFIC BACKGROUND*

Transmissible Spongiform Encephalopathies (TSEs) are chronic degenerative nervous diseases characterised by the accumulation of an abnormal isoform of a cellular glycoprotein known as PrP or prion protein). The abnormal isoform of PrP (PrP^{Sc}) differs from normal PrP (PrP^{C}) in being highly resistant to protease and heat denaturation treatments. PrP^{Sc} is considered to be the infective agent responsible for transmitting TSE disease.

TSE diseases in animals include:

— bovine spongiform encephalopathy (BSE) in cattle,

— scrapie in sheep and goats,

— chronic wasting disease (CWD) in cervids (deer and elk),

— transmissible mink encephalopathy (TME) in farmed mink,

— feline spongiform encephalopathy (FSE) in felidae (specifically domestic cats and captive large cats), and

— spongiform encephalopathy of exotic ungulates in zoos.

In humans, spongiform encephalopathies include different forms of Creutzfeldt-Jakob disease (CJD), kuru, Gerstmann-Sträussler-Scheinker syndrome (GSS), and fatal familial insomnia (FFI).

Iatrogenic transmission of spongiform encephalopathies has been reported. In sheep, scrapie has been accidentally transmitted by the use of Louping Ill vaccine prepared from pooled formaldehyde treated ovine brain and spleen in which material from scrapie-infected sheep had been inadvertently incorporated. In man, cases of transmission of CJD have been reported which have been attributed to the parenteral administration of growth hormone and gonadotropin derived from human cadaveric pituitary glands. Cases of CJD have also been attributed to the use of contaminated instruments in brain surgery and with the transplantation of human dura mater and cornea.

Interspecies TSE transmission is restricted by a number of natural barriers, transmissibility being affected by the species of origin, the prion strain, dose, route of exposure and, in some species, the host allele of the PrP gene. Species barriers can be crossed under appropriate conditions.

Bovine spongiform encephalopathy (BSE) was first recognised in the United Kingdom in 1986 and a large number of cattle and individual herds have been affected. It is clear that BSE is a food borne disease associated with feeding meat and bone meal derived from TSE affected animals. Other countries have experienced cases of BSE, either in animals imported from the United Kingdom or in indigenous animals. There is convincing evidence to show that the variant form of CJD (vCJD) is caused by the agent which is responsible for BSE in cattle. Therefore, a cautious approach continues to be warranted if biological materials from species naturally affected by TSE diseases, especially bovine species, are used for the manufacture of medicinal products.

Scrapie occurs worldwide and has been reported in most European countries. It has the highest incidence in the United Kingdom. While humans have been exposed to naturally occurring scrapie for over 200 years, there is no epidemiological evidence directly linking scrapie to spongiform encephalopathies in humans. However, there remains a theoretical and currently unquantifiable risk that some BSE-contaminated protein supplement may have been fed to sheep. If such feed causes a recurrent BSE infection in sheep, it may be diagnosed as scrapie and might as such pose a risk of human TSEs. Further, it should also be assumed that any BSE agent introduced into the small ruminant population via contaminated feed is likely to be recycled and amplified.

1.2. *REGULATORY COMPLIANCE*

Risk assessment — Since the use of animal-derived materials is unavoidable for the production of some medicinal products and that complete elimination of risk at source is rarely possible, the measures taken to manage the risk of transmitting animal TSEs via medicinal products represent risk minimisation rather than risk elimination. Consequently, the basis for regulatory compliance should be based on a risk assessment, taking into consideration all pertinent factors as identified in this note for guidance (see below).