

MANUFACTURING METHOD FOR INTRAVENOUS IMMUNE
GLOBULIN AND RESULTANT PRODUCT

BACKGROUND OF THE INVENTION

The present invention relates to an integral,
5 multi-step commercial process for the production of
intravenously administrable immune globulin
containing IgG (γ -globulin) as the main ingredient.

Various processes are known for obtaining
10 intravenously administrable γ -globulin solutions from
starting materials resulting from Cohn fractionation
of human plasma. Certain of the Cohn fractions
contain higher titres of γ -globulin than others.
Usual starting materials for a γ -globulin solution
15 are Cohn Fraction II or Cohn Fraction II + III.

Although prior art processors employ various
separation and sterilization techniques, process
modifications are constantly sought for improving
20 final product purity and safety, and overall yield.

Many commercial processes employ either a
solvent/detergent step for viral inactivation, or a
heat treatment step for viral inactivation. To date,

the art has not provided a multi-step process beginning with Cohn Fraction II paste or II + III paste including two different viral inactivation procedures as part of an efficient, continuous high yield γ -globulin manufacturing process.

U.S. Patent 5,151,499 by Kameyama et al. is directed to a process for producing viral inactivated protein compositions in which a protein composition is subjected to a viral inactivation for envelope viruses in a solvent/detergent treatment of the protein composition and a viral inactivation for non-envelope viruses in a heat treatment of the protein composition. The '499 patent teaches that preferably the solvent/detergent step occurs first and in the presence of a protease inhibitor, followed by a heat treatment. Where the heat treatment is carried out in the liquid state, the protein is first recovered from the solvent/detergent by adsorption onto an ionic exchange column, prior to any heat treatment. The liquid heat treatment can be carried out in the presence of a sugar, sugar alcohol or amino acid stabilizer. Although the '499 patent lists many starting protein compositions including immunoglobulin, its production examples employ

Factor IX, thrombin, fibrinogen and fibronectin. Removal of denatured protein produced in a heat treatment step through fractionation is not considered.

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U.S. Patent 5,371,196 by Yuki et al. is directed to purifying secretory immunoglobulin A. A liquid heat treatment or various combinations of liquid heat treatment and solvent treatment inactivation are described. A polyethylene glycol fractionation is employed following each step and always as a final step. This patent does not relate to immune globulin of high γ -globulin titre.

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Certain prior art processes for production of intravenously injectable γ -globulin solutions describe the incorporation of a liquid heat treatment carried out in the presence of sorbitol heat stabilizer in a multi-step purification procedure beginning with Cohn Fraction II + III paste. In U.S. Patent 4,845,199 by Hirao et al., Cohn Fraction II + III is subjected to polyethylene glycol (hereinafter "PEG") fractionation (8% w/v PEG followed by 12% w/v PEG), then ion exchange chromatography (DEAE-Sephadex) and removal of human

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blood group antibody prior to a liquid heat treatment in the presence of sorbitol as a protein stabilizer.

On the other hand, Example 1 of U.S. Patent 4,876,088 by Hirao et al. describes the preparation of intravenously injectable γ -globulin solution from Cohn Fraction II + III paste in which the paste is suspended in water, its pH adjusted to 5.5 and centrifuged, with the supernatant then being heat treated for viral inactivation in the presence of 33% w/v of sorbitol, followed by PEG fractionation (6%/12%) which would remove heat denatured protein and then by other purification steps including DEAE-Sephadex ion exchange chromatography.

SUMMARY OF THE INVENTION

An object of the present invention is to provide an integral, commercially useable process for producing a highly purified γ -globulin solution from the Cohn fractionation process.

Another object of the present invention is to provide very pure intravenously administrable γ -globulin solution free of both envelope and non-envelope viruses, including all heat sensitive

viruses.

5 A further object of the present invention is to provide a commercial γ -globulin process enabling removal of any denatured protein produced during heat sterilization prior to a second stage viral inactivation.

10 A further object of the present invention is to provide a continuous commercial γ -globulin production process without the need for intermediate recovery of γ -globulin protein through the carrying out, in order, of a heat sterilization, a PEG fractionation and a solvent detergent viral inactivation.

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The above and other objects which will be apparent to the skilled artisan are provided by the present invention in which an alcoholic Cohn fraction, which may be partially purified, but is
20 rich in γ -globulin, is heat treated in aqueous medium in the presence of a heat stabilizer for viral inactivation, the heat treated solution is thereafter first subjected to PEG fractionation, and then without intermediate γ -globulin protein recovery to a
25 second viral inactivation in the presence of a

solvent, preferably a solvent-detergent mixture, for disruption of envelope viruses, followed by separation from the solvent or solvent-detergent mixture.

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In one preferred embodiment of the present invention, bentonite is admixed with a collected PEG fractionation product for additional virus removal, prior to the solvent or solvent-detergent viral inactivation.

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In a preferred embodiment of the present invention, sorbitol is the heat stabilizer and trialkyl phosphate is the solvent.

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In another preferred embodiment of the present invention, denatured products of the heat treatment viral inactivation are removed by the PEG fractionation prior to the second viral inactivation for providing an exceedingly pure heat treated γ -globulin.

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In another preferred embodiment of the present invention, any particulates present are removed prior to the solvent-detergent treatment.

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In preferred embodiment of the present invention, the γ -globulin solution is treated with an anion exchange resin.

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In preferred embodiments of the present invention, a single stage polyethylene glycol fractionation step is carried out without precipitation of the desired γ -globulin.

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In yet another preferred embodiment of the present invention, the γ -globulin solution is treated with a cationic exchange resin, or by diafiltration and/or tangential flow filtration, following the completion of viral inactivation.

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In still another preferred embodiment of the invention, there is provided a heat-sterilized and solvent-detergent sterilized γ -globulin suitable for intravenous administration.

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DETAILED DESCRIPTION OF THE INVENTION

The manufacturing method disclosed herein is a continuous process in the sense that once the process

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is started with a quantity of impure starting fraction containing immunoglobulin, such as Cohn Fraction II + III paste, the process runs through until its completion (providing highly purified gamma globulin as a resultant product) without the intermediate recovery of partially purified gamma globulin solids. Of note, during the polyethylene glycol fractionation stage of the process disclosed herein, partially purified gamma globulin paste is not recovered as an intermediate product.

A fraction containing immunoglobulin is used as the starting material. This fraction is not particularly limited in so far as it originates from human plasma and contains an immunoglobulin fraction.

Specific examples of such an immunoglobulin-containing fraction include Fraction II + III and Fraction II obtainable by ethanol fractionation of Cohn, and paste of immunoglobulin-containing fractions equivalent thereto. Other starting materials are Fractions I + II + III, and Fraction II + IIIw and Fraction III paste. The starting material may contain impurities, such as human blood-group antibodies, plasminogen, plasmin, kallikrein, prekallikrein activator, IgM, IgA, IgG polymers (hereinafter "aggregates"), etc.

The preferred starting materials are Cohn Fraction II + III or Cohn Fraction II paste. Cohn Fraction II + III paste can be used as is as a starting material or it can first be subjected to a preliminary washing procedure to form Fraction II + IIIw, which is thereafter used in the process of this invention. "Fraction II + IIIw" is a disodium phosphate solution-washed Cohn Fraction II + III precipitate.

Fraction II + IIIw can be obtained by suspending Fraction II + III precipitate in cold water for injection in a ratio of about 1 kilogram of II + III paste per about 20 volumes of water. A sodium phosphate solution is added to the final concentration of approximately 0.003M sodium phosphate for solubilizing lipids, lipoproteins and albumin. Cold ethanol is added to bring the final alcohol concentration to about 20%. During the alcohol addition, temperature is gradually lowered to $-5 \pm 1^\circ\text{C}$ and pH is maintained or adjusted to 7.2 ± 0.1 , for example by using acetate buffer or dilute sodium hydroxide. The Fraction II + IIIw precipitate which forms is recovered by centrifugation and/or

filtration while maintaining the temperature at -
5±1°C.

5 Prior to the first viral inactivation step of
the present invention, various preliminary
purification and/or aggregate-reducing steps can be
carried out. For example, when Fraction II + IIIw
paste is used, typically containing about 20% alcohol
and with more than 70% of the protein present as IgG,
10 it can be suspended in 3 to 20 volumes, preferably 10
to 15 volumes, of cold water at a temperature of
about 0 to 5°C and with pH being adjusted to be
between 4.5 to 6.0, preferably 5.0 to 5.5 using pH
4.0 acetate buffer or hydrochloric acid. The mixture
15 is agitated for about 2 to 15 hours to allow all of
the γ -globulin to go into solution. Thereafter,
undissolved protein such as albumin and α -globulins
can be removed by centrifugation and/or filtration.

20 With Fraction II + III paste starting material,
each kilogram of Fraction II + III paste is suspended
in 3 to 20 kg, preferably 13 to 17 kg, of cold water.
The pH of the suspension is adjusted to 4.5 to 6.0,
preferably 4.8 to 5.4. The suspension is mixed for 1
25 to 20 hours, preferably 2 to 10 hours, at 0 to 25°C,

preferably 0 to 10°C. The insoluble material is then removed by filtration using depth filters or centrifugation. If filtration is used, about 1 to 5 w/w% filter aid may be added before separation. The centrifugate or the filtrate may be further clarified by a membrane filter. The clarified solution may be concentrated to about 1 to 12%, preferably 4 to 8%, protein by ultrafiltration using 10,000 to 100,000 molecular weight cut off (MWCO) membranes.

Where a different starting Cohn fraction is employed, the initial step or steps of the process can be appropriately selected where desired for carrying out a preliminary purification for obtaining a fraction of high IgG content to be further processed. For example, where Cohn Fraction II (contains over 95% IgG) has been separated from Cohn Fraction III, with Fraction II to be further processed, the initial processing can be at an acid pH of 3.2 to 5.0, preferably 3.8 to 4.2, as described by Uemura et al. U.S. Patent 4,371,520, in order to break down immune globulin aggregates present into immune globulin monomers and dimers, since aggregates are known to possess anti-complementary activity (ACA). As another alternative, with Cohn Fraction II + III starting material, the Uemura, et al. patent

low pH treatment can be carried out as an additional step following an initial purification step as above described and prior to the viral inactivating heat treatment step.

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For the heat sterilization step, the immune globulin protein in the form of the aqueous mixture collected from the above-described partial purification, such as the filtrate from Fraction II +
10 III paste purification, can be used as is or concentrated to about 1 to 12%, preferably 4 to 8%, protein by ultrafiltration, and a sugar, sugar alcohol and/or amino acid heat stabilizer is added thereto. The heat stabilizer is preferably sucrose,
15 maltose, sorbitol or mannitol, most preferably sorbitol. The sugar or sugar alcohol is added to the immune globulin solution as a powder or first mixed with a small volume of water and then added, to provide a final concentration of about 25 to 50 w/w%,
20 up to saturation, preferably 30 to 40 w/w%. At this point, the aqueous solution of immune globulin contains sufficient water so that this solution contains about 1 to 8% total protein, a typical Fraction II + III starting material containing about
25 300 grams protein per kilogram paste.

Following addition of the heat stabilizer, the solution pH is adjusted to 4.5 to 6.5, preferably 5.0 to 6.0 and the mixture is heated at about 50-70°C for about 1-20 hours, preferably for 10 to 11 hours at about 60°C, for viral inactivation of heat sensitive viruses. The heat treatment step not only inactivates viruses, but also through the protein denaturation effect thereof, can preferentially reduce the amount of certain undesirable proteins normally associated with Cohn Fractions II + III, such as prekallikrein, plasmin, plasminogen and IgA.

After the heat treatment, the solution is either processed directly or diluted with cold water up to 5 times the volume of the heat treated solution. The solution is then cooled to 0-10°C, preferably 0 to 5°C.

Next, PEG fractionation is carried out on the heat treated solution. PEG fractionation is a well known procedure in the art of purification of immune globulin in order to separate the desired IgG monomer and dimer from IgG aggregate and from other impurities naturally occurring in the starting plasma protein fraction. However, in the present process,

the PEG fractionation also accomplishes a separation between the desired IgG monomer and dimer, and unwanted denatured protein products produced by the heat treatment. These denatured protein products are denatured prekallikrein activator, plasminogen, plasmin, IgA, IgM and aggregates.

Any of the PEG fractionation procedures documented in the prior art can be used as long as PEG concentration and pH are selected so that the desired IgG monomer and dimer remain in solution while undesired proteins such as aggregate are precipitated out of solution. The PEG is added as a powder, flakes or as a 50% solution directly to the heat treated solution for providing the desired PEG concentration.

For example, the PEG fractionation can be carried out at a pH of about 5.0 to 7.5, preferably within about 6.0 to 7.5 pH when Fraction II + IIIw paste is used as starting material, and preferably within about 5.5 to 6.0 pH when Fraction II + III paste is used as starting material, with a PEG concentration ranging from about 4 to 8%, preferably either 4 to 6% when Fraction II + IIIw paste is used

as starting material, or 6 to 8% when Fraction II + III paste is used as starting material.

While maintaining cold temperatures of about 0-2°C, the PEG fractionation can be carried out for about 1 to 8 hours, after which the precipitate is removed by either centrifugation or filtration.

As an optional viral removal step, bentonite is added to the centrifugate or filtrate to a final concentration of about 0.05 to 2.0 w/w%, preferably 0.1 to 1.0 w/w%, and the mixture is mixed for 1 to 5 hours, and then the bentonite paste is removed by filtration.

The final essential step of the present invention is to carry out a second viral inactivation procedure utilizing a solvent or solvent-detergent mixture. As described below, further purification procedures, specifically those involving the use of ionic exchange resins, can be carried out prior to and/or following the solvent-detergent treatment. One option is to carry out an anionic exchange treatment prior to the solvent detergent viral inactivation for further removal of albumin, transferrin and prekallikrein activator. In a

preferred embodiment, a cationic exchange treatment is carried out after the solvent detergent viral inactivation. By this procedure, certain undesirable protein materials (such as IgA, IgM and albumin) found within human plasma and PEG can be removed from the IgG through the cationic exchange procedure along with the residual reagents used in the solvent-detergent treatment.

If not otherwise accomplished during the overall process the solution to be subjected to the solvent-detergent should be treated for removal of all particulate matter, which can include denatured protein. Therefore, it is preferred to filter the solution with a 1 micron or finer filter prior to solvent-detergent addition. This will also reduce the likelihood of virus being present within a large particle and thereby possibly avoiding exposure to the solvent-detergent.

The filtrate may be diafiltered and/or concentrated up to about 12% protein, preferably 5-10% protein, and then subjected to the solvent, or solvent-detergent treatment.

Today, the preferred solvent for inactivation of

envelope viruses is trialkyl phosphate. The trialkyl phosphate used in the present invention is not subject to particular limitation, but it is preferable to use tri(n-butyl)phosphate (hereinafter "TNBP"). Other usable trialkyl phosphates are the tri(ter-butyl)phosphate, the tri(n-hexyl)phosphate, the tri(2-ethylhexyl)phosphate, and so on. It is possible to use a mixture of 2 or more different trialkyl phosphates.

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The trialkyl phosphate is used in an amount of between 0.01 to 10 (w/w)%, preferably about 0.1 to 3 (w/w)%.

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The trialkyl phosphate may be used in the presence or absence of a detergent or surfactant. It is preferable to use trialkyl phosphate in combination with the detergent. The detergent functions to enhance the contact of the viruses in the immune globulin composition with the trialkyl phosphate.

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Examples of the detergent include polyoxyethylene derivatives of a fatty acid, partial esters of anhydrous sorbitol such as Polysorbate 80 (Tradename: Tween 80, etc.) and Polysorbate 20

(Tradename: Tween 20, etc.); and nonionic oil bath rinsing agent such as oxyethylated alkylphenol (Tradename: Triton X100, etc.) Examples include other surfactants and detergents such as Zwitter 5 ionic detergents and so on.

When using the detergent, it is not added in a critical amount; for example, it may be used at concentrations between about 0.001% and about 10%, 10 preferably between about 0.01% and 3%.

In the present invention, the trialkyl phosphate treatment of the immune globulin containing composition is carried out at about 20 to 35°C, 15 preferably 25 to 30°C, for more than 1 hour, preferably about 5 to 8 hours.

During the trialkyl phosphate treatment, immune globulin is present at about a 5 to 10% protein 20 solution in aqueous medium.

If not carried out prior to the solvent-detergent treatment, an optional anionic exchange treatment can be carried out on the solvent detergent 25 treated immune globulin. Preferably, at least a

cationic exchange treatment is carried out on the solvent-detergent treated product. The ionic exchange treatments are carried out on the immune globulin aqueous solution from solvent (or solvent detergent) processing, generally having a pH of about 4.5 to 6.5, with where desired low ionic strength for maximum adsorption of IgG. The protein concentration generally is within the range of about 1-15 w/v%, more preferably from about 3 to 10 w/v%. The ionic exchanger is equilibrated with the same aqueous solvent as used.

A continuous system is carried out by passing immune globulin solution through a column of the anionic exchanger at a ratio from about 10 to 100 ml per ml of the ionic exchanger and recovering the non-adsorbed fraction.

The anionic exchanger to be used, for example, comprises anion exchanging groups bonded to an insoluble carrier. The anion exchanging groups include diethylaminoethyl (DEAE), a quaternary aminoethyl (QAE) group, etc., and the insoluble carrier includes agarose, cellulose, dextran, polyacrylamide, etc. 1 gram of DEAE Sephadex A-50 resin swells to about 20 to 30 grams wet weight in

0.4% sodium chloride solution.

5 Usable cationic exchangers are carboxy methyl
Sephadex (CM-Sephadex) CM-cellulose, SP-Sephadex, CM-
Sephadex and SP-Sephadex. Pretreated cationic
exchanger (for example, 1 gram of CM-Sephadex C-50
resin swells to about 25-35 grams wet weight in 0.4%
sodium chloride solution) is used as a column bed
through which the immune globulin solution from
10 solvent (or solvent detergent) processing is passed
in a continuous process at about 0-5°C.

When the above-described conditions are used
with the cationic exchanger, the IgG will be
15 adsorbed, and thereafter following washing of the
protein-adsorbed cationic exchange resin, IgG can be
eluted, for example by about a 1.4 N sodium chloride
solution.

20 When ionic exchange treatments are not employed,
the solvent (solvent detergent) treated solution is
diafiltered and concentrated by tangential flow
filtration for removal of solvent detergent and PEG.
Where very low levels of solvent detergent and PEG
25 are desired in the final product, a preferred
processing is treatment with a cationic exchanger

followed by tangential flow filtration.

Following the steps of the above process, the IgG is clarified, diafiltered and concentrated to the extent needed. If desired, a stabilizer such as D-sorbitol can be added and final adjustments made to yield a solution of a composition containing about 50 to 100 mg/ml IgG, and 50 mg/ml D-sorbitol, with pH being at about 5.4. For additional removal of viruses, this solution may be filtered through 35 nanometers or less porosity filters. This stabilized and optionally nanofiltered solution is then sterile filtered through sterilized bacterial retentive filters and filled into vials.

The following example is set forth to illustrate the invention but is non-limiting.

EXAMPLE

Manufacturing Method for Intravenous Immune Globulin and Resultant Product

One thousand eight hundred grams of Fr II+III paste was suspended in 15 kg of cold water. After mixing for one hour at 0 to 5°C, pH of the suspension was adjusted to about 5.0 with dilute acetic acid. After mixing the suspension for 3 hours,

approximately 900 grams of filter aid (acid washed celite) was added and mixed for 45 minutes. The insoluble material along with the celite was removed by filtration. The filtrate was clarified and then concentrated by ultrafiltration, using 100,000 molecular weight cut off (MWCO) membranes, to an approximate protein concentration of 6%.

D-sorbitol was added to the concentrated protein solution to a final concentration of 33 w/w% and mixed at pH 5.0 until all the sorbitol was dissolved. The solution was then heated at 60°C for 10 hours. The heated solution was cooled to less than 10°C and diluted with equal weight of cold water. The pH of the diluted solution was adjusted to 5.7 with dilute sodium hydroxide solution and then a solution of 50% polyethylene glycol (PEG) 3350 was added to a final concentration of 6 w/w%. After mixing for approximately 2 hours at pH 5.7, the precipitate so formed was removed by filtration with acid washed celite filter aid added to 3% w/w. Approximately 3.5 kg of the 6% PEG filtrate was set aside for other experiments. After adjusting pH of the remaining 6% PEG filtrate to 4.9, bentonite was added in the amount of 1 g per kg of filtrate and the pH was allowed to go up to about 5.1. After mixing for 2

hours, the suspension was filtered to remove bentonite. The filtrate was then concentrated and diafiltered by ultrafiltration, using 100,000 MWCO membranes.

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The pH of the solution was adjusted to about 6.5 with dilute sodium hydroxide and then about 0.4 kg pre-swollen DEAE Sephadex A-50 resin was added to the solution. After mixing the protein solution with
10 resin, the resin was removed by filtration. A solvent detergent (SD) solution containing a mixture of tri-n-butyl phosphate (TNBP) and polysorbate 80 was added to the filtrate to a final concentration of 0.3 w/w% and 1.0 w/w%, respectively. After
15 incubating the solution containing SD at 27°C for 6 hours, the solution was cooled to 0 to 5°C, the conductivity was adjusted to approximately 7mS/cm with sodium chloride solution and the pH was adjusted to 5.8. About 2.7 kg of pre-treated Cm Sephadex C-50
20 resin was added to the solution, mixed and then filtered to retain the resin. The resin containing the adsorbed IgG was washed with 0.3% sodium chloride solution and then the adsorbed IgG was eluted with
25 1.4M sodium chloride solution. The eluate was clarified, concentrated and diafiltered with cold water. D-sorbitol was added and final adjustments

were made to yield a solution of a composition containing about 100 mg/ml IgG and 50 mg/ml D-sorbitol with pH being at about 5.4. After final adjustments, the solution was sterile filtered and filled into glass vials. Test results of the resultant product are presented in the following Table.

Table

Test Results of Example Product

Test Parameter	Result
Protein (mg/ml)	99.2
IgG purity (%)	100
Molecular distribution: (by HPLC)	
Monomer (%)	89
Dimer(%)	11
Prekallikrein activator (% CBER Ref. Lot No. 3)	<2.5
Anticomplementary activity (CH ₅₀ U/mg IgG)	0.2

Variations of the invention will be apparent to the skilled artisan.

Claims:

1. A continuous process for preparing an intravenously administrable gamma globulin solution which comprises:

(a) heat treating an impure gamma globulin solution under time and temperature conditions sufficient for inactivating heat sensitive viruses;

(b) without recovery thereof, subjecting the heat treated gamma globulin solution to polyethylene glycol fractionation, without causing precipitation of the desired gamma globulin, for obtaining a purified gamma globulin solution; and

(c) without recovery thereof, treating the purified gamma globulin solution with an organic solvent for inactivating envelope viruses.

2. The process of claim 1 wherein the impure gamma globulin solution contains Cohn Fraction I + II + III, Cohn Fraction II + III paste, Cohn Fraction II + IIIw, or Cohn Fraction II.

3. The process of claim 1 wherein the impure gamma globulin solution contains proteins from Cohn Fraction II+III paste.



4. The process of claim 1 wherein the impure gamma globulin solution is subjected to at least one step of purification prior to the heat treating step (a) and the partially purified solution is subjected to the heat treatment step (a) without its intermediate recovery.

5. The process of claim 1 wherein the heat treating step (a) is carried out at about 50 to 70°C for about 10 to 20 hours.

6. The process of claim 5 wherein the heat treating step (a) is carried out for about 10 to 11 hours at about 60°C.

7. The process of claim 1 wherein the polyethylene glycol fractionation is carried out in a single stage comprising at least one step in which impurities are removed as a precipitant and the desired gamma globulin remains in solution.

8. The process of claim 6 wherein the impure gamma globulin solution contains proteins from Cohn Fraction II+III paste.



9. The process of claim 1 wherein the organic solvent used in step (c) is an alkyl phosphate.

5 10. The process of claim 7 wherein the organic solvent used in step (c) is an alkyl phosphate.

11. The process of claim 10 wherein the alkyl phosphate is tri-n-butyl phosphate.

10 12. The process of claim 1 wherein the organic solvent contains a detergent.

13. The process of claim 11 wherein the organic solvent contains a detergent.

15 14. The process of claim 1 wherein after step (c) the gamma globulin solution without recovery thereof is treated with a cationic exchange resin.

20 15. The process of claim 7 wherein a bentonite clarification step is carried out on the gamma globulin solution obtained after the polyethylene glycol fractionation.

25 16. The process of claim 15 wherein the bentonite treated solution is treated with an anionic exchange



resin.

17. The process of claim 1 wherein after step (b)
the gamma globulin solution is treated with an
5 anionic exchange resin.

18. The process of claim 14 wherein after the
cationic exchange treatment, the gamma globulin
solution is concentrated by tangential flow
10 filtration.

19. The process of claim 1 wherein after step (c),
the gamma globulin solution without recovery thereof
is concentrated by tangential flow filtration.

20. An intravenously-administrable gamma globulin
solution produced by the process of claim 1.

21. An intravenously-administrable gamma globulin
20 solution produced by the process of claim 18.