Registration Application

for

AAA Solution

50mL

Submitted to

Myanmar Food and Dr ug Board of Authority,

Union of Myanmar

By

ABC Company Limited.

March 20, 2009

INDEX

ADMINISTRATIVE DOCUMENTS

COVERING LETTER

ABC Company Limited

Address: xxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxx

March 20th, 2009

To,
The Chief Drug Administrator,
Myanmar Food and Drug Board of Authority
Union of Myanmar

Dear Sir,

Subject: **Product Registration Application for** AAA **Solution – 50mL**

The medical biotechnology initiative covers biopharmaceuticals, molecular diagnostics & genetics and cell-based therapies. In biopharmaceuticals, RLS is developing a range of products in the categories of plasma proteins, recombinant proteins, monoclonal antibodies and siRNA molecules.

RLS is now planning a global expansion of its biopharmaceuticals business and as part of this process, wishes to register itself with Myanmar Food and Drug Board of Authority, Union of Myanmar to supply high quality biological products.

Please find enclosed the product registration file as per the requirement of Myanmar Food and Drug Board of Authority, Union of Myanmar.

Request you to kindly review the document and provide us with your feedback.

Thanking you,

Yours Sincerely,

For ABC Company Limited.

Signature

Authorized signatory

Stamp

LETTER OF AUTHORIZATION

ABC Company Limited

Address: xxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxx

March 20th, 2009

To,
The Chief Drug Administrator,
Myanmar Food and Drug Board of Authority
Union of Myanmar

Dear Sir,

Subject: **Authorization Letter**

We hereby authorize **M/s. Medipower Company Ltd., Bldg(10), Rm(18/19), Hnin Si Street, Mingalar Taung Nyunt Tsp, Yangon, Union of Myanmar.** to submit dossier of AAA **Solution) – 50 mL** and follow up on our behalf.

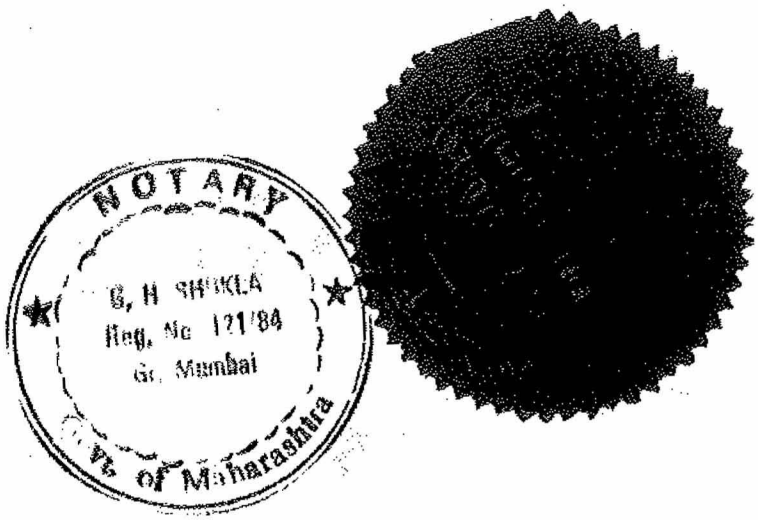
Hope you will find this in order.

Thanking you,

Yours Sincerely,
ABC Company Limited

Authorized Signatory

MANUFACTURING LICENSE



Address

To,

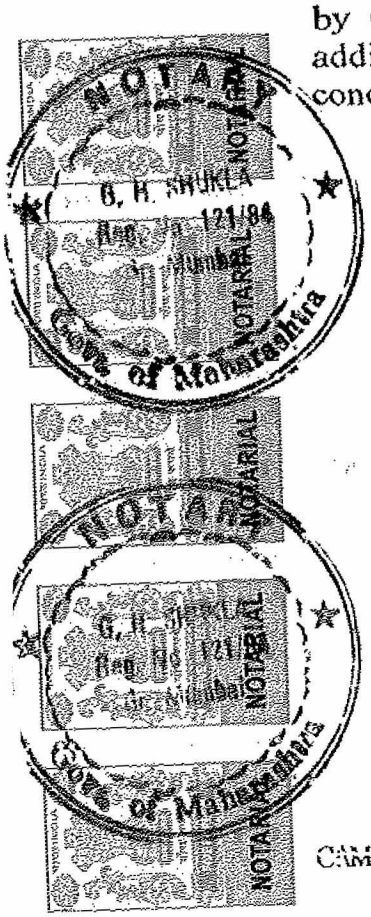
Ms. ABC Company Limited

Subject:- Approval of endorsement to the Manufacturing Licence

Sir,

I am enclosing herewith the copy of endorsement duly approved and signed by CLAA to the manufacturing licence No. 28E-3 for the manufacturing of additional blood products. The endorsement is approved subject to the following conditions:

1. The samples of five initial lots of the pooled plasma shall be sent to NIB, Noida for the testing of HIV, HbsAg, HCV along with the protocols.
2. The final product shall be manufactured from the intermediates viz fraction II and V imported from M/s. DRK-mbH, Germany. The samples of each batch of the finished product shall be forwarded to NIB, Noida along with the protocols for testing before release.
3. The blood banks from which the plasma will be procured and the manufacturer shall maintain all the records as per WHO norms.
4. In case, if the manufacturer intends to change the source of plasma, then approval of this office shall be obtained.
5. The firm shall carry out the all the test for infectious disease by Elisa kits approved by this office.



TRUE COPY
ATTESTED BY ME
Sign
NOTARY GR.

Yours
Sign
Joint Commissioner (H.Q.)
Food and Drug Administration, M.S.

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- 4 APR 2008

NOTARY
G. H SHUKLA
Reg. No 171/84
Gr. Mumbai
of Maharashtra

ABC Company Limited

List of the Additional Products to be Manufactured by ABC Company Limited

1) Name of Product

Pooled plasma, Solvent/Detergent Treated. BP

100ml/200ml

2) Name of Product

Immunoglobulin Intravenous B.P.

2.5gms/50ml

0.5gms/10ml

5gms/100ml

3) Name of Product

Human Normal Immunoglobulin I.P.

10% Solution in vials of 1m/2ml/5ml

4) Name of Product

20% Albumin 10gms/50ml

20% Albumin 2gms/10ml

20% Albumin 20gms/100ml

5%Albumin 5gms/100ml

5% Albumin 0.5gms/10ml

TRUE COPY
ATTESTED BY ME

G. H. SHUKLA
NOTARY GR. MUMBAI
4 APR 2008

Joint Commissioner (H. Q.)
Food & Drug Administration
Maharashtra State, Bombay

NOTARY
G. H. SHUKLA
Regn. No 121'84
at Mumbai
Govt. of Maharashtra

ABC Company Limited

Undertaking

01. The above are the only drugs intended for manufacture at present and we undertake that any addition or deletion in the formula of the product will not be carried out.
02. We undertake to comply with all the provisions of the Act in force and the directions issued from time to time by the Licensing Authority and not to manufacture and product under name belonging to another manufacturer.
03. We undertake not to manufacture or sell or distribute any drug/cosmetic even if it is included in the approval list of products if it is or as and when it will be banned by Licensing Authority or drugs Controller (India) or Government of India.
04. The Brand names art works and designs of the products submitted for approval in this application are not copied from others. It is further declared that these or similar brand names, art works and designs are not used by any other manufacturer to the best of our belief. If the brand names, art works or designs of our products are found to be imitation of or resemble in a manner likely to deceive another drugs manufactured by another company prior to ours, we undertake to stop, to sell or distribute our products and we understand that we shall be liable for legal action in such eventuality.

Authorised Signatory

Joint Commissioner (H. Q.)
Food & Drug Administration
Maharashtra State, Bombay

TRUE COPY,
ATTESTED BY ME
G. H. SHUKLA
NOTARY GR. MUMBAI
4 APR 2008

MEMBER
RELIANCE
GROUP

WHO – GMP CERTIFICATE

No. GMP(WHO) /Cert / Hq-Ext-29-09/432/11
Office of the commissioner
Food and Drugs Administration, M.S.
Bandra Kurla Complex, Bandra(E)
Mumbai –400 051
Date: 09/03/2009

VALIDITY OF WHO-GMP CERTFICATE

This is to certify that **M/s** ABC Company Limited at Company Address holding valid drug manufacturing licence in form No. 28E bearing No. 3, issued under the provision of Drugs & Cosmetics act, 1940 and rules thereunder.

The said firm observes **GOOD MANUFACTURING PRACTICES (GMP)** as laid by **WORLD HEALTH ORGANISATION (WHO)** in respect of manufacturing and testing of Pharmaceutical Formulations (Blood Products) as per list annexed.

The Certificate was valid up to **27th February 2009** and Validity is extended by a period of **6** months and it will be valid till **27th August.2009**

COMMISSIONER, FOOD AND DRUGS ADMINISTRATION
MAHARASHTRA STATE

Name of the Authorised Person : **P.R. Uttarwar.**

Signature:

Stamp & Date :
Joint Commissioner (Law)
Food & Drugs Administration,
Maharashtra State, Bandra.

- 9 MAR 2009

Annexure to WHO-GMP CERTIFICATE – List of Pharmaceutical Products

Certificate No. : WHO-GMP CERT/HQ-Ext-29-09/432/11
Date of Issue :
Valid upto : **27 August 2009**
Name of the firm : **ABC Company Limited**
Site Address : **Address.**

LIST OF PRODUCTS

Sr.No.	Product Brand Name Generic Name	Composition
1	AAA	Fibrinogen Not Less than 70mg/ml Thrombin Not less than 500 IU/ml Aprotinin Not less than 3000kiu for reconstitution of Fibrinogen. Water for Injection 1ml for reconstitution of Thrombin.
2	BBB	Fibrinogen B.P. 250 mg.
3	CCC	Thrombin U.S.P. 500 IU
4	DDD	Pooled Plasma, Solvent /Detergent Treated B.P. 100ml / 200ml
5	EEE	Immunoglobulin Intravenous B.P. 2.5 gms/50ml , 5gms/100ml 0.5 gms/10ml
6	FFF	Human Normal Albumin I.P. 20% Solution
7	GGG	Human Normal Albumin I.P. 5% Solution
8	HHH	Dried Factor VIII Fraction I.P. 250 I.U.
9	KKK	Each 100ml Contains: Total Protein 200g/l Sodium Caprylate 6.65g/l Na+Not more than 160mM K+ Not more than 2mM Aluminium ≤200 µg/l

COMMISSIONER, FOOD AND DRUGS ADMINISTRATION
MAHARASHTRA STATE

Name of the Authorised Person : **P.R. Uttarwar.**

Signature:

Stamp and Date:
Joint Commissioner (Law)
Food & Drugs Administration,
Maharashtra State, Bandra.
Tel. : (022) 26592363-65
Fax : (022) 26591959

F- 9 MAR 2009

CERTIFICATE OF PHARMACEUTICAL PRODUCT (CoPP)

FOOD & DRUGS ADMINISTRATION MAHARASHTRA STATE, MUMBAI 400 051
CERTIFICATE OF A PHARMACEUTICAL PRODUCT[1]

This certificate conforms to the format recommended by the World Health Organization
(General instructions and explanatory notes attached)

No. of certificate : WHO-GMP-CERT/HQ-EXT/29 Valid up to 27th Aug. 2009

Exporting (certifying) country : INDIA

Importing (requesting) country : AS PER ANNEXURE

1. Name and dosage form of product : AAA

1.1 Active ingredient (s)[2] and amount (s) per unit dose[3] :

1.2 Is this product licensed to be placed on the market for use in the exporting country?[5] Yes ☒ No ☐

1.3 Is this product actually on the market in the exporting country? Yes ☒ No ☐ Unknown ☐

If the answer to 1.2 is yes, continue with section 2A and omit section 2 B.
If the answer to 1.2 is no, omit section 2A and continue section 2B [6].

2 A

A.1 Number of product License[7]. 28E-3
And date of issue : 2nd Nov.2004

A.2 Product License holder : ABC Company Limited
(Name and address)

A.3. Status of product-license Holder [8] :
a ☒ b ☐ c ☐

A.3.1 For categories b and c the name and address of the manufacturer producing the dosage form are 9 :
Not applicable

A.4 Is summary basis of Approval appended?[10]
Yes ☐ No ☒

A.5 Is the attached, officially approved product information complete and consonant with the license?[11]
Yes ☐ No ☐ Not provided ☒

A.6 Applicant for certificate if different from license holder.[12]:
Not applicable.

2 B

B.1 Application for certificate (name and address):

B.2 Status of applicant
a ☐ b ☐ c ☐ d ☐

B.2.1 For categories b and c the name and address of the Manufacturer producing the dosage form are9

B. 3 Why is marketing authorization lacking?
Not Required ☐ Not Requested ☐ Under Consideration ☐ Refused ☐

B.4 Remark : [13]

FOOD AND DRUGS ADMINISTRATION COMMISSIONER MAHARASHTRA STATE

4. Does the certifying authority arrange for periodic inspection of the manufacturing plant in which the dosage form is produced ?

Yes ☒ No ☐ Not applicable[14] ☐

If no or not applicable proceed to question 4.

4.1 Periodicity of routine inspections (years): Once in a year

3.2 Has the manufacture of this type of dosage form been inspected? Yes ☒ No ☐

3.3. Do the facilities and operations conform to GMP as recommended by the World Health Organisation ?[15]
Yes ☒ No ☐ Not applicable ☐

4. Does the information submitted by the applicant satisfy the certifying authority on all aspects of the manufacture of the product?[16]

Yes ☒ No ☐

If no, explain.

Address of certifying authority:

Food & Drugs Administration
Maharashtra State, 2nd Floor, Survey No. 341,
Bandra-Kurla Complex, Bandra (E),
Mumbai 400 051
Tel : (022) 26592363-65
Fax : (022) 26591959

Name of the authorized person: P.R.Uttarwar

Signature:

Stamp and date: Joint Commissioner (Law)
Food and Drug Administration
M.S. Mumbai

- 9 MAR 2009

ANNEXURE

No. of certificate : WHO-GMP-CERT/HQ-EXT/29 Valid up to 27th Aug.2009

Exporting (certifying) country : INDIA

Importing (requesting) country : AS PER ANNEXURE

NAME AND ADDRESS OF THE MANUFACTURING SITE : ABC Company Limited
Address

NAME OF THE PRODUCT : AAA

List of countries to which the above product will be Exported / locally supplied.

1.Algeria	25.Ecuador	49.Kyrgyzstan	73.Oman	97. Tadjikistan
2.Albania	26.Egypt	50.Laos	74.Pakistan	98.Taiwan
3.Argentina	27.El Salvador	51.Latvia	75.Panama	99.Tanzania
4.Armenia	28.Estonia	52.Lebanon	76.Papua New Guinea	100.Thailand
5.Azerbaijan	29.Ethiopia	53.Liberia	77.Paraguay	101.Togo
6.Bahrain	30.Fiji	54.Libya	78.Peru	102.Tonga
7.Bangladesh	31.France	55.Lithuania	79.Philippines	103.Trinidad & Tobago
8.Belize	32.Gabon	56.Malawi	80.Poland	104.Tunisia
9.Belorussia	33.Ghana	57.Malaysia	81.Qatar	105.Turkey
10.Benin	34.Guatemala	58.Male	82.Romania	106.UAE
11.Bolivia	35.Guyana	59.Mali	83.Russia	107.Uganda
12.Brazil	36.Haiti	60.Mauritania	84.Samoa	108.Ukraine
13.Bulgaria	37.Honduras	61.Mauritius	85.Saudi Arabia	109.United Kingdom
14.Burkina Faso	38.Hungary	62.Mexico	86.Senegal	110.Uruguay
15.Cambodia	39.Indonesia	63.Moldova	87.Sierra Leone	111.USA
16.Cameroon	40.Iran	64.Mongolia	88. Singapore	112.Uzbekistan
17.Chile	41.Iraq	65.Morocco	89.Slovakia	113.Venezuela
18.China	42.Israel	66.Myanmar	90 Slovenia	114.Vietnam
19.Columbia	43.Ivory Coast	67.Namibia	91.South Africa	115.Yemen
20.Congo	44.Jamaica	68.Nepal	92.South Korea	116.Zaire
21.Costa Rica	45.Jordan	69.New Zealand	93.Sri Lanka	117.Zambia
22.Cuba	46.Kazakhstan	70.Nicaragua	94.Sudan	118.Zimbabwe
23.Czech Republic	[illegible]	71.Niger	95.Suriname	
24.Dominican Republic	48.Kuwait	72.Nigeria	96.Syria	

Address of certifying authority:

Food & Drugs Administration
Maharashtra State, 2nd [illegible] Survey No. 341,
Bandra-Kurla Complex, Bandra (E),
Mumbai 400 051
Tel : (022) 26592363-65
Fax : (022) 26591959

Name of the authorized person: P.R.Uttarwar

Signature:

Stamp and date: Joint Commissioner (Law)
Food and Drug Administration
M.S. Mumbai

PROFORMA STATEMENT

PROFORMA STATEMENT

Sr. No.	TRADE NAME	GENERIC NAME OR FORMULA	INDICATION	REMARKS
01.	AAA	xxxxxxx	1. Hypo-volaemic shock 2. Burns 3. Hypo-proteinemia 4. Ascites 5. Plasma exchange/dialysis	

PACKING : 1 x 50 mL

SHELF LIFE : 3 years from the date of manufacturing

FOB PRICE :

MANUFACTURER : ABC Company Limited.
Address.

SUMMARY DRUG INFORMATION SHEET

PHARMACEUTICAL DOCUMENTS

NAME OF DRUG
&
PRODUCT COMPOSITION

ABC Company Limited.

4. PRODUCT COMPOSITION

Trade Name: AAA

Generic Name: XXXXXXXXXXXX

Composition:

Each 50 mL vial contains:

Total protein: 200 Gm/L

Sodium Caprylate: 6.65 Gm/L

Na^+ Not more than: 160 mM

K^+ Not more than: 2 mM

Aluminum: $\leq$ 200 µg/L

Presentation: 50 mL in clear glass vial

PHARMACOPOEIAL REFERENCE

INDIAN PHARMACOPOEIA 2007

Volume 3

सत्यमेव जयते

Government of India
Ministry of Health & Family Welfare

Published By
THE INDIAN PHARMACOPOEIA COMMISSION
GHAZIABAD

of the clotting time immediately. Repeat the procedure with each of at least 3 dilutions, in the range stated above, of a reference preparation of thrombin, calibrated in International Units. Calculate the activity of the test preparation by the usual statistical methods. The confidence limits (P = 0.95) are not less than 80.0 per cent and not more than 125.0 per cent of the estimated activity.

Storage. Store protected from light.

Labelling. The label states (1) the amount of fibrinogen (mg of clottable protein), thrombin (International Units) per container, and coagulation factor XIII, if this is greater than 10 Units per ml; (2) where applicable, the name and volume of solvent to be used to reconstitute the components.

Human Albumin

Human Normal Albumin; Human Albumin Solution

Human Albumin is a sterile non-pyrogenic solution of the albumin component obtained from pooled human blood or from normal placentae frozen immediately after collection. It is obtained by fractionating source material such as blood, plasma, serum or placentae from healthy human donors and tested individually for the absence of hepatitis B surface antigen, HCV antibodies and HIV antibodies and complies with other tests and requirements prescribed by the appropriate national control authority. Source material obtained from donors who do not meet all the requirements stated may be used provided that it has been demonstrated to the national control authority that the process of fractionation will remove any known agent capable of adversely affecting the health of subjects treated with the preparation. It may be prepared from pooled source materials by precipitation with organic solvents under controlled conditions of pH, ionic strength and temperature or by chromatography or by any other method which does not affect the integrity of the product and has been shown to yield consistently a product containing not less than 95.0 per cent w/v of the total protein as albumin which is safe for intravenous injection. Residual organic solvent, if present, is removed by freeze-drying or other suitable treatment. The product is dissolved in sufficient water to obtain a suitable concentration, and a suitable stabilising agent is added to stabilise it to heat. It is prepared as a solution containing 15.0 to 25.0 per cent w/v of total protein or as an isotonic solution containing 4.0 to 5.0 per cent w/v of total protein. No antimicrobial agent is added at any stage during preparation and all processing steps are conducted in a manner to minimise risk of contamination from either micro-organisms or other deleterious matter. The solution is sterilised by filtration and distributed aseptically into containers which are then sealed so as to exclude micro-organisms. The solution is then heated to and maintained at 60° ± 0.5° for 10 hours so as to prevent the transmission of agents of infection transmissible by transfusion of blood or blood derivatives. Finally, the containers are stored for not less than 14 days at 30° to 32° or for not less than 4 weeks at 20° and examined visually. Those showing abnormalities such as abnormal colour, turbidity, microbial contamination, or presence of atypical particles must be discarded.

Albumin Solution should be tested in accordance with the requirements decided by the National Regulatory Authority; in particular, tests for the absence of hepatitis B surface antigen and HIV antibodies are carried out by suitably sensitive methods.

Human Albumin contains not less than 95.0 per cent and not more than 105.0 per cent of the stated amount of protein. It contains not less than 95.0 per cent and not more than 105.0 per cent of the contents of Na and K stated on the label which are, in any case, not more than 160 millimoles of Na per litre and 2 millimoles of K per litre.

Description. A clear, slightly viscous liquid, ranging in colour from almost colourless to greenish-yellow or amber depending on protein concentration and the method of fractionation used.

Identification

A. It contains plasma proteins of human origin only as determined by precipitation tests with specific antisera.

B. Determine the cellulose acetate by electrophoresis (2.4.12), using *barbitone buffer pH 8.6*, ionic strength 0.1 and *human albumin for electrophoresis RS*; 96.0 per cent of the protein has the mobility of human albumin.

Tests

Acidity or alkalinity (2.4.24). Dilute with sufficient *saline solution* to produce a solution containing 1.0 per cent w/v of protein; pH of the resulting solution, 6.7 to 7.3.

Alkaline phosphatase. Not more than 0.1 Unit per g of protein, determined by the following method. Transfer a mixture of 0.5 ml of the substance under examination and 0.5 ml of *diethanolamine buffer pH 10.0* to a spectrophotometer cell maintained at a temperature of 37° ± 0.2° and add 0.1 ml of *nitrophenyl phosphate solution*. Using a continuously recording spectrophotometer record the absorbance of the solution at about 405 nm (2.4.7), over a period of at least 30 seconds from the time of addition of the *nitrophenyl phosphate solution*. Calculate the alkaline phosphatase activity at 37° in Units per g of protein from the expression 118.3x/P, where x is the rate of increase of absorbance per minute and P is the content of total protein in g per litre, as determined in the Assay.

Haem content. Dilute with sufficient *saline solution* to produce a solution containing 1.0 per cent w/v of protein; absorbance of the resulting solution at about 403 nm, not more than 0.15 (2.4.7).

Denatured protein. Equilibrate a column (60 to 75 cm x 2.5 to 3.0 cm) of a gel of a cross-linked dextran suitable for fractionation of proteins in the range of molecular weight from 5,000 to 3,50,000 with a lower molecular weight for complete exclusion of globulin proteins of molecular weight between 4,00,000 and 5,00,000 (Sephadex G 150 is suitable) at 20° to 25° with a *saline-phosphate solution* prepared by mixing 2 volumes of *saline solution* and 1 volume of *mixed phosphate buffer pH 7.0* with *azide*. Apply to the column 2.5 ml of normal human serum, previously clarified by centrifuging, and elute with the *saline-phosphate solution* at a rate of 20 ml per hour. Prepare a chromatogram by recording the absorbance (2.4.7), of the eluate at about 280 nm in relation to its volume. The chromatogram exhibits three well-defined peaks. Determine the volume, V, of the eluate from the entry of the sample into the column to the apex of the first peak.

Dilute the substance under examination with the *saline-phosphate solution* to contain about 5.0 per cent w/v of protein, apply 2.5 ml to the column and elute under the above conditions, collecting the eluate in 5-ml portions. Three peaks may appear in similar positions to those in the chromatogram obtained from the normal human serum but the relative peak heights may be different. To the fraction eluted between volume 0.85 V and 1.15 V, add for each 10 ml, 0.4 ml of a 7.5 per cent w/v solution of *sodium molybdate* and 0.4 ml of a mixture of 1 part of *nitrogen-free sulphuric acid* and 30 parts of *water*, shake, centrifuge for 5 minutes and complete the Assay described under Human Plasma beginning at the words "decant the supernatant...". The weight of protein in the fraction of the eluate is not more than 3.5 per cent of the weight of protein in the volume of the substance under examination applied to the column.

Heat the substance under examination for 50 hours at 56.5° to 57.5° and repeat the chromatographic separation and the determination of the weight of protein in the fraction eluted between 0.85 V and 1.15 V. When expressed as a percentage of the weight of protein in the volume of the substance under examination applied to the column, it exceeds the percentage obtained before heating by not more than 1.5 per cent w/v.

Protein composition. Not less than 95.0 per cent w/v of the total protein as albumin, when determined by the following method. Carry out Method II for cellulose acetate electrophoresis (2.4.12), using one strip of cellulose for each solution.

Test solution. Dilute the substance under examination with *saline solution* to contain 2.0 per cent w/v of total protein.

Reference solution. Dilute *human albumin for electrophoresis RS* with *saline solution* to obtain a solution containing 2.0 per cent w/v of total protein.

Not more than 5.0 per cent of total protein is contained in bands other than the principal band in the strip obtained with test solution. The test is not valid if the proportion of the protein in the principal band is not within the limits stated in the leaflet supplied with human albumin for *electrophoresis RS*.

Stability. The contents of the final container remain unchanged, as determined by visual inspection, after heating at 57° for 50 hours, when compared to its control consisting of a sample from the same lot which has not undergone this heating.

Pyrogens (2.2.8). Complies with the test for pyrogens, using 3 ml per kg of the rabbit's weight, irrespective of the protein content, in rabbits that have not previously received blood products.

Sterility (2.2.11). Complies with the tests for sterility.

Abnormal toxicity (2.2.1). Complies with the test for abnormal toxicity, using Method B and 0.5 ml of the solution for each mouse and 5 ml for each guinea-pig irrespective of the protein content.

Assay

For protein. Dilute to about 0.75 per cent w/v of total protein with *saline solution*. Take 2 ml of this solution in a round-bottomed centrifuge tube, add 2 ml of a 7.5 per cent w/v solution of *sodium molybdate* and 2 ml of a mixture of 30 volumes of *water* and 1 volume of *nitrogen-free sulphuric acid*. Shake, centrifuge for 5 minutes, decant the supernatant liquid and let the inverted tube stand on a filter paper to drain the fluid. Carry out Method E for determination of nitrogen (2.3.30), on the residue thus obtained and multiply the result by 6.25 to obtain the protein content.

For sodium. Dilute to 0.01 per cent w/v of protein with *water* and determine by Method A for atomic absorption spectrophotometry (2.4.2), or by Method B for flame photometry (2.4.4), measuring at about 589 nm and using *sodium solution FP* suitably diluted with *water* as the standard solution.

For potassium. Dilute to 0.25 per cent w/v of protein with *water* and determine by Method A for atomic absorption spectrophotometry (2.4.2), or by Method B for flame photometry (2.4.4), measuring at about 767 nm and using *potassium solution FP* suitably diluted with *water* as the standard solution.

Human Albumin intended for administration to patients undergoing dialysis or to premature infants complies with the following additional test.

Aluminium (2.3.8). Not more than 200 µg of Al per litre. Determine by atomic absorption spectrophotometry (2.4.2), with a furnace as atomic generator and measuring at 309.3 nm and using as standard solutions a suitable range of dilutions in *water* of *aluminium standard solution* (10 ppm Al) further diluted, as necessary, with a solution containing 0.17 per cent w/v of *magnesium nitrate* and 0.05 per cent w/v of *octoxinol 10* in a solution of *nitric acid* containing 1 per cent w/v of *nitric acid*. Prepare suitable dilutions of the preparation under examination and *human albumin for aluminium validation RS* with *water*. Dilute the solutions, as necessary, with the *magnesium nitrate-octoxinol 10-nitric acid solution* used for dilution of the standard solution. The test is valid only if the aluminium content determined for *human albumin for aluminium validation RS* is within 20 per cent of the stated value.

NOTE — Wash all equipments with a solution containing 20.0 per cent w/v of nitric acid before use and use plastic containers only to prepare all solutions.

Storage. Store protected from light, at a temperature between 2° and 25°. Human Albumin stored at 2° to 8° may be expected to continue to meet the requirements of the monograph for 5 years from the date on which it was heated at 60° for 10 hours. Human Albumin stored at a temperature not exceeding 25° may be expected to continue to meet the requirements of the monograph for 3 years from the date on which it was heated at 60° for 10 hours.

Labelling. The label states (1) the volume in the container; (2) the total amount of protein in the container expressed in g per litre or as percentage; (3) the concentration of sodium and potassium ions expressed in millimoles per litre; (4) the names and concentrations of any stabilising agents and any other additives in the final solution; (5) the type of source material used to manufacture the product; (6) the words "Do not use if turbid"; (7) that the contents must not be used more than 4 hours after the container has been penetrated and any remnant portion must be discarded; (8) the storage conditions; (9) the date after which the solution is not intended to be used; (10) either that the preparation is suitable for administration to patients undergoing dialysis and to premature infants or that it is not intended for such purpose.

Human Coagulation Factor IX

Human Coagulation Factor IX is a plasma protein fraction containing coagulation factor IX, prepared by a method that effectively separates factor IX from other prothrombin complex factors (factors II, VII and X). It is obtained from human plasma that complies with the monograph on Human Plasma for Fractionation.

The potency of the preparation, reconstituted as stated on the label, is not less than 20 IU of factor IX per ml.

Production

The method of preparation is designed to maintain functional integrity of factor IX, to minimise activation of any coagulation factor (to minimise potential thrombogenicity) and includes a step or steps that have been shown to remove or to inactivate known agents of infection; if substances are used for inactivation of viruses during production, the subsequent purification procedure must be validated to demonstrate that the concentration of these substances is reduced to a suitable level and that any residues are such as not to compromise the safety of the preparation for patients.

The specific activity is not less than 50 IU of factor IX per mg of total protein, before the addition of any protein stabiliser.

The factor IX fraction is dissolved in a suitable liquid. Heparin, antithrombin and other auxiliary substances such as a stabiliser may be included. No antimicrobial preservative is added. The solution is passed through a bacteria-retentive filter, distributed aseptically into the final containers and immediately frozen. It is subsequently freeze-dried and the containers are closed under vacuum or under an inert gas.

Consistency of the method

The consistency of the method of production is evaluated by suitable analytical procedures that are determined during process development and which normally include (1) assay of factor IX; (2) determination of activated coagulation factors; (3) determination of activities of factors II, VII and X which shall be shown to be not more than 5.0 per cent of the activity of factor IX.

Description. A white or pale yellow, hygroscopic powder or friable solid.

Reconstitute the preparation under examination as stated on the label, immediately before carrying out the Identification, Tests (except those for solubility and water) and Assay.

Identification

It complies with the limits of the Assay.

Tests

pH (2.4.24). 6.5 to 7.5.

Osmolality (2.4.23). Minimum 240 mosmol per kg.

Total protein. If necessary, dilute an accurately measured volume of the preparation under examination with a 0.9 per cent solution of *sodium chloride*, to obtain a solution which may be expected to contain about 15 mg of protein in 2 ml. To 2.0 ml of that solution, in a round-bottomed centrifuge tube, add 2 ml of a 7.5 per cent solution of *sodium molybdate* and 2

MANUFACTURING PROCESS
AND
FLOW CHART

6. MANUFACTURING PROCESS AND FLOW CHART

AAA
Generic XXXXXX

Dispensing
The definite quantity of all the raw materials i.e Sodium Chloride, Sodium Hydroxide Pellets Purified, Sodium Caprylate, Ortho phosphoric are dispensed after performing line clearance of the dispensing area in the prescence of stores and QA person. Fraction V paste is to be dispensed just before processing. The accuracy of the dispensed material is verified before the commencement of the process. The dispensed material is to be reconciled at the end of every operation

Solution preparation
The standard quantity of all solutions are prepared in the buffer room i.e of Sodium Chloride, Sodium Hydroxide and Sodium Caprylate.

Dilution of Solution
Sodium Chloride is then diluted with Water for Injection in required concentrations.

Dissolution of Fraction V Paste
All the required production solutions from the buffer room are brought to common fractionation room. The paste is dissolved in 270L of 0.15M Sodium chloride Solution in mixing vessel with continous stirring for not less than 60 min.

Depth filtration
Clarify the Fraction V solution with depth filter stack followed by 1.5µ capsule filter in series. Flush 60L of 0.005M Sodium chloride solution through Fraction V dissolution tank depth filter and 1,5µ capsule filter in series.

Concentration and Diafiltration
Process for Albumin volume reduction and diafiltration
The Ultra filtration system is cleaned with WFI till pH comes to neutral.Albumin solution is connected to feed pump, **retentate** is connected to albumin solution tank and permeate is kept to drain.The volume reduction of albumin solution is started and is reduced to the volume of approximately 100 L. 430L of Sodium chloride solution is continuously added through 0.22µ capsule filter to concentrated albumin solution and the volume is reduced to reach 28-30% albumin concentration. This concentration is determined by hand held refractometer.The pH of albumin concentrate is adjusted to 6.8 to 7.0 with 1.0M solution of Sodium Hydroxide. Feed pump is stopped and the retentate is disconnected from the tank. The permeate is closed and the retentate is collected in 20 L bottles. The feed pump is started to collect entire retentate from the tank. The ultra filtration system is flushed with sodium chloride solution till the refractometer reading of the retentate comes to ≤ 1%. The final volume of the concentrate is measured and the bulk is mixed thoroughly. The bulk is transferred to sterile 50L pressure vessel and 10ml sample is collected for QC testing.
The inbetween process stopping and starting of the feed pump should not be more than five minutes.

Addition of stabilizer
Calculation required

Calculated quantity of sodium caprylate solution is added to Albumin bulk.. The solution is stirred with continuous mixing.

Bulk filtration
The pre-filtration integrity of 0.22 filter is checked as per The minimum bubble point is 51 psi and the observed is 52 psi. Aseptically the sterile 1.0µ and 0.2µ filters are connected to pressure vessel containing albumin bulk. The post filtration integrity of 0.22 filter is checked.

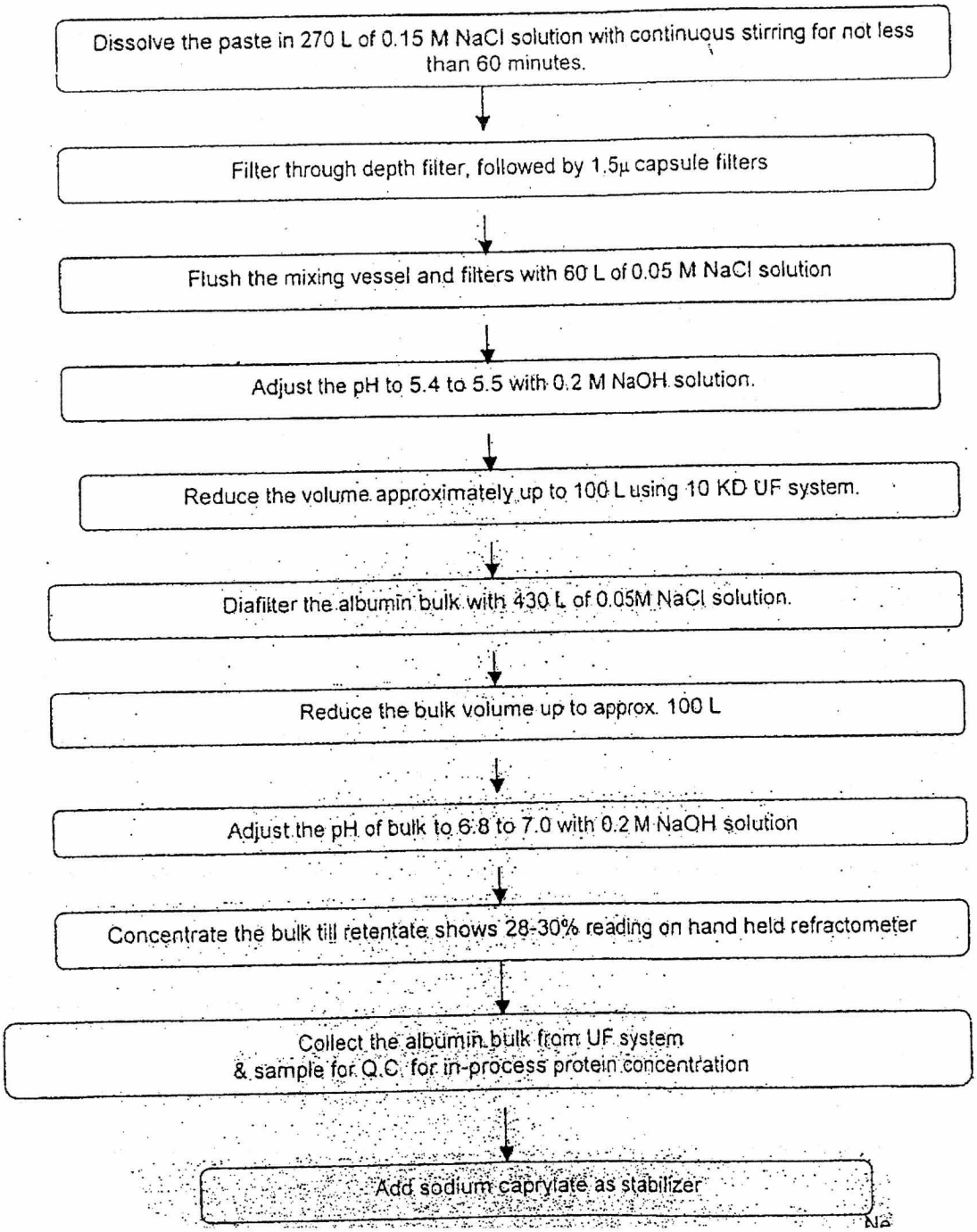
Bulk pasteurization
The jacketed mixing vessel containing albumin bulk is connected to circulatory bath and the temperature of the circulatory bath is set to 60°c. The temperature is maintained at 60°C.± 1°C for 10 hours. The observations are recorded. The temperature is recorded at every 30 min intervals.

Sterile filtration
Sterile 20L Naglene bottles, Sterile 1.0µ and 0.22µ filters, are kept on trolley and the trolley is transferred to sterile filtration area. All the material from the trolley is shifted to Bio safety cabinet. The pre-filtration integrity is checked. The minimum bubble point is 51 psi and the observed psi is 53 psi. The 1.0µ and 0.22µ capsule filters is connected to bulk vessel with triclover fitting. The compressed air is connected to pressure vessel and the vessel is pressurized to 1.0 ± 0.5kg/cm2 and the filtration is started. The filtrate is collected in 20L aliquots using 20L polypropylene bottle or 20L capacity plastic bags. The post filtration integrity is checked at 0.22 filter. The minimum bubble point is 51 psi and observed bubble point is 53psi. Six samples of 5ml aliquots in sterile glass vials is aseptically collected in sterile glass vials of 10ml size and sealed.

Storage of Albumin Bulk
The bottle is labeled as Albumin Bulk. The batch No, quantity of bulk, date and number of containers is mentioned on it and signed. The bottles are stored in Walk in cooler at +4°c.

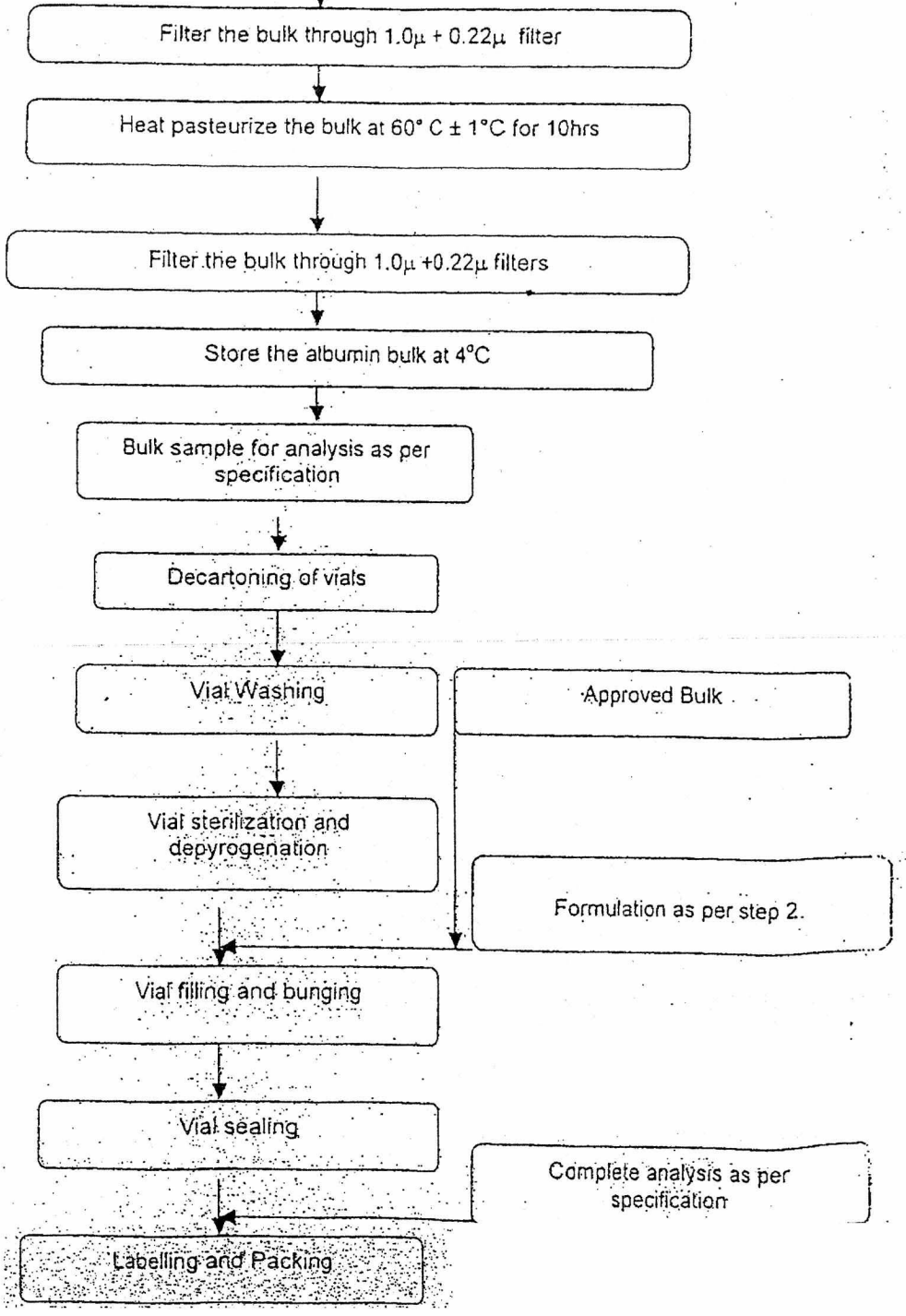
Product		PROCESS FLOW CHART	
Date: 30th Jul' 2007		Location:cGMP Plant I, Worli, Mumbai	
Product Code: 4B4	Lot Size : 60 Kg		

Process Flow chart of Bulk manufacturing and filling:



Product Registration Application- AAA

Product	XXXXXXXXXX	PROCESS FLOW CHART	ABC
Date: 30th Jul' 2007		Location:cGMP Plant I, Worli, Mumbai	
Product Code: 4B4		Lot Size : 60 Kg	



RAW MATERIAL SPECIFICATION
AND
TESTING METHOD

Talecris BIOTHERAPEUTICS

2007

US/ICON Plasma Master File

Annual Update

Data Package

Table of Contents

Table of Contents

The US/ICON Plasma Master File (PMF) 2006 annual update contains detailed information on the plasma origin, including the list of plasmapheresis centers and testing laboratories. This Plasma Master File relates to the human plasma-derived medicinal products identified in Chapter 1.1, *Plasma-Derived Products List* which are manufactured from Source Plasma (Human) pooled, fractionated and purified at the Clayton, NC manufacturing facility. The country of origin of the plasma is exclusively the United States (US) and the plasma is obtained by plasmapheresis to be used for the preparation of medicinal products. The plasma is frozen immediately after collection at -20ºC or colder as specified in the US Code of Federal Regulations (CFR) and meets all US license criteria for Source Plasma (Human) as specified in the US CFR.

The overall safety strategy employed by Talecris to assure that safe plasma donations and manufacturing pools are processed for plasma-derived therapeutic products is presented in Chapter 1.2 *Overall Safety Strategy* along with a flow diagram of the plasma supply-chain logistics in Chapter 1.3 *General Logistics*. The plasma qualification strategy provides assurance that the starting material used is safe for the manufacture of the plasma-derived therapeutic products.

All plasma collection facilities supplying plasma to Talecris listed in Chapter 2.1.1.a. *Information on Collection Centers*, for use in the manufacture of plasma-derivatives must be licensed by the US FDA and are inspected on a routine basis by the US FDA. Plasma centers must also be licensed and inspected for compliance with the Clinical Laboratory Improvement Amendments of 1988 (CLIA regulations) and comply with any applicable state or local regulatory agency requirements. Audits of the collection facilities are performed annually by Quality Operations (QO) unless the requirements for an extended audit frequency have been met. Plasma centers must also be inspected and determined to meet the international Quality Plasma Program (IQPP) standards established by the Plasma Protein Therapeutics Association (PPTA).

An update of the epidemiological data at the plasmapheresis centers, collected in accordance with the PPTA Industry Viral Marker Voluntary Standard is included in Chapter 2.1.1.b *Epidemiological Data*. Data tables with the viral marker information for each plasmapheresis center by owner group are presented.

According to the US Code of Federal Regulations (CFR), each donor must be certified to be in good health on the initial donation, i.e., applicant donors, and on the day of donation, i.e., qualified donors. According to the IQPP an applicant donor is defined as one who has never donated at the facility or who has not donated at the facility within the last six months. Selection of an applicant donor includes a routine physical examination and interview with a Medical Supervisor, testing samples, and answering questions regarding medical history, AIDS risks, travel risks, behavior, and other high risk activities. An applicant donor must have two consecutive acceptable sets of viral marker test results within a six month period to become a qualified donor. The company traceability system to trace any donation through to finished product and vice versa is included in Chapter 2.1.4 *System to Trace Donations*.

Compliance standards for plasma and quality aspects for plasma which are addressed in the General Specification - Source Plasma are presented in Chapter 2.2.1 *Compliance Standards for Plasma*. Plasma donations and plasma manufacturing pools are tested for markers of infection in accordance with the applicable US regulations. Detailed information on the plasma donation test laboratories, specifications, methods and validation are included in Chapters 2.1.2 *Information on Test Laboratories* and 2.2.2 *Testing of Donations and Pools for Infectious Agents*. The plasma donation Nucleic Acid Amplification Technology (NAT) minipool test strategy is presented.

Currently, all plasma manufacturing pools processed at the Clayton, NC fractionation facility are tested at sites under the control and license of Talecris. Plasma manufacturing pool viral marker testing is performed at the Clayton, NC fractionation facility while NAT testing is performed at the Raleigh Test Laboratory. If needed, manufacturing pools might be tested at National Genetics Institute, which serves as a backup facility for NAT testing. Information on the test methods and validation data are presented in Chapter 2.2.2 *Testing of Donations and Pools for Infectious Agents*. Validation reports of Viral Marker plasma manufacturing pool test methods are presented in Chapter 2.2.2.a *Viral Marker Testing of the Plasma Pools*. The ICH Harmonized Tripartite Guideline on the Validation of Analytical Procedures was used for the validation of the Viral Marker test methods. Validation reports for NAT plasma manufacturing pool test methods are presented in Chapter 2.2.2.b *NAT Testing of the Plasma Pools*. The ICH Harmonized Tripartite Guideline on the Validation of Analytical Procedures and the European Directorate for the Quality of Medicines (EDQM) document PA/PH/OMCL (98) 22, DEF *Validation Of Nucleic Acid Amplification Technology (NAT) For The Detection Of Hepatitis C Virus (HCV) RNA In Plasma Pools,* were followed for the validation of the NAT test methods.

Technical characteristics of collection materials and information on the anticoagulant solutions are given in Chapter 2.2.3 *Technical Characteristics of Collection Materials*. All Source Plasma (Human) procured by Talecris is collected using High Density Polyethylene bottles.

Plasma is collected, frozen and stored under the control of the plasma collection organizations until it is shipped to the manufacturing site. As necessary, plasma units may be transported to an interim off-site storage facility. Chapter 1.3 *General Logistics* provides a flow chart in which the overall logistics and transport flow of plasma from plasma centers to storage facilities and the fractionation site is described. All plasma units must have satisfactory viral marker and NAT test results to be acceptable for further manufacturing. Any plasma units testing reactive/positive for HBV, HCV or HIV by viral marker or NAT testing are identified and removed along with the corresponding lookback units prior to pooling.

Donations from applicant donors are held at the collection establishment until a second set of viral marker tests and standard donor screening criteria are met. No single unit from a non-returning donor is used for further processing. Moreover, each unit of plasma from qualified donors is held in inventory for 60 days, measured from the date of the plasma donation, prior to pooling. Characteristics of the plasma manufacturing pools are presented in Chapter 2.2.6 *Characterization of the Plasma Pool*.

All approved plasma collection organizations have signed a contract whose terms include specific Quality Criteria, e.g., Source Plasma Specifications (collection materials, plasma donor criteria, plasma donation specifications), storage and transport requirements, donation tracing, and communication to Talecris of post donation information. A quality assurance system is required to be established, documented and maintained for each plasma collection organization. Adherence to the quality specifications as stated in the respective contracts is verified by Quality Operations through the audit procedure.

Outline Number	Title	Current TRD Rev #	TRD Rev. #	Notes
I	**TABLE OF CONTENTS**			
	Table of Contents			
II	**SUMMARY**			
	Plasma Master File Summary			
III	**DETAILED LIST OF CHANGES**			
	List of Changes			
IV	**PLASMA MASTER FILE**			
1.	**GENERAL INFORMATION (SUMMARY)**			
1.1	**Plasma-derived products' list**			
	Plasma Derived Products List	T.18.48-02US	T.18.48-02US	No changes
1.2	**Overall safety strategy**			
	Overall Safety Strategy	T.18.49-03US	T.18.49-03US	No changes
1.3	**General logistics**			
	General Logistics	T.18.50-01US	T.18.50-02US	Added the word "Talecris" as it had been inadvertently left out. of flow chart
2.	**TECHNICAL INFORMATION ON STARTING MATERIALS**			
2.1	**Plasma origin**			
2.1.1	**Information on centers or establishments in which blood/plasma collection is carried out, including inspection and approval, and epidemiological data on blood transmissible infections.**			
a.	**Information on collection centers or establishments in which blood/plasma collection is carried out**			
	List of Plasmapheresis Centers	T.18.09-12US	T.18.09-13US	• Name change from IBR to TPR • Inspection dates were updated • Document was updated with current active centers • Add ABS centers
	Document Separator Intentionally Blank			
	Procedure for Approval of Plasma Suppliers	T.18.05-04	T.18.05-04	No changes
	Document Separator Intentionally Blank			
	Remuneration of Donors	T.18.14-03	T.18.14-03	No changes
b.	**Epidemiological data on blood transmissible infections**			

Outline Number	Title	Current TRD Rev #	TRD Rev. #	Notes
	Epidemiology at the Plasmapheresis Centers	T.18.11-05US	T.18.11-06US	• Document was updated with 2006 data • Document was updated to reflect EU format • 2005 and 2006 data were compared
2.1.2	**Information on centers or establishments in which testing of donations and plasma pools is carried out, including inspection and approval status.**			
	Test Sites for the Plasma Donation	T.18.16-09US	T.18.16-10US	• Inspection dates were updated • Updated LifeSera FDA # • Delete Interstate Blood Bank in Chicago (IBTL)
	Document Separator Intentionally Blank			
	Test Sites for the Plasma Manufacturing Pool	T.18.16-07US	T.18.16-08US	Inspection dates were updated
2.1.3	**Selection/exclusion criteria for blood/plasma donors.**			
	Donor Qualification, Examination and Interview	T.18.12-03	T.18.12-03	No changes
	Document Separator Intentionally Blank			
	Donor Exclusion Criteria	T.18-15-04US	T.18.15-04US	No changes
2.1.4	**System in place which enables the path taken by each donation to be traced from the blood/plasma collection establishment through finished products and vice versa.**			
	System to Trace Each Donation	T.18.21-04US	T.18.21-05US	Information was added to clarify lookback process
2.2	**Plasma quality and safety**			
2.2.1	**Compliance standards for plasma.**			
	Compliance Standards for Plasma	T.18.26-04US	T.18.26-05US	Revised wording to make more generic
	Document Separator Intentionally Blank			
	General Specification – Source Plasma	T.18.01-04	T.18.01-05	Added paragraph on freezing for labile components
2.2.2	**Testing of blood/plasma donations and pools for infectious agents, including information on test methods and, in the case of plasma pools, validation data on the tests/used.**			
	Test Specification for the Plasma Donation	T.18.01-12	T.18.01-12	No changes
	Document Separator Intentionally Blank			
	Test Information for the Plasma Donation	T.18.02-08US	T.18.02-09US	Added B19 FDQA as alternate test
	Document Separator Intentionally Blank			
	Test Specification for the Plasma Manufacturing Pool	T.18.01-09	T.18.01-09	No Changes
	Document Separator Intentionally Blank			
	Test Information for the Plasma Manufacturing Pool	T.18.02-10US	T.18.02-11US	Added B19 FDQA as alternate test
	Validation of testing methods			
a.	**Viral marker testing of the plasma pool(s)**			

Outline Number	Title	Current TRD Rev #	TRD Rev. #	Notes
	Table of Contents for Plasma Manufacturing Pool Viral Marker Validation Reports			No changes
	Document Separator Intentionally Blank			
	Determination of Hepatitis B Surface Antigen (HBsAg) in Plasma or Plasma Derived Products by EIA	T.2.53-01R	T.2.53-01R	No change
	Document Separator Intentionally Blank			
	Qualitative Detection of Antibody to Human Immunodeficiency Virus Types 1 and 2 in Plasma Pools	T.2.53-01R	T.2.53-01R	No change
	Document Separator Intentionally Blank			
	Addendum 1, Qualitative Detection of antibody to Human Immunodeficiency Virus Types 1 and 2 in Plasma Pools	T.2.53-02R	T.2.53-02R	No change
b.	**NAT testing of the plasma pool(s)**			
	Table of Contents for Plasma Manufacturing Pool NAT Validation Reports			
	Document Separator Intentionally Blank			
	Detection of HCV RNA in Plasma Pools using the Roche AmpliScreen™ HCV Test Kit, Version 2.0, on the COBAS Amplicor™ Analyzer	T.18.47-03	T.18.47-03	No change
	Document Separator Intentionally Blank			
	Detection of HIV-1 RNA in Plasma Pools using the Roche AmpliScreen™ HIV-1 Test Kit, Version 1.5, on the COBAS AMPLICOR™ Analyzer	T.18.47-02	T.18.47-02	No change
	Document Separator Intentionally Blank			
	Detection of HBV DNA in Plasma Pools using the Roche AmpliScreen™ HBV Test Kit on the COBAS AMPLICOR™ Analyzer	T.18.47-02	T.18.47-02	No change
	Document Separator Intentionally Blank			
	Process for the Detection of Parvovirus B19 DNA in Plasma Manufacturing Pools using Polymerase Chain Reaction Methodology: The Parvo B19 Test (Digene Corp., Gaithersburg, MD)	T.18.47-03	T.18.47-03	No changes
	Document Separator Intentionally Blank			

Outline Number	Title	Current TRD Rev #	TRD Rev. #	Notes
	Epidemiology at the Plasmapheresis Centers	T.18.11-05US	T.18.11-06US	• Document was updated with 2006 data • Document was updated to reflect EU format • 2005 and 2006 data were compared
2.1.2	**Information on centers or establishments in which testing of donations and plasma pools is carried out, including inspection and approval status.**			
	Test Sites for the Plasma Donation	T.18.16-09US	T.18.16-10US	• Inspection dates were updated • Updated LifeSera FDA # • Delete Interstate Blood Bank in Chicago (IBTL)
	Document Separator Intentionally Blank			
	Test Sites for the Plasma Manufacturing Pool	T.18.16-07US	T.18.16-08US	Inspection dates were updated
2.1.3	**Selection/exclusion criteria for blood/plasma donors.**			
	Donor Qualification, Examination and Interview	T.18.12-03	T.18.12-03	No changes
	Document Separator Intentionally Blank			
	Donor Exclusion Criteria	T.18-15-04US	T.18.15-04US	No changes
2.1.4	**System in place which enables the path taken by each donation to be traced from the blood/plasma collection establishment through finished products and vice versa.**			
	System to Trace Each Donation	T.18.21-04US	T.18.21-05US	Information was added to clarify lookback process
2.2	**Plasma quality and safety**			
2.2.1	**Compliance standards for plasma.**			
	Compliance Standards for Plasma	T.18.26-04US	T.18.26-05US	Revised wording to make more generic
	Document Separator Intentionally Blank			
	General Specification – Source Plasma	T.18.01-04	T.18.01-05	Added paragraph on freezing for labile components
2.2.2	**Testing of blood/plasma donations and pools for infectious agents, including information on test methods and, in the case of plasma pools, validation data on the tests/used.**			
	Test Specification for the Plasma Donation	T.18.01-12	T.18.01-12	No changes
	Document Separator Intentionally Blank			
	Test Information for the Plasma Donation	T.18.02-08US	T.18.02-09US	Added B19 FDQA as alternate test
	Document Separator Intentionally Blank			
	Test Specification for the Plasma Manufacturing Pool	T.18.01-09	T.18.01-09	No Changes
	Document Separator Intentionally Blank			
	Test Information for the Plasma Manufacturing Pool	T.18.02-10US	T.18.02-11US	Added B19 FDQA as alternate test
	Validation of testing methods			
a.	**Viral marker testing of the plasma pool(s)**			

Plasma Donor

Plasma Derived Products List

Number of Pages
(including cover page)

2

Original is signed

_____ _____

Sign and Rank Date

_____ _____

Sign and Rank Date

Valid from:

This Plasma Master File relates to the human plasma-derived medicinal products identified in Table 1 which are manufactured from Source Plasma (Human) pooled, fractionated and purified at the Clayton, NC manufacturing facility.

Table 1

Product	Trade-Name(s)
Albumin (Human) 5%, 20%, 25%	Plasbumin® -5, -20, -25
$Alpha_1$-Proteinase Inhibitor (Human)	Prolastin®
Antihemophilic Factor (Human)	Koate® DVI
Antithrombin III (Human)	Thrombate III®
Immune Globulin (Human)	GamaSTAN™ S/D (formerly BayGam®)
Immune Globulin Intravenous (Human) 5%, 10%	Gamimune® N, 5% and 10 %
Immune Globulin Intravenous (Human) 10% Caprylate/Chromatography Purified	Gamunex®
Plasma Protein Fraction (Human)	Plasmanate®
Rabies Immune Globulin (Human)	HyperRAB™ S/D (formerly BayRab®)
Tetanus Immune Globulin (Human)	HyperTET™ S/D (formerly BayTet®)
Hepatitis B Immune Globulin (Human)	HyperHEP B™ S/D (formerly BayHep B®)
RhoD Immune Globulin (Human)	HyperRHO™ S/D (formerly BayRho D®)

Intermediate starting materials derived from Source Plasma (Human) and procured to manufacture plasma derivatives are required to meet the PPTA Voluntary Standard for Intermediates made from Source Plasma (Human). The quality attributes of Intermediates procured to manufacture plasma derivatives are documented in the specification for each vendor approved Intermediate fraction.

Plasma Donor

Overall Safety Strategy

Number of Pages
(including cover page)

36

Original is signed

_____ _____

Sign and Rank Date

_____ _____

Sign and Rank Date

Valid from:

1. Overall Safety Strategy

Plasma-derived medicinal product safety is achieved using a controlled, step-by-step process beginning with donor suitability during plasma collection, donation testing procedures, donation traceability, the implementation of an inventory hold step, plasma manufacturing pool testing, and finally, the use of validated viral inactivation/removal steps in the manufacturing process. The strategy to ensure safe plasma donations and subsequent plasma manufacturing pools are used to manufacture plasma derivatives is presented in Figure 1.

The main plasma safety strategy points are as follows:

- Approval of Plasma Suppliers
- Plasma Donor Selection
- Plasma Donation Testing (Viral Marker and Nucleic Acid Amplification Technology (NAT))
- Plasma Donation Traceability, Inventory Hold and Lookback Procedures
- Testing of Plasma Manufacturing Pools (Viral Marker and NAT)
- Validated Virus Inactivation and Removal Technologies within the Manufacturing Process

Plasma obtained by plasmapheresis is a well-established procedure in the United States (US) dating back to the 1960s.[1] All plasma intended for further manufacture into injectable therapeutic biological products meets the US license criteria for Source Plasma (Human) as specified in the US Code of Federal Regulations.

2. Approval of Plasma Suppliers and Plasma Donor Selection

Safety of plasma donations depends on the use of qualified plasma donors, the strict exclusion of potential donors who bear one or more potential risks and the use of qualified plasma suppliers. Talecris purchases Source Plasma (Human) for further manufacture from approved suppliers. All plasma suppliers must be US FDA licensed and have establishment and product licenses, Clinical Laboratory Improvement Amendments (CLIA) certification, and Plasma Protein Therapeutics Association (PPTA) international Quality Plasma Program (iQPP) certification.

The centers must be regularly inspected by the following authorities and be deemed acceptable: the US FDA, the US Department of Health and Human Services Health Care Finance Administration (HCFA) and other federal, state, and local authorities as required. Additionally, the centers must undergo inspection of facilities, procedures and records by Quality Operations (QO).

An applicant donor must have two consecutive acceptable sets of viral marker test results and screening interviews within a six-month period to become a qualified donor as defined by the PPTA Qualified Donor Voluntary Standard. Any qualified donor who either donates at a different center or has donated at a center before, but more than 6 months has elapsed since their last donation, must be re-qualified.

The qualification of a donor involves a well-documented series of steps including routine physical examination, testing and interview(s) by the Medical Supervisor or designated, trained staff. During the interview(s), very direct and specific questions are asked about risk factors. The practice of screening donors with interview questions excludes approximately 90 percent of donors who are unsuitable to donate plasma for further manufacture.[2] Talecris purchases plasma collected from qualified donors only.

To ensure viral safety for recipients with respect to major pathogenic agents, certain donors are excluded (either permanently or temporarily) from participating in the plasmapheresis program. Plasma suppliers must follow 21 CFR 640.63, which states that each donor must be in good health at the initial donation and on the day of each subsequent donation.

Donor suitability criteria to reduce the risk of (v)CJD are followed in accordance with the current US FDA guidance document *Revised Preventive Measures to Reduce the Possible Risk of Transmission of Creutzfeldt-Jakob Disease (CJD) and Variant Creutzfeldt-Jakob Disease (vCJD) by Blood and Blood Products*, January, 2002. Additionally, Talecris fulfills the requirements to reduce the risk for (v)CJD as laid down in EMEA/CPMP/BWP/2879/02/rev 1 and Directive 2001/83/EC amended by Directive 2004/33/EC. The donor exclusion criteria specific to the reduction of the risk for (v)CJD are listed in the donor exclusion criteria documentation. Furthermore, the plasma-derivative manufacturing process has been investigated and found to have significant steps for the reduction of TSE infectivity.

Donors are remunerated for their time and the travel costs associated with plasmapheresis; however, the reimbursement is nominal.

Centers supplying plasma to Talecris collect plasma from a population not at high risk for bloodborne infections. Data on epidemiology at the plasmapheresis centers are collected, analyzed and presented in the format as required by EMEA/CHMP/BWP/125/04, Guideline on Epidemiological Data on Blood Transmissible Infections. An evaluation of the incident rates (Table 1) shows differences between the three viral infections. Hepatitis infections were generally detected at higher frequencies than were HIV infections. This is in correlation with the previously published epidemiological studies.[3] No detectable