資料１：「Indian Plasma Regulatory Framework and Challenges」

Dr.Surinder Singh

INDIAN PLASMA REGULATORY FRAMEWORK AND CHALLENGES

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Bali, 3rd September,2013

India-Major importer of plasma derived products

Imported from*

Austria	Albumin, Fibrin sealant kit, Factor-VIII, IX
Belgium	Factor-VIII,
China	Normal and specific Immunoglobulin.
Germany	Albumin, Normal and specific Immunoglobulin, Factor-IX
Hungry	Albumin, Normal and specific Immunoglobulin.
Italy	Albumin
Israel	Fibrin Sealant Kits.

*NIB Data

Market Overview- India Plasma Products

Total market for plasma products in India is estimated to be >$100 million with overall demand growing about 10-15% annually

Albumin	• Estimated to be the largest component contributing • 17-18000 kg.
IVIG	• Estimated immunoglobulin total quantity contribution is ~15000 kgs
Plasma derived factor VIII	• Estimated total served market ~40 mn IUs.

India-Major importer of plasma derived products :

Imported from*

South Korea	Albumin, Normal IgG (also by contract fractionation)
Spain	Albumin, Normal and specific Immunoglobulin, Factor-VIII
UK	Albumin, IVIG, Factor-VIII & IX
USA	Albumin, PPF, Factor-VIII & Factor-IX

*NIB Data23

INDIA- A POTENTIAL MARKET* FOR MANUFACTURING PLASMA PROTEIN

Owing to the presence of a quarter of the world's haemophilic patients

With over 100,000 patients the country requires approximately 900,000 litres of plasma protein per year

* Source: Biotechnology industry in India : opportunities for growth-Export-import bank of India; Jan 2010

3

IMPORT OF BLOOD PRODUCTS* :

Name of Products	Volume per annum	Name of Importer
Human Albumin	395438 (bottles)	BSV, Baxter, Biocon, Synergy, Alpha drugs, Criticare, Paviour, Celestial, Claris
Plasma Protein Fraction	7500 (Bottles)	Bharat Serums & Vaccine (BSV)
Human Normal Immunoglobulin	79174 Bottles 243401.11 g (Bulk)	Biocon, Paviour, Reliance, Trigenesis, VHB Bharat Serums & Vaccine Celestial, Claris
Specific Immunoglobulin (HB, Rabies, Tetanus, Anti-D)	304279 vials 29482.33 MIU (Bulk)	J&J, Kiron, Paviour, Synergy, Ranbaxy & EL Shaddai Bharat Serums & Vaccine
Coagulation Factor-VIII	154881 (Vials)	Alpha Drugs, Paviour, Baxter, Celestial, Claris

*NIB Data

IMPORT OF BLOOD PRODUCTS*:

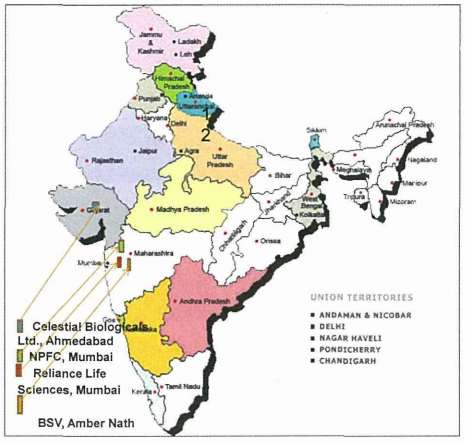
Name of Products	Volume per annum	Name of Importer
Coagulation Factor-IX	13065 vials	Alpha Drugs, Synergy, Baxter
Fibrin Sealant kits	19526 (Kits)	Baxter
FEIBA (Anti-inhibitor coagulant complex)	1000 vials	Baxter
Human Fibrinogen	3000 (Vials)	EL Shaddai
Fraction II +III	744.00 kg	Reliance

*NIB Data

Regulation of Blood and Blood Products India

Central Drugs Standard Control Organization (CDSCO)	State Licensing Authority (SLA)	National AIDS Control Organization (NACO)	Indian Pharmacopoeia Commission (IPC)	National Institutes Biologicals (NIB)
Ministry of Health & Family welfare (Govt. of India)	Ministry of Health & Family welfare (State Govt.)	Ministry of Health & Family welfare (Govt. of India)	Ministry of Health & Family welfare (Govt. of India)	Ministry of Health & Family welfare (Govt. of India)
Drugs Controller General of India is Central License Approving Authority (CLAA)	Licenses are issued by SLA after approval of CLAA based on joint inspection of blood banks / manufacturing facilities by Central and State Drugs Inspectors along with experts	Responsibility of planning and management of Blood Transfusion Services / Blood Safety Program	Preparation of Monographs and Reference Standard	Quality control testing of All Biologicals including Blood Products Haemovigilance

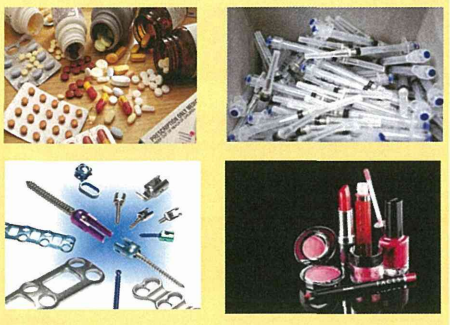
PLASMA FRACTIONATION CENTERS INDIA



DRUGS AND COSMETICS ACT AND RULES

Objective:

To ensure safety, efficacy and quality of:



- ✓ Drugs
- ✓ Biologicals (**Blood Products**)
- ✓ Medical Devices
- ✓ Cosmetics
- ✓ Veterinary Drugs.

Regulation of Blood & Blood Products

DRUGS AND COSMETICS ACT

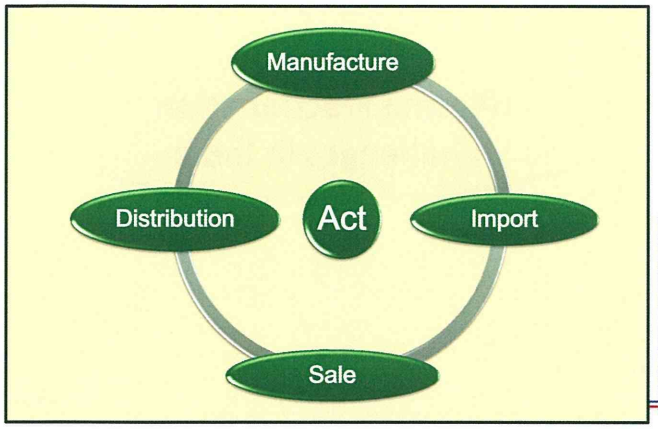
PRINCIPLE:

"Through system of licensing"

BASIC PHILOSOPHY:

- Manufacturers are responsible for quality of drugs manufactured by them
- Government regulatory agencies will monitor the quality of drugs by
  - Periodic inspections of the manufacturing and sales premises for confirmation to the provisions of drugs & cosmetics act
  - Monitoring the quality of drugs moving in the market by carrying out post market surveillance.

WHAT IS REGULATED UNDER THE ACT:



Quality of Plasma For Fractionation Indian Pharmacopoeia -2010

- Donor selection: :Carefully elected, healthy donor ascertained after medical examination. Laboratory blood tests , medical history & is free from detectable agents of infection
- Immunization of donor: Recommendations for immunization formulated by WHO TRS 840, 1994 or subsequent version.
- Records: Records of donors and donations made are kept in such a way, so that identity of donors, origin of each donation in a plasma pool and laboratory test can be traced.
- Laboratory Tests: are carried out for each donation to detect the viral markers: Anti-HIV1/2, Anti-HCV and HBsAg. (Repeat reactive test is found in any of these tests the donation is not accepted.
- Pooled plasma : First homogenous plasma pool tested for HIV & HCV antibodies and HBsAg and also HCV by NAT

Plasma Derived Medicinal Products

Indigenous Manufacture

- License for Manufacture, Sale and Distribution

Imported

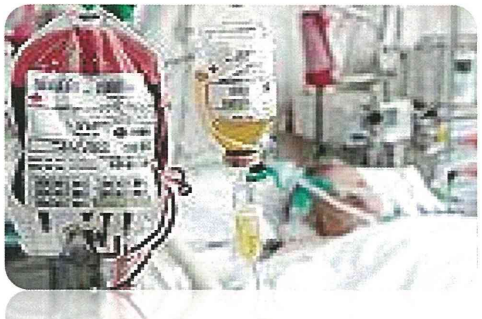
- Registration Certificate and Import License

Requirements for Marketing Authorization

- Administrative Information (Constitution, Fees, Layout etc.)
- Product Quality Data
- Product Safety Data
- Product Clinical Data.

Marketing Authorization for the Plasma as a "Product" is not required.

BLOOD & PLASMA COLLECTION IN INDIA: CURRENT SCENARIO



REQUIREMENTS FOR MANUFACTURE OF BLOOD PRODUCTS (SCH.F.PT.XII-C OF DRUGS & COSMETICS RULES 1945)

- REQUIREMENTS FOR MANUFACTURING OF BLOOD PRODUCTS GENERAL REQUIREMENTS
- COLLECTION AND STORAGE OF PLASMA FOR FRACTIONATION
- PERSONNEL
- PRODUCTION CONTROL
- VIRAL INACTIVATION PROCESS
- QUALITY CONTROL
- TESTING OF BLOOD PRODUCTS
- STORAGE OF FINISHED PRODUCT
- LABELLING
- RECORDS
- MASTER FORMULA RECORDS

Blood Banks in India-2012*

S. No	Licensed Blood Banks	Number
1	Government	981
2	Private	1564
3	Total	2545

*Source: CDSCO India

EVOLUTION OF BLOOD SAFETY PROGRAMME IN INDIA

- Blood safety programme in India began in 1987 with the establishment of NACO
- In1992 , Drug Controller General of India was vested with the power of Central License Approving Authority for approving licensing of blood and blood products
- NACP-I : 1992-1999 NACO modernized 850 blood banks and setup 40 blood component separation facility to promote rational use of blood , 90% in government sector
- In 1996 NBTCs and SBTCs were created to develop policies and programmes for improving blood transfusion services in India
- 2003 Establishment of National Blood Policy
- NACP II 1999-2004 modernization of more blood banks and setting up of more blood storage centres in rural India

Plasma Fractionation Challenges in India

STATUS OF BLOOD TRANSFUSION SERVICES(BTS)

- Indian blood transfusion service is the largest in the South Asian region
- No. of units collected per year 8 million units.
- As per norm of 1% blood donation by population there is a gap of about 4 million unit collection.
- 20% blood units are separated into components.
- All collected units are tested for five transfusion associated infection(HIV,HBsAg,HCV, Malaria & Syphillis) .
- BTS in India is mainly concentrated in metros and major cities and those in sub urban and rural areas needs improvement

WHO MODEL LIST OF ESSENTIAL MEDICINES

- Blood Coagulation Factors : Factor VIII, Prothrombin Complex Concentrate
- Human normal immunoglobulin (IV & IM)
- Anti-D immunoglobulin
- Anti- tetanus immunoglobulin

BLOOD AND PLASMA COLLECTIONS- INDIA

No. of Blood units collected (bags of 450ml)	8,000,000
% of components separation (RBC, PLT, Plasma)	20%
Plasma units	1,600,000
Plasma (in liters - 200ml/bag)	320,000
% Plasma used as FFP, cryo, etc or waste	50%
Balance Plasma avalable for fractionation (litres)	160,000

* MRB 2011 report

- Only 20% of the blood collected is separated into components, with wide variations between rural and urban areas.
- 300-400,000 units becomes the production capacity in terms of the API (Plasma as an active ingredient)- Plasma separated from whole blood
- After some of it used as FFP/ Cryo or wasted, potential only 100-150,000 litres plasma
- Estimation of the potential volume of the recovered plasma (Separated from Whole blood) currently discarded in India

80% (1200-1300,000 liters) of plasma wasted today
If this can be stopped, India could be net exporter of plasma products instead of importer

NATIONAL LIST OF ESSENTIAL MEDICINES OF INDIA 2011

Medicines	Route of administration/ dosage form	Strengths
Albumin	Injection	5%, 20%
Cryoprecipitate	Injection	
Factor VIII Concentrate	Injection	Dried
Factor IX Complex	Injection	Dried
Platelet rich plasma	Injection	

SETTING A PLASMA FRACTIONATION PLANT: FUNDAMENTAL INFRASTRUCTURE REQUIREMENT

- Well organized centralized BTS
- Sufficient and consistent plasma available
- Efficient and functioning QMS/ GMP programme
- Skilled personnel
- Large Capital Funding
- Regulation and Control

KEY ISSUES

- Formation of Plasma Policy for use of plasma for plasma fractionation
- Guidelines for transfer of plasma from blood centers to fractionating company
- Plan for making use of surplus plasma by toll fractionation

PLASMA FRACTIONATION CHALLENGES - INDIA

- Availability of safe and consistent plasma
- Regulatory issues
- Sustainable model
- Governance Deficit

No inclusive commercial facility in India

REGULATORY CHALLENGES

- Change in Drug & Cosmetic Act
- Harmonization of product testing policy
- Change in IP : Inclusion and deletion
- Multiple organization : coordination
- Time delay
- Compliance

Plasma: Recovered

Fragmented blood bank
- Non-uniform donor recruitment
- Low repeat donor base
- Poor retention
- No deferral registry

Challenges in availability of safe and consistent plasma

Component therapy
- Rampant whole blood therapy
- Clinical and patient awareness
- Infrastructure

Screening and testing
- ELISA based : Different generation
- NAT Vs ELISA: Cost consideration

Management inputs : Modern practice

INITIATIVES OF GOVT. OF INDIA

- Create 4 large blood centers
- Set up first public owned plasma fractionation center
- Implement quality management system in blood banks
- Increase voluntary blood donation

REGULATIONS AND OPERATIONAL VIEW : 2013

DCGI

- Change in Drug and Cosmetic Act
- Setting up new offices
- Developing skills of regulatory officials

NIB

- Constituted 3 committees for change in Monographs/IP, Viral Testing in products and product testing protocols (March 2012)
- Drug testing labs with equipment and new technology
- Upgrading present labs
- Timely clearance
- Haemovigilance

TURN AROUND TIME OF RELEASING OF QC REPORTS FROM NIB 2012-2013

DAYS TAKEN FOR REPORTING	NUMBER OF SAMPLES	PERCENTAGE	
10-20 DAYS	80	36.52%	91.3%
21-30 DAYS	120	54.79%	
31-45 DAYS	11	5.02%	
45-60 DAYS	4	1.83%	Due to pendency in document submission or clarification of queries
60 OR MORE	4	1.83%	

RECOMMENDATIONS OF BLOOD PRODUCTS COMMITTEE CONSTITUTED BY NIB

1. Review of Drugs and cosmetic acts

- Inclusion of donor registry and donor deferral strategies
- Inclusion of epidemiological surveillance in donor population
- Plasma pool testing : introduction of NAT for HIV, HBV, HCV and Parvovirus B19
- Defining plasma pool size and validation of immunoassay and NAT for plasma pool testing
- Strategy to replace final product testing for viral markers

2. Harmonization of pharmacopeia monographs for plasma derived products

3. Developing National Testing policy for plasma products

Haemovigilance Programme*

- Year 2014 member of IHN
- Indigenous software – Haemo-Vigil launched on 24th Jan 2013 & 1st Haemovigilance Newsletter published
- Haemovigilance Programme launched on 10th Dec,2012 in 90 Medical Colleges across the country
- TRRF & Guidance Document on 7th Dec 2012
- Core Group & Advisory Committee constituted in Nov,2012
- Decision to launch Haemovigilance Programme across the country on 26th Oct 2012

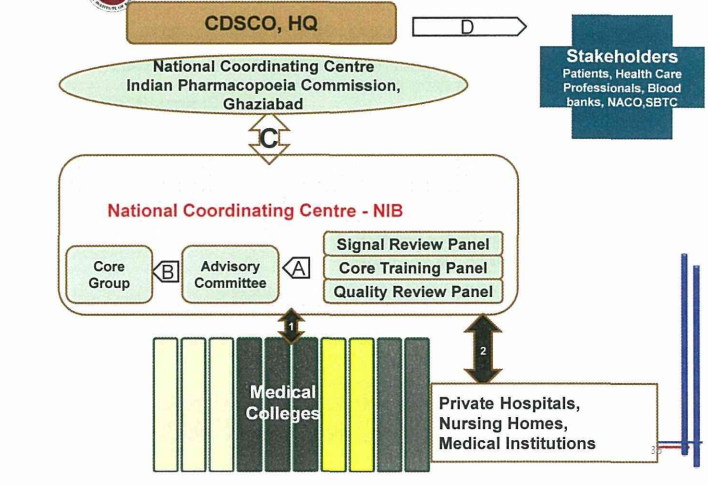
NIB, Noida

* Budget of 4.4 Mn USD upto March 2017

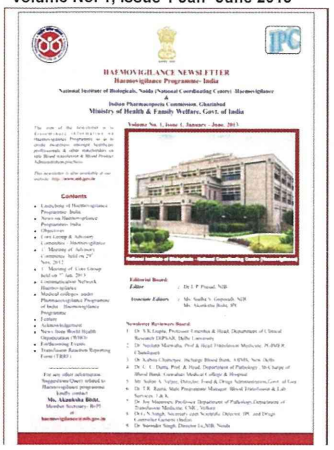
NATIONAL INSTITUTE OF BIOLOGICALS

- Blood Products Laboratory established in 2002
- Pre-release certification of 13 types of plasma derived products
- NABL certified laboratory
- CDL notification under process
- Testing capacity of 500 batches per annum
- Turn around time for release of reports- 45 days

Haemovigilance– Communication Network

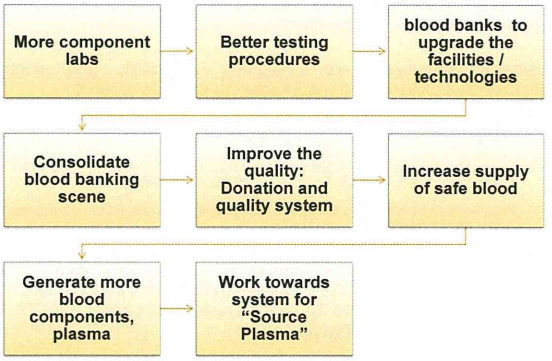


Volume No. 1, Issue 1 Jan- June 2013

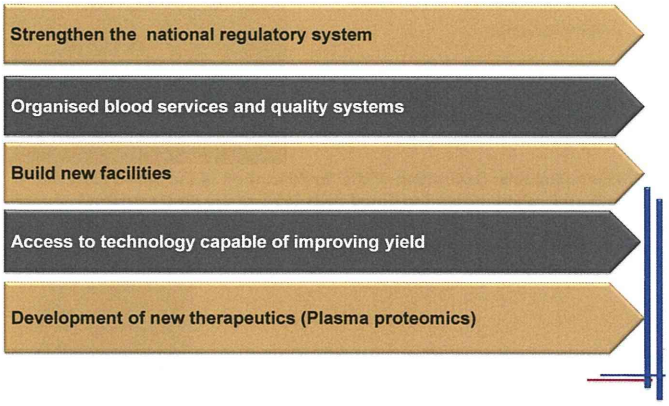


Volume No. 1, Issue 2 July- Dec 2013

Challenges : Effort and End Point



KEY TO FUTURE OF PLASMA FRACTIONATION INDIA



資料 2：「Safety and Manufacturing of Baxter's Albumin and IGIV」

Wolfgang Teschner

Baxter

Safety and Manufacturing of Baxter´s Albumin and IGIV

Wolfgang Teschner Ph.D.

Baxter Bioscience, Vienna, Austria

Agenda

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- Characterization of Albumin
- Baxter´s plasma safety program
- Overview of plasma fractionation
- The unique flexible bag for delivery of Albumin
- Prevention of Aluminum leaching in Albumin packed in glass containers
- Removal of pro-coagulant activity in Baxter´s KIOVIG process, an example of implementation of safety measures in an IGIV manufacturing process

Characteristics of Human Albumin

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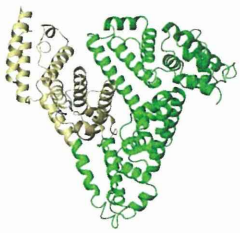


- Human Albumin has a protein molecular weight of ~ 66 kDa
- The plasma concentration ranges between 35-45 g/L
- The physiological half-life is 19 days
- The total albumin concentration in the body is 360 g (60 % extravascular (muscle, liver, skin etc.), 40% intravascular

Albumin is indicated for restoration and maintenance of circulating blood volume where volume deficiency has been shown and use of a colloid is appropriate

History of Albumin

Baxter

Hippocrates first mentioned some of the physiologic properties of albumin, but albumin was not named or studied until the early 1800s

The modern use of human albumin was established during World War II due to demand for plasma substitutes by E.J. Cohn and colleagues at the Plasma Fractionation Laboratory of the Harvard University Department of Physical Chemistry

The first documented clinical use of human albumin occurred on December 8, 1941 with seven sailors severely burned during the attack at Pearl Harbor

1954 Hyland Laboratories launched Buminate

1955 Immuno launched Human Albumin

1994 Immuno introduced Quality assured PCR testing

11.Oktober 2005 Flexbumin was approved in the US

Baxter´s Fractionation

Baxter

Baxter has almost 60 years of Albumin fractionation experience

Baxter will fractionate 6.45 Mill liters of plasma in 2013 resulting in approximately 135 tons of albumin

Baxter´s processes are designed, operated, and continuously documented under "good manufacturing practice" (GMP)

Final container must meet pre-determined specifications

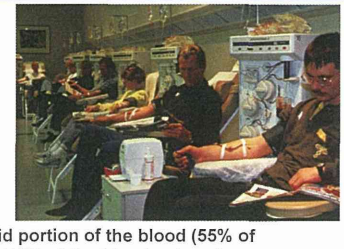
- Pharmacopoeias (e.g. USP, Pharm. Eur.) require minimum standards which have to be tested on each lot (e.g. for purity, sterility)
- Additional specification limits are set to fulfill special user requirements or authority requests

Pharmacovigilance data demonstrates the excellent safety of Baxter´s albumin. Only 107 initial AE´s were reported in the periodic safety update from July 1, 2010 to June 30, 2011. During this period 105.179.280 g of Albumin were sold world wide

Plasmapheresis

Baxter

- **Protein content of the plasma: ~70g/ L**
  - **~60% Albumin**
  - **~20% Immunglobulines**
  - **~10% IgG (~7g/L plasma)**



- **Plasmapheresis: Separation of the liquid portion of the blood (55% of the blood volume) from the blood cells (45% of the blood volume)**
- **The majority of Baxter's plasma is source plasma from qualified donors**

The Pathogen Safety Program

Baxter

Donor related measures
- Plasma origin
  (licensed and regularly inspected centers)
- Qualified donor program

Donation related measures
- Serological test program
  (HIV-1, HIV-2, HCV, HBs)
- Inventory hold and look back procedure (PCR)
- PCR test program
  (HIV, HBV, HCV, HAV, Parvo B19)

Avoid contamination (product neutral)

Production related measures
- Virus removal / inactivation steps

Inactivate contamination

Product surveillance system
- Pharmacovigilance

The Albumin Manufacturing from Crude V till Final Container

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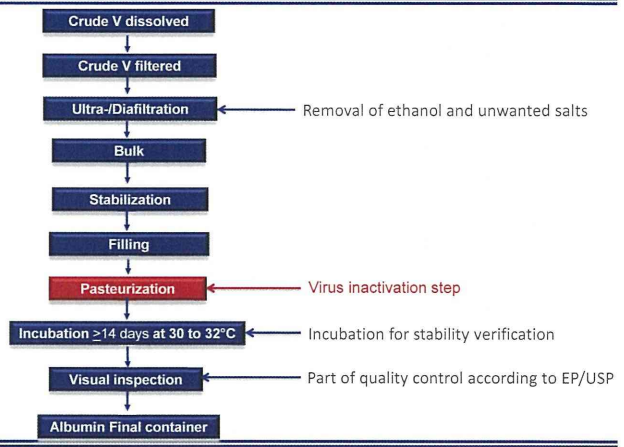

The Plasma Fractionation Process

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The plasma fractionation process is based on the method of Cohn *et al.* 1940´s

Plasma

5 Parameter system
- pH
- Temperature
- Ethanol concentration
- Conductivity
- Protein concentration

Separation methods
- Centrifugation
- Filtration

Edwin Joseph Cohn, Ph. D.

Virus Inactivation/Reduction Measures in the Albumin Process

Baxter

A number of manufacturing steps have a demonstrated virus removal capacity, e.g. removal of Fraction II+III, removal of Fraction IV, filtration of resuspended Fraction V, pasteurization

As some of them are based on similar mechanisms of action (e.g. co-precipitation of viruses and removal of precipitate by filtration) only reduction factors for removal of Fraction IV and for the final heat treatment are added to cumulative virus reduction factors according to regulatory guidelines

Virus clearance is shown in small scale using widely accepted model viruses

Overall log reduction factors for the Albumin manufacturing process:

	Virus				
Manufacturing step	HIV-1	HAV	PRV	BVDV	B19V
Fraction IV	>5.5	>4.5	>5.5	>4.4	2.9
Pasteurization	>7.9	3.7	>7.3	>6.6	?4
Overall reduction factor	>13.4	>8.2	>12.8	>11.0	>6.9

Cold Ethanol Fractionation

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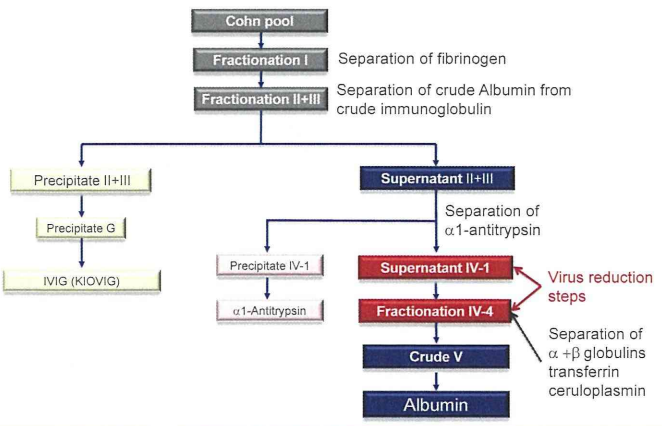

Baxter´s Flexbumin Advantages

FLEXBUMIN (Albumin (Human))

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Baxter´s Flexbumin is the first and only albumin in a flexible container

Efficient
- **Takes up 60% less space** than glass bottles on shelves
- **Weighs 40% less** than glass (based on comparison with BUMINATE 25% [Albumin (Human)] Solution)

Safety
- **No risk of glass breakage**
- **Environmentally friendly**: Flexbumin is the first and only medical product certified by the Carbon Trust for carbon footprint reduction
- **No aluminum leaching from glass** into the albumin

Simple
- **1-2-3 (suspend, remove, attach) preparation** streamlines infusion set-up
- **Eyelet** allows easier handling
- **Flexibility to use** with vented or non-vented standard IV administration sets

Aluminum Leaching from Glass

Baxter

- Residual citrate bound to Albumin solubilizes aluminum out of glass which poses a health risk for many patients, including
  - those with impaired renal function,
  - those with burns
  - elderly patients
  - preterm infants undergoing total parenteral nutrition
- The European Pharmacopoeia defines an aluminum limit of 200 µg/L, which has to be fulfilled at the end of shelf-life

Aluminum content in Baxter´s albumin after 36 months storage at 30°C

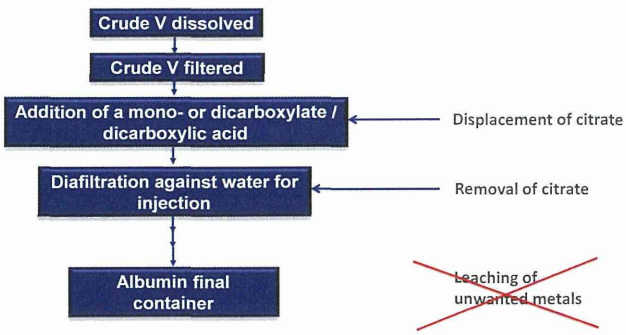
Lot	Concentration (%)	Vial size (mL)	Aluminum content (µg/mL after 36 months at 30°C)
VNA1J088	5	500	<25
VNA1J086	20	100	<50
VNA1J122	25	50	<50

Lots produced in 2009

Baxter´s Proprietary Process to Minimize Aluminum Leaching from Glass

Baxter

- Residual citrate bound to Albumin and citrate bound metals have to be displaced from the albumin before the final diafiltration process



Thromboembolic Events after Injection of IGIV

Baxter

A thromboembolic event is a rare, yet serious side effect of IGIV administration. Besides patient risk factors, product characteristics might increase risk

In 2010 an increased number of reported thromboembolic events led to the market withdrawal of a competitor product[1]

The root cause was traced back to the increased presence of FXIa (activated Factor XI) after a manufacturing process change as the major procoagulant activity [2]

Baxter has not seen a similar signal. Tests indicative for the thromboembolic potential were already included in the development of KIOVIG (US trade name: Gammagard Liquid), Baxter´s 10% liquid immunoglobulin for intravenous injection (KIOVIG approval: 2005)

- Pre-clinical lots were tested using Non-Activated Partial Thromboplastin Time (NAPTT) in FXI deficient plasma, chromogenic substrates and Wessler test
- Clinical and conformance lots (also after manufacturing changes) were tested using NAPTT and chromogenic substrates

1 http://www.fda.gov/BiologicsBloodVaccines/SafetyAvailability/Recalls/ucm227133.htm
2 Roemisch J.R. Kaar W., Zoechling A. Kannicht C. Putz M. Kohla G. Schulz P. Pock K. Huber S. Fuchs B. Buchacher A. Krause D. Weinberger J. Rempeters G. www.wfhmedicentral.com/article_view/2002_ID WMC002002

Overview of Characterization Tests Available at Baxter

Baxter

Assays to determine procoagulant activity

- Global *in vitro* assays
  - Thrombin generation assay (TGA)
  - Non-activated partial thromboplastin time (NAPTT) assay in Factor XI (FXI) deficient plasma
- FXIa (activated Factor XI) specific *in vitro* assay
  - FXIa determination with a Factor IX (FIX) based assay
- *In vivo* assay
  - Wessler test

Amidolytic activity assays

- *Chromogenic substrates* S-2288, S-2266, S-2222, S-2251, S-2302/CS3102, PL-1

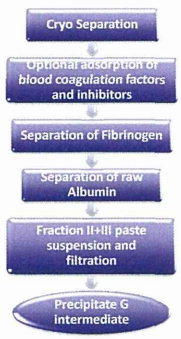
Factor XI zymogen

- ELISA assay susceptible for FXI and FXIa

Removal of FXI / FXIa in the KIOVIG Upstream Process

Baxter

KIOVIG upstream process



FXI zymogen / FXIa at various intermediates of alcohol fractionation

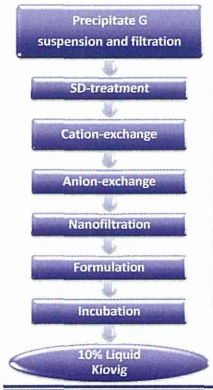
Sample	FXI zymogen / FXIa (Mean +/- STD of 3 lots) (% of Cohn pool)
Cohn pool	100.0
Supernatant I	90.5 ± 2.5
Supernatant II+II	20.0 ± 3.1
II+III paste	74.6 ± 6.4
Filtrate	2.9 ± 0.6
Ppt G dissolved	1.9 ± 0.7

Conclusion:
Only 1.9% of FXI zymogen / FXIa present in Cohn pool are found in Precipitate G intermediate

Removal of FXIa in the KIOVIG Downstream Process – Spiking of FXIa

Baxter

KIOVIG downstream process



Procoagulant activity (mean values +/- STD) in downstream fractions after spiking of 100 U/L FXIa into Precipitate G suspension

Test	Protein	TGA	NAPTT	FXIa
Unit	%	[% of norm. plasma]	[mg]	[U/L at 10% protein]
PptG suspension	7.0 ±0.7	116.3 ± 8.0	> 7	0.5 ± 0.2
PptG susp. + 100 U/L FXIa	7.0 ±0.7	493.1 ± 52.2	0.2 ± 0.1	121.3 ± 11.8
After cation-exchange	2.7 ± 0.2	334.8 ± 67.8	> 2.9	5.0 ± 2.5
After anion-exchange	1.0 ± 0.1	304.1 ± 72.0	> 0.7	17.1 ± 4.4
Bulk before incubation	10.4 ± 0.8	172.4 ± 47.1	>10; >10; 9.17	3.7 ± 2.7
Final container	10.3± 0.8	124.0 ± 9.2	>10	0.2 ± 0.1

Conclusions:
- **Procoagulant activity is already low at PptG**
- **The downstream process has a high procoagulant activity removal capacity**