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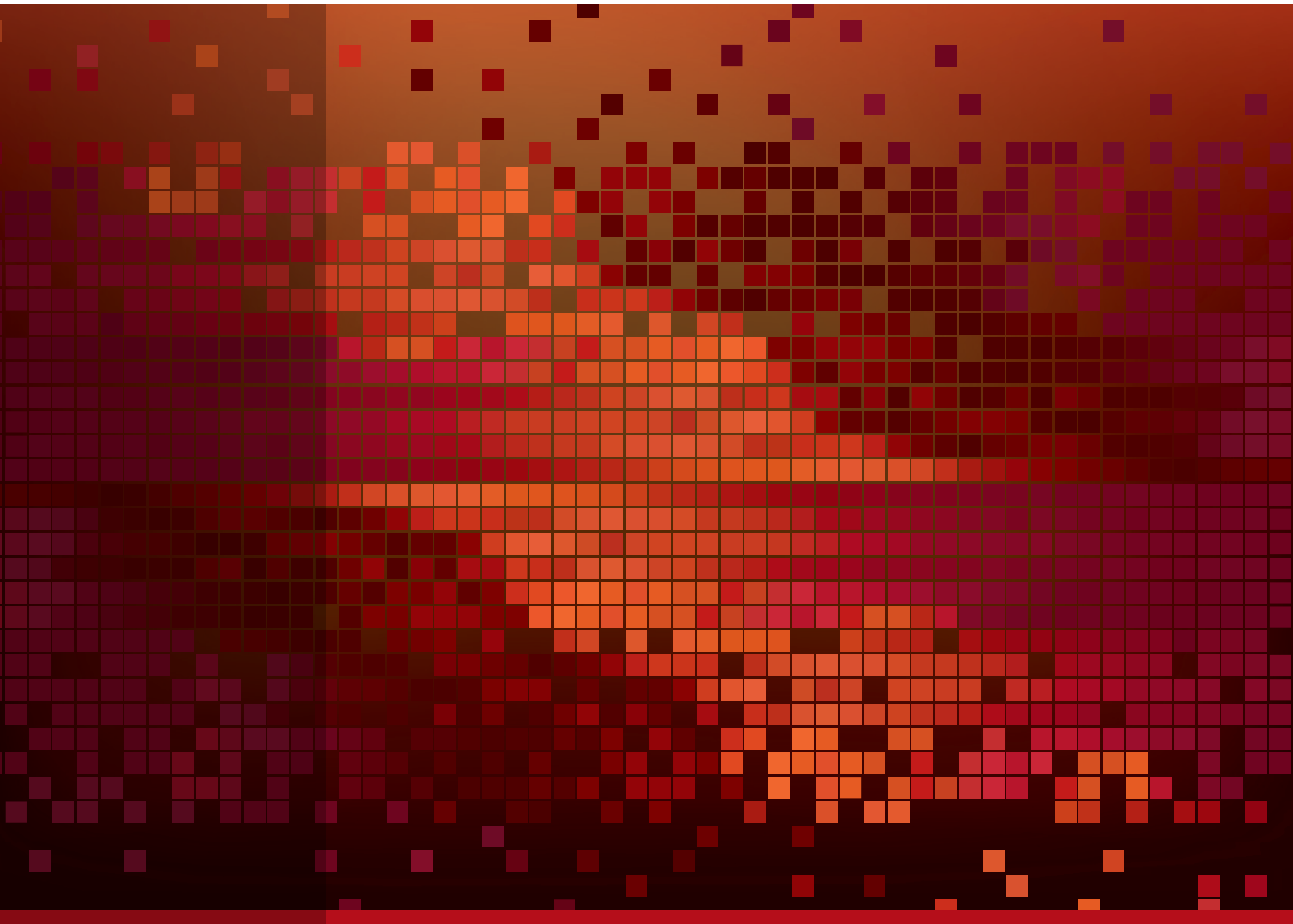


Bioactive opportunities for the Australian red meat industry

Introduction to blood based bioactive products

Published January 2011
ISBN 9781741915457

As a part of MLA's continued commitment to extracting value for the Australian red meat industry, MLA has surveyed the opportunities in the bioactive products from co-products space. The survey resulted in the *MLA Bioactives Compendium* that has been prepared to enable red meat processors and value adders with a ready reference about the various bioactives that may be derived from red meat sources. Following on from this initiative, MLA has selected an initial series of bioactive candidates with large global markets as potential opportunities for the industry. The following brief invites processors to consider the opportunity to add revenue to their business from alternate nontraditional markets[1].

contents

1 This report was not prepared as a comprehensive market research report. Interested readers are encouraged to purchase reliable commercial market research reports for detailed and specific information.

Section 1 Introduction to blood-based bioactive products

Blood is a major source of functional proteins and bioactives, typically comprising 6% of the live carcase weight and yielding around 8–14 recoverable litres per head. Despite its potential value as a food ingredient and bioactive, most blood in Australia is sent to rendering.

Blood is a suspension of red and white blood cells in a liquid called plasma.

Blood that is to be used as a feedstock for further processing for the extraction of bioactives needs to be collected via a different methodology than that typically employed in meat processing plants. MLA has prepared a publication on blood collection that outlines the processes and requirements for the sanitary collection of blood[2].

Four of the bioactive candidates selected by MLA have blood as a common feedstock.

- Bovine serum albumin (BSA)
- Thrombin (TH)
- Immunoglobulin G (IgG)
- Haemoglobin (Hb)

Using the same feedstock provides several opportunities with respect to the manufacturing technologies available.

Figure 1 below shows the flow of bioactive product from blood utilising conventional processing technologies.

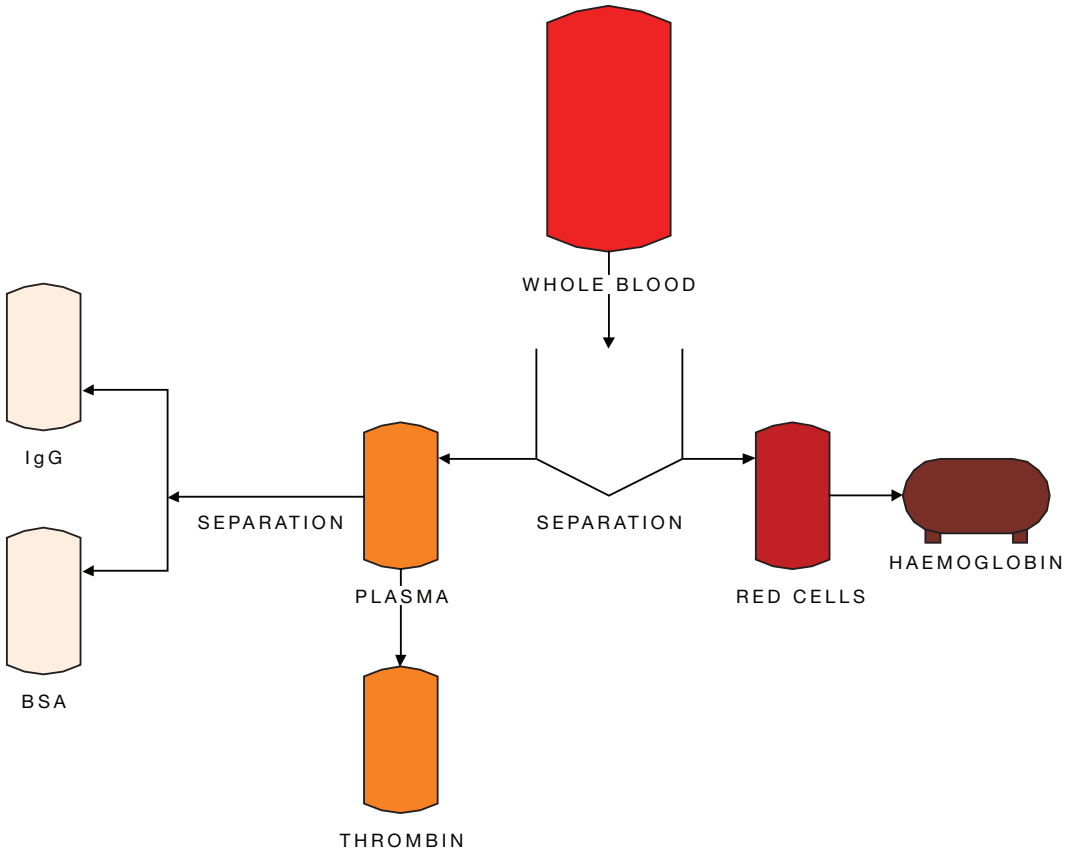


Figure 1: Schematic of the feedstock flow and points of derivation of the bioactive candidates.

The next sections will discuss various approaches for processing these bioactives.

2 *Pharmaceutical blood collection from adult cattle* MLA, 2005. An updated publication is currently being drafted.

Section 2 Bovine Serum Albumin (BSA)

Bovine Serum Albumin (BSA) is the most abundant plasma protein in blood and is a major contributor to blood pressure as well as maintaining blood pH. Low levels of BSA find their way into bovine milk where, as milk derived albumin, it maintains its' structure and properties and behaves identically to the blood serum molecule.

2.1 Markets

BSA has a range of applications, including the technical and diagnostics markets where a high purity of up to 98% is required.

It was estimated in 2007[3] that the global sales of BSA into these markets were 250 tonnes per annum, supplied as a dried high purity technical grade BSA at an estimated value of US$150 million (US$600/kg).

There is also a market for a food grade BSA used as a food ingredient or as a nutraceutical, selling at US$39/kg with an estimated market of US$17 million[4], equating to 436 tonnes per annum of 40% pure product.

Market sources have indicated that the majority of the nutraceutical BSA at present appears to be supplied from milk derived sources.

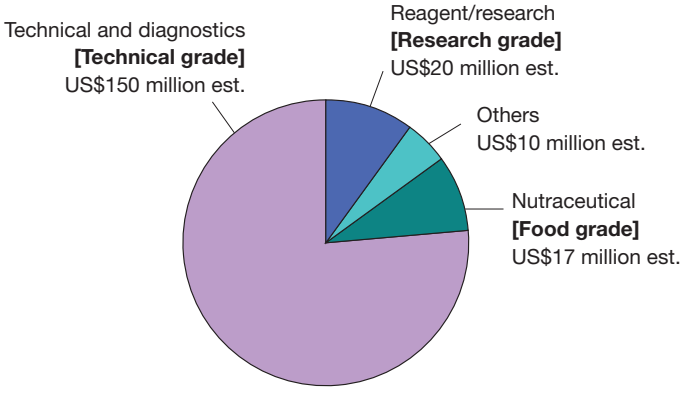


Figure 2: Summary of market segmentation

In the technical market, BSA is used as:

- an additive in growth media for pharmaceutical production
- in media for tissue and cell culture and for the production of monoclonal antibodies

In the nutraceutical market BSA is:

- included in products that are sold to promote immune health (for both humans and animals)

Table 1: Examples of products using BSA as a food ingredient or nutraceutical

Brand	Product	Description
Protein Factory	Super plasma protein US$72/kg	>90% protein isolate made from hydrolysed beef plasma. The powder is spray dried and concentrated into edible bovine plasma and made into bovine serum and concentrated to have an immunoglobulin content of 40% minimum
Pro Health	ImmunoPlexTM US$66/kg	A superior whey protein isolate with the highest levels of essential amino acids and immune boosting nutrients
MyoPure	Whey protein concentrate US$27.5/kg	MyoPure WPC is rich in serum albumin (typically 6%) and lactoferrin (typically 2%)

BSA is a mainstay in the diagnostics industry with a range of uses as:

- a protein standard
- diluent, coating agent
- buffer and stabiliser.

BSA has been tested for applications in anti-wrinkle cream, although most albumins used in cosmetics are derived from milk.

2.2 Global trends

The biggest market use of bovine serum albumin is in the pharmaceutical industry in the production of vaccines and monoclonal antibodies by mammalian cell culture.

The biggest threat to the BSA and sera industries is regulatory pressure in the USA to move away from animal derived media. These pressures reflect a concern by authorities that animal-derived products may contain infectious agents such as viruses, mycoplasma or transmissible spongiform encephalopathy (TSE) agents that could be carried through into biological products.

This is balanced to a significant degree by the difficulty and expense that would be faced by a pharmaceutical manufacturer in changing any aspect of their production process (including media formulation) as all safety and efficacy validation work would need to be repeated.

Therefore, at this stage, there is a solid demand that is still increasing at an estimated rate of 1–3% per annum and no apparent trend of declining demand for BSA as a research and manufacturing product.

3 MLA BSA product information – Bioactive Compendium v2.0 July 2009

4 WPI is approximately US$4.50/lb:US$9.90/kg (Davisco Foods International, MN, 2004) – Comparison of sensory properties of whey and soy protein concentrates and isolates, T.A. Russell 2004. Assuming 10% of WPI is BSA, and that food grade BSA is 40% pure, an estimate of the price of food grade BSA is US$39.60/Kg of 40% pure BSA.

Section 2 Bovine Serum Albumin (BSA)

Currently, Australian and New Zealand BSA enjoy BSE-free status, which may be used to some advantage in marketing the product.

Key market drivers:

- Market growth due to expanding application of the biotechnologies which are dependent on BSA as a processing raw material;
- Purchasing requirements need access to secondary suppliers in alternate geographical regions for risk mitigation;
- The difficulty of replacing BSA with an ingredient of equivalent technical and economic attributes

2.3 Overview of BSA supply chain

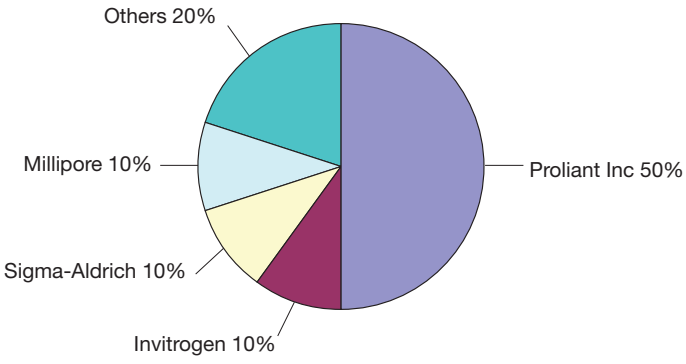
Table 2: General overview of the BSA supply chain (refer to Appendix A for details of the companies)

	Manufacturer	Distributor	User
Bovogen Biologicals (AUS)	✔	✔	
Moregate Biotech (AUS and NZ)	✔	✔	
Millipore Corporation (US)	✔	✔	
Sigma-Aldrich (US)	✔	✔	
Invitrogen (US)	✔	✔	
Equitech –Bio Inc (US)	✔	✔	
Biocell Laboratories Inc (US)	✔	✔	
SeraCare Life Sciences (US)	✔	✔	
Nova Biologics Inc (US)		✔	
Desert Biologicals (US)		✔	
PAA Cell Culture (AUSTRIA)		✔	
Gemini Bio-Products (US)		✔	
Thermo Scientific		✔	
Tico Europe		✔	
BioClot GmbH		✔	
AusGeneX		✔	
VWR International		✔	
ICPbio International Ltd	✔		
Calbiochem		✔	
Diagnostics Product Corp			✔
Pfizer Global Manufacturing			✔
CryoLIfe			✔
Europa Bioproducts		✔	
Proliant Inc	✔	✔	

A survey of the companies that are making an impact in the BSA supply globally found there were at least 10 major players manufacturing BSA. These suppliers include: Proliant Inc, Millipore, Sigma, Invitrogen, Equitech and Australian suppliers Bovogen Biologicals and Moregate Biotech.

These companies were found to manufacture BSA ranging from standard grade to cell culture grade. The market is dominated by Proliant with 50% market share:

Figure 3: Estimated market share of BSA by company



The market is mature with many current suppliers having been in the market for decades; however, this does not preclude new entrants who bring an attractive value proposition.

2.4 Competitive landscape

Competition on entry for this market is high but there appears to be a trend of increasing demand for consistent quality and low risk BSE products.

Currently, Australia has an advantage in its BSE-free health status. Australian manufactured BSA supplied at a competitive price may present an edge over its competitors from North and South America.

To date Chinese and Indian manufacturers have not entered this market in any significant manner.

Section 2 Bovine Serum Albumin (BSA)

2.5 Customers

Customers or users of BSA include:

- pharmaceutical companies
- diagnostic product companies
- biotechnology research and development companies
- veterinary/animal health companies

Business to business customers can include the major players listed above who in some instances seek to add additional sources of BSA to their product catalogue.

Life science product distribution companies are a key customer group to access fragmented research end users both in Australia and foreign markets.

The following describe the points of value to potential customers of BSA.

Cost (pricing) Drivers:

- Production efficiencies by having the bioactive production plant alongside the primary meat processing plant sharing common utilities, infrastructures and processes.
- The product pricing is influenced by and dependent on the production scale and raw material internal transfer pricing, both of which are controlled by the processor.

Quality and Safety Drivers:

- strong focus on quality
- manufactured in the country of animal origin
- geographical Bovine Spongiform Encephalopathy (BSE) Risk category 1 (lowest risk) country status

2.6 Product specifications

Grades and specifications for BSA vary depending upon the end users requirements.

Two product presentations are available in the market:

- a freeze dried powder (pH 5.2 or 7), or
- an aqueous solution of either 20 or 30% BSA W/V

The two main grades typically used in the research and manufacturing market are standard grade and premium grade.

As there is no defining guideline relating to the grading, suppliers have used other titles such as reagent grade or biotechnological grade to suggest a higher quality product.

To help provide a target specification for a standard grade product several supplier specifications were reviewed and a specification for both standard grade and high purity grade were established[5].

A critical marker of quality is the endotoxin level.

Endotoxin is introduced into products by the bacterial contamination. As BSA is derived from blood plasma from slaughtered cattle, hygiene is important to decrease the chance of bacterial contamination or growth and thus endotoxin contamination.

Hollow knife technology is available for blood collection that minimizes contamination[6]. All blood pipe works should be designed to be able to be heat and chemically cleaned, preferably with a small Cleaning in Place (CIP) system.

2.7 Manufacturing considerations

BSA can be produced using a variety of methodologies, including cold ethanol fractionation and heat shock[7].

The bulk of standard grade BSA is produced using a heat shock method. BSA production via the heat shock protocol is a well established six step process, which involves chemical and physical manipulation for the extraction and purification of the protein.

The process requires careful monitoring to ensure the operating ranges established are maintained. This is to minimise variations during critical steps that can significantly change the characteristics of the final product.

Critical manufacturing requirements:

- availability of specialised equipment and maintenance backup;
- consistent source of quality raw material and;
- qualified staff to operate the plant to required standards.

Continuous SEParation (CSEP) technology can be designed to extract BSA and other bioactives via a process that could provide a reduction in the cost of goods. MLA has demonstrated the extraction IgG and BSA in collaboration with CSIRO Food Science Australia[8] at small scale.

2.8 Regulatory considerations

BSA that is aimed at the global market place should meet the following regulatory accreditations:

- Processed from AQIS inspected and passed bovine plasma.
- Manufactured according to ICH Q7A or FDA cGMP[9].
- Validated for Prion (TSE) clearance[10].
- EDQM TSE Certificate of Suitability[11].
- AQIS Registered for shipment to the EU/USA.

5 Please refer to MLA for specification information

6 Report: *Pharmaceutical blood collection from adult cattle* MLA, 2005

7 See Appendix B

8 Feasibility study: *Development of cost effective large scale blood plasma fractionation systems*, MLA/CSIRO 2002.

9 November 2000 CPMP/ICH/4106/00 ICH Topic Q 7 *Good Manufacturing Practice for Active Pharmaceutical Ingredients*

10 This is optional but recommended

11 http://www.edqm.eu/en/Certificates-of-Suitability-97.html

2.9 Revenue model

A revenue model was developed assuming wholesale manufacturing of BSA. Under this model processors would create a business unit for bioactives and drive business development activities under the unit's banner. Sales are derived from direct sales or tenders to bulk end users, distributors or channel partners/agents who may re-label or sell on directly.

Website information and trade conference promotion will be essential marketing tools.

Based on a plant processing 120,000 head per year, then by the fifth year of operation:

Payback	< 3 years (based on net profit before tax)
Capital cost	$850,000 (all used equipment, including blood separation equipment)
Sales price	$AUD500/kg
Market share	0.75% fifth year

- Net benefit per head of BSA sales is ~$8.2 (excluding sales of surplus plasma and red cells).*

A revenue model was also prepared assuming the combined production of BSA, Immunoglobulin, Thrombin and Haemoglobin. Greater revenue and product offering could be considered by combining production of up to four blood derived bioactives in the one plant.

Any processor interested in taking the next step is invited to contact MLA to receive more detailed information and to discuss it further.

2.10 Potential processor benefits

- Net benefit per head from BSA sales is attractive.
- Decreased waste burden (and cost) by value adding the waste stream.
- Adding greater value to blood waste stream than currently available.
- Access to a non food markets thus differentiating existing business product mix.
- Adding further to revenue.
- Potential to add other bioactive products with incremental modification to existing plant.

Partnerships

MLA has access to research and development partners who can provide development of pilot scale plants and process development and scale up. MLA is also able to provide funding support through its donor funding company on a dollar for dollar basis for suitable projects.

Further information

MLA has assembled an information package with revenue modeling based on recently collected data. Any processor interested in taking the next step should contact MLA to receive this information and discuss the opportunity further.

** Calculated as Net Profit Before Tax in year five by 120,000 head. Number of head required to produce bioactoive product is 16,000.*

Section 3 Bovine Immunoglobulin G (IgG)

Bovine Immunoglobulin (IgG) is a protein component of circulating whole blood providing secondary immune protection.

IgG provides the majority of antibody-based immunity against invading pathogens[12] and is the only antibody capable of crossing the placenta to give passive immunity to the foetus.

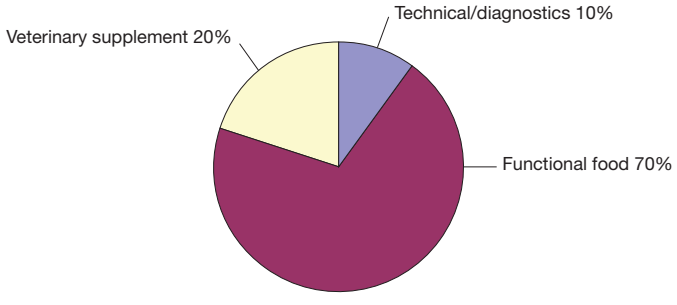
3.1 Markets

IgG is sold into several different market sectors including the:

- technical and diagnostics market, where it has applications as an antibody
- food ingredients market, where it has applications as a nutritional supplement

The estimated global market for IgG is greater than US$50 million per annum when combining the technical and food ingredients markets. This business case looks at the supply of serum derived IgG for the technical market. This market is estimated at ~AUD$6 million pa with a trading price of US2500-2800/kg. Growth is similar to BSA at an estimated 1–3% Compound Annual Growth Rate (CAGR).

Figure 4: Summary of market segmentation



Bovine IgG is used as a technical product in enzyme/conjugate antibodies systems with applications in *in-vitro* diagnostic kits, immunology and immunobiochemistry assays in research.

Significant consumers of IgG are diagnostic manufacturing companies and manufacturers of diagnostic instruments that utilize IgG as a consumable with their instrument systems.

Most of the functional food and nutraceutial products with immunoglobulins appear to be based on colostrum. While the current business case does not look specifically at the food ingredient market, this market should be monitored carefully. Should a processor build the capability to produce IgG, differing grades and more suitable production economics may allow access to the very large food ingredients market.

The price point of $72/Kg for food ingredient IgG is a function of the level of purity, scale of manufacture combined with the feedstock price for milk derived IgG products. The global functional food market is valued at US$90 billion and distributed as follows: The US at 35%, Asia-Pacific at 27 % and Europe at 32%[13].

In Australia domestic sales of functional foods are approximately AUD$1.5 billion per annum[14] and market research indicates that more than 70% of Australians under 35 take dietary supplements.

3.2 Global trends

Technical Grade IgG

Key market drivers (Technical Grade IgG) include:

- Market growth due to expanding application in the biotechnologies.
- Decreased market perception of risk regarding animal derived products with a return to using animal derived products.

Food Grade IgG

The consumer trend of consuming bovine blood derived IgG in products such as sports nutrition and dietary supplements is slowly gaining acceptance with an increase in product mixes on the market.

This is driven by the US market, by companies such as Proliant Inc which have, in the last 5 years, introduced NutraGammax™ (functional food ingredient) and ImmunoLin™ as dietary supplements to boost the immune system.

ImmunoLin™ was the first bovine purified immunoglobulin™. It claims to boost immunity and has more than 45% IgG.

Zymogen's IgG 2000 DF™, Nature Body & Mind Inc's Extreme Immunity™ and Protein Factory's Super Plasma Protein all claim to use ImmunoLin™ as an ingredient.

Beneficial characteristics of IgG are well documented and accepted by consumers both in whey protein and colostrum products.

Traditionally IgG products were derived from bovine colostrums (nutraceutical) and milk (functional food). Blood derived IgG has advantages over these products, where whey protein is unsuitable to consumers who are lactose intolerant. Approximately 70% of the global population cannot tolerate lactose in some form or another in adulthood[15].

12 Pier GB, Lyczak JB, Wetzler LM (2004). *Immunology, Infection, and Immunity.* ASM Press.

13 *A Study of Bovine and Ovine Bioactives for Functional Food.2005* A Report by Innovation Dynamics Pty Ltd

14 www.austrade.gov.au/Natural-healthcare-overview/default.aspx

15 Heyman MB (2006). *Lactose intolerance in infants, children, and adolescents.* Pediatrics 118 (3): 1279–86

Section 3 Bovine Immunoglobulin G (IgG)

IgG derived from plasma has been utilised by animal wellness companies like Mach One and APC as supplements.

Blood derived IgG is proving a popular choice for farmers of beef and dairy cattle in the US, with recognition of IgG as an efficacious source of protein supplement.

Key market drivers (Food Grade IgG):

- dietary tolerance an increasing barrier for milk-derived products
- better efficacy from blood derived proteins
- increasing consumer interest in functional foods and nutraceuticals
- the emergence of veterinary nutraceuticals and functional foods

3.3 Overview of serum derived IgG supply chain

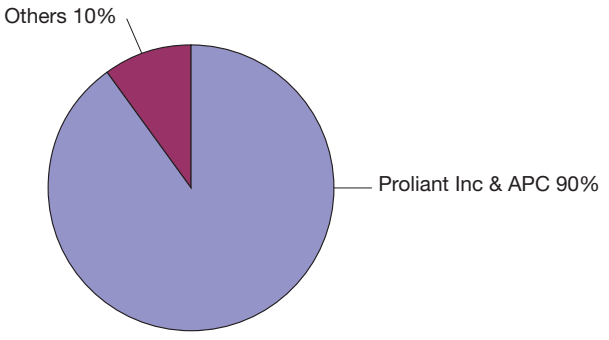
Table 3: General overview of serum derived IgG supply chain (see Appendix C for details of the major companies)

	Manufacturer	Distributor	User
Protein Biosystems		✔	
Bethyl Laboratories	✔		
Innovation Research		✔	
Equitech-Bio Inc		✔	
Fitzgerald Industries Ltd		✔	
Jackson Immuno Research	✔		
VWR International		✔	
Proliant Inc	✔		
APC Inc	✔		
Mach One Corp	✔		
Bovogen	✔		
Moregate Biotech	✔		
Pel-Freez Bio	✔	✔	
ICPBio Ltd	✔		
Xymogen Ltd			✔
Galea lifesciences			✔

The major suppliers into the IgG technical grade market are in the US and include Proliant Inc, Sigma, Equitech Bio with two manufacturers/suppliers in Australia: Bovogen Biologicals and Moregate Biotech.

Some manufacturers (e.g. Proliant), cover the supply chain through to distribution.

Figure 5: Estimated serum derived IgG market share by company



Proliant and APC Inc have dominated the supply of IgG for inclusion as functional food products for human consumption and APC Inc products for animal feed and supplements (see Appendix C for details of these companies).

3.4 Competitive landscape

Competition is high on entry into the functional food market and serum derived IgG would have to compete with the big milk (functional food), colostrum and serum processing manufacturers globally.

Murray Goulbourn and Fonterra are large suppliers of milk-derived IgG.

3.5 Customers

The following points describe the points of value to potential customers of IgG:

Cost (pricing) Drivers:

- Production efficiencies by having the bioactive production plant along side the primary meat processing plant sharing common utilities, infrastructures and processes.
- The product pricing is influenced by and dependent on the production scale and raw material internal transfer pricing, both of which are controlled by the processor.

Quality and Safety Drivers:

- a strong focus on quality
- manufactured in the country of animal origin
- geographical Bovine Spongiform Encephalopathy (BSE) Risk category 1 (lowest risk) country status

Section 3 Bovine Immunoglobulin G (IgG)

3.6 Product specifications

Technical grade IgG has a purity of ≥97% achieved through multi-step chromatography and an ammonium sulphate fractionation step.

The purified IgG is supplied in a buffer such as borate buffer saline or lyopholised. Food grade IgG has a lower purity level (between 25–46%) and is spray dried.

3.7 Manufacturing considerations

IgG can be produced using a variety of methods.

Typically, a salt fractionation is used first for primary extraction, in which ammonium sulphate is added to bovine serum or plasma resulting in the precipitation of Immunoglobulins[16].

The precipitate is separated from the other serum proteins which remain in the liquid phase and is then resolubilised in a saline solution and diafiltered against saline. A caprylic acid precipitation can be included to remove contaminating BSA.

The IgG can be further purified by ion-exchange chromatography and acid-charcoal treatment.

Critical manufacturing requirements:

- availability of specialised equipment and maintenance backup.
- consistent source of quality raw material.
- qualified staff to operate the plant to required standards.

Continuous chromographic separation (CSEP) can be designed to extract IgG and other bioactives via a process that could provide a reduction in the cost of goods. MLA has demonstrated the extraction IgG and BSA in collaboration with CSIRO Food Science Australia[17] at small scale.

3.8 Regulatory cosiderations

IgG that is aimed at the global market place should meet the following regulatory accreditation;

- Processed from AQIS inspected and passed bovine plasma.
- EDQM TSE Certificate of Suitability[18].
- AQIS Registered for shipment to the EU/USA.

3.9 Revenue model

A revenue model was developed assuming wholesale manufacturing of IgG. Under this model processors would create a business unit for bioactives and drive business development activities under the unit's banner. Sales are derived from direct sales or tenders to bulk end users, distributors or channel partners/agents who may re-label or sell on directly.

Website information and trade conference promotion will be essential marketing tools.

Based on a plant processing 120,000 head per year, then by the fifth year of operation:

Payback	< 5 years (based on net profit before tax)
Capital cost	$900,000 (all used equipment, including blood separation equipment)
Sales price	$3,000AUD/kg
Market share	10% fifth year

- Net benefit per head of IgG sales is ~$4.8 (excluding sales of surplus plasma and red cells).*

The value of the surplus plasma and red blood cells is not presented within the model outputs, however based on the plant scale in the underlying assumptions at the current market price this could add (if all product were sold as liquid plasma @ $1.20/L and red blood cells @ $0.90/L) approximately $500,000 to revenue. This would improve the payback and net benefit per head.

A revenue model was also prepared assuming the combined production of BSA, Immunoglobulin, Thrombin and Haemoglobin.

Greater revenue and product offering could be considered by combining production of up to four blood derived bioactives in the one plant.

Any processor interested in taking the next step should contact MLA to receive more detailed information and to discuss in further detail.

16 See Appendix D for process flow diagram

17 Feasibility study: *Development of cost effective large scale blood plasma fractionation systems*, MLA/CSIRO 2002.

18 http://www.edqm.eu/en/Certificates-of-Suitability-97.html

** Calculated as Net Profit Before Tax in year five by 120,000 head. Number of head required to produce bioactoive product is less.*

3.10 Potential processor benefits

- net benefit per head of IgG sales is attractive
- decreased waste burden (and cost) by value adding the waste stream
- adding greater value to blood waste stream than currently available
- access to a non food market thus differentiating existing business product mix
- adding further to revenue
- potential to add other bioactive products with adaptive modification to existing plant

Partnerships

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Further Information

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Section 4 Thrombin (TH)

Thrombin (TH) is an enzyme that catalyses the cleavage of soluble fibrinogen yielding insoluble fibrin.

These fibrin monomers subsequently interact with each other to form a fibrin clot.

Thrombin (activated Factor IIa) is commonly distributed as prothrombin and has many functions in the coagulation cascade. Prothrombin is a stable inactive precursor of thrombin. Thrombin's applications, therefore, include cessation of blood loss during surgery and site-specific protein cleavage.

4.1 Markets

The major market application of thrombin is the Medical Device/Therapeutics market. The worldwide tissue sealant market is projected to enjoy fast growth due to the speed and simplicity it offers in wound sealing. The market is dominated by the United States, Europe (France, Germany, Italy and UK) and Japan with the tissue sealants market in the United States expected to reach US$266 million by 2010[19].

Currently, King Pharmaceuticals is the only known supplier and manufacturer of bovine thrombin for the US market.

There are four main types of materials used in surgical sealants:

Fibrin glues	Fibrin glues are made from fibrinogen and thrombin (typically of bovine or pooled human origin) and, as such, provide the two essential components of the clotting cascade. In the presence of calcium and Factor XIII, fibrin glues rapidly form a clot.
Thrombin-based	Thrombin derived from bovine or pooled human blood is used as topical haemostat agent. Often thrombin is used in combination with absorbable gelatin sponge.
Collagen-based sealants	Collagen (typically derived from bovine or porcine sources) provides a lattice for natural clot formation. When combined with thrombin (typically bovine), it can provide rapid clotting in areas where diffuse bleeding is present.
Synthetic polymer-based sealants	These sealants consist of a range of artificial components such as polyethylene glycol, synthetic peptides and protein polymers that do not have any inherent hemostatic properties. As these agents are either toxic or cannot be resorbed by the body, their use is typically limited to topical applications or an adjunct to conventional means of bleeding control.

There is a market for thrombin as a stand-alone product as demonstrated by the dominance of King Pharmaceutical's Thrombin JMI® with a direct market of US 254 million (US $72/5000U for pharmaceutical (USP) grade thrombin) as reported in 2008 and additional sales of Thrombin JMI® to Baxter and other manufacturers for incorporation into hemostasis kits.

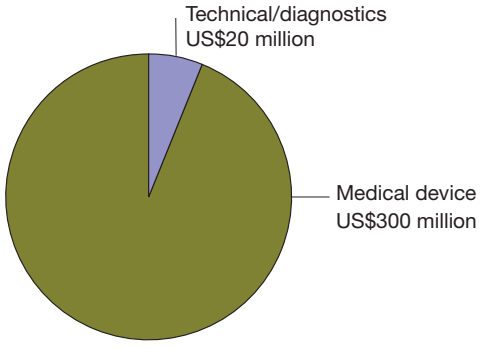


Figure 6: Market share of bovine thrombin by commercial applications

This business case looks at the supply of bovine prothrombin concentrate as a barium salt (pTH barium salt) to the existing and emerging manufacturers of thrombin. This market is estimated at ~USD$3.5-5 million.

4.2 Global trends

Bovine origin thrombin (TH) incurs a lower cost in raw materials when compared with human thrombin and also being non human moves away from human viral risk. That is not to say bovine viral issues are negligible but significant advances in technology can provide assurance to regulatory bodies with respect to safety.

TH will see an increase in demand as both a stand-alone hemostatic agent (surgical sealant) and as an in-vitro technical reagent used for coagulation diagnostics.

There are competing products such as fibrin glues and synthetic devices in the surgical sealant market.

Different sources of thrombin include human thrombin (Evithrom) and recombinant thrombin (Recothrom) as well as bovine derived thrombin (Thrombin JMI®).

Thrombin JMI® has a long association with surgery since it's reported use in 1989 (Jones Medical Industries) and enjoyed being the only player in the active haemostat market until new products, such as Evithrom (2007) and Recothrom (2008), entered into the market. The next few years will test Thrombin JMI's position in the market place and its ability to innovate or run the risk of sales erosion due to the popularity of Recothrom, Evithrom and generic thrombin.

19 *Surgical Incision Closures: A Global Strategic Business Report.* Global Industry Analysts Inc

Section 4 Thrombin (TH)

Key market drivers [Active Pharmaceutical Ingredient (API) thrombin and therefore Barium Salt (pTH)]:

- increase in demand due to the aging population
- technological advancement leading to ease of use of biological sealants
- market growth due to expanding applications in biotechnologies

4.3 Overview of TH supply chain

Below are the major brands and their suppliers and manufacturers of topical formulations of thrombin to aid in the control of haemostasis.

Table 4: A list of companies supplying topical thrombin (see Appendix E for details of the companies)

Marketing Company	Manufacturing Company	Brand	Source	Market Approved	Revenue 2008
King Pharmaceuticals	GenTrac Inc	Thrombin JMI™ pump/ syringe spray	Bovine	US	US $254million
		Thrombin JMI Epistaxis	Bovine	US (2007)	$72/5000 IU (vial)
		Thromi-Pad™			
	Vascular Solutions	Hemostasis pad	Bovine	US (2007)	
	Vascular Solutions	Thrombi-Gel™	Bovine		
ZymoGenetics Bayer	ZymoGenetics Abbott	Recothrom™	Recombinant	US(2008) EU	US$8.8million $86/5000 IU (vial)
Ethicon – J&J	Omrix Pharmaceuticals	Evithrom	Human	US (2007)	US$20million* $90/vial
Baxter	Baxter	FloSeal ®	Human thrombin/gelatin	US (1999)	US$408million✦
		Hemostatic Matrix			
		FloSeal® Matrix Hemostasis Sealant	Bovine thrombin/gelatin	EU	
		GelFoam Plus	Human thrombin/gelatin	US(2007)/JP	

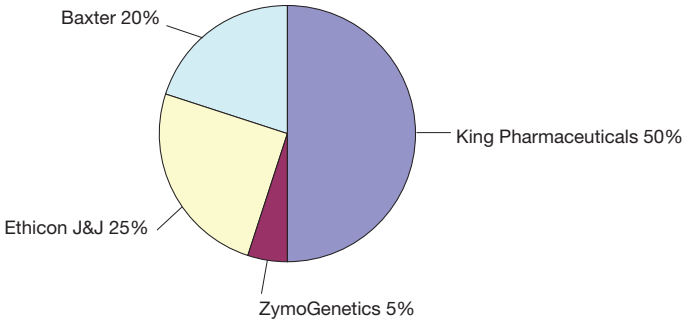
* A value of $20 million was extrapolated from Johnson & Johnson 2008 Annual Report with an increase of 240 million in sales to $2.5 billion for the Ethicon franchise due to its haemostasis, meshes and biosurgical lines.

✦ Total sales reported to include FloSeal, Tisseel and CoSeal. Baxter Annual Report 2008 pg 35

The bovine thrombin used in these products is King's Pharmaceuticals Inc registered Thrombin JMI®. Thrombin JMI® is manufactured by GenTrac Inc, Tennesse USA, and also supplied to Baxter Pharmaceuticals for their product FloSeal® Matrix Hemostasis Sealant (Japan market).

There are several suppliers of bovine sourced prothrombin in Australia. Prothrombin is a precursor to make thrombin. Bovogen Biologicals supplies prothrombin as a crude product and Selborne Biological Services supplies prothrombin extracted by barium precipitation from bovine plasma. ICPBio supplies thrombin via a chromatography purification system.

Figure 7: Market share by company in the thrombin-based hemostasis market



4.4 Competitive landscape

Bovine derived thrombin faces two levels of competition in the surgical sealants market.

First, it must compete with the various materials used in the tissue sealant market such as fibrin, synthetic and collagen and gelatin based products. For example, Baxter's biosurgery product portfolio includes fibrin glue (Tisseel), FloSeal (thrombin+Gelatin) and CoSeal (synthetic).

Secondly, within the thrombin based sealants market, bovine thrombin faces new competition from human derived thrombin (Evithrom) and recombinant Recothrom.

4.5 Customers

The following points describe the points of value to potential customers of TH:

Cost (pricing) Drivers:

- Production efficiencies by having the bioactive production plant along side the primary meat processing plant sharing common utilities, infrastructures and processes.
- The product pricing is influenced and dependent on the production scale and raw material internal transfer pricing, both of which are controlled by the processor.

Quality and Safety Drivers:

- a strong focus on quality
- manufactured in the country of animal origin
- geographical Bovine Spongiform Encephalopathy (BSE) Risk category 1 (lowest risk) country status

4.6 Product specifications

Table 5: Thrombin technical specifications

	Haematologic Technologies Inc	Sigma-Aldrich
Physical appearance	50% glycerol/ water	Lyophilized powder
Biological activity	~3800 NIH units/mg	≥2,000 NIH units/mg
Purity	>95%	

A simple specification with accompanying AQIS certification regarding traceability and origin is required.

For the purposes of this project, given the regulatory requirements for producing an active pharmaceutical ingredient (API) under strict GMP conditions, we have chosen not to include a production cost analysis of the final product.

In Australia to produce a medicinal API plant would require Therapeutic Goods Administration (TGA) certification for production of an API, under the current Australian Code of Good manufacturing practice – Medicinal Products, August 2002. A new plant of this type and nature would at least cost ~AUD$15-20 million to construct and commission and have significant ongoing compliance costs ($0.5-1 million p.a.) regarding maintenance and quality systems/audits on top of operating overheads.

With careful review of the manufacturing guidelines it may be possible to produce pro-thrombin as a raw material for future processing by using a sound quality system approximating cGMP and full traceability of all materials.

4.7 Manufacturing considerations

Barium salt (pTH) can be produced via selective precipitation using barium chloride.

Preparation of pTH starts with the slow addition and consequent precipitation of bovine plasma. The barium precipitate of pTH is formed and is recovered by centrifugation, washing with saline buffer and re-centrifuged[20].

The pTH (barium salt) can be further processed by ammonium sulphate precipitation and consequent ion exchange and ligand chromatography.

Thrombin can be made from purified prothrombin using a modification of the Lundblad[21] procedure as described by Neisheim[22] et al.[23]

Critical manufacturing requirements include:

- availability of specialised equipment and maintenance backup
- consistent source of quality raw material and
- qualified staff to operate the plant to required standards

4.8 Regulatory considerations

pTH that is aimed at the global market place should meet the following regulatory accreditation:

- Processed from AQIS inspected and passed bovine plasma.
- EDQM TSE Certificate of Suitability[24].
- AQIS Registered for shipment to the EU/USA.
- Manufactured following guidelines to ICH Q7A or FDA cGMP[25].

20 See Appendix F for the process flow diagram

21 Lundblad, R.L. et al., Methods Enzymol.,45, 156 (1976)

22 Neisheim, M.E. et al., J.Bio. Chem.,258,5386 (1983)

23 Haematologic Technologies Inc. Thrombin product information

24 http://www.edqm.eu/en/Certificates-of-Suitability-97.html

25 November 2000 CPMP/ICH/4106/00 ICH Topic Q 7 *Good Manufacturing Practice for Active Pharmaceutical Ingredients*

Section 4 Thrombin (TH)

4.9 Revenue model

There are three products that can be sold for greater value than plasma alone:

- pTH (Barium salt)
- purified pro-thrombin
- purified activated thrombin

The approximate value increases on a standard weight basis for these products are:

Table 6: Value inflections as thrombin product is transformed to final product form[26]

Material	Thrombin yield	$ value low	$ value high	Uplift
Raw plasma	100mg	$0.90	$1.50	
pTH (barium salt)	100mg	$3.90	$4.50	3.00
Purified prothrombin	100mg	$500.00	$625.00	138.89
Purified activated thrombin	100mg	$1,000.00	$1,250.00	2.00
Sales	100mg	$ –	$4,000.00	3.20

A revenue model was developed assuming wholesale manufacturing of pTH. Under this model processors would create a business unit for bioactives and drive business development activities under the unit's banner. Sales are derived from direct sales or tenders to bulk end users, distributors or channel partners/agents who may re-label or sell on directly.

Website information and trade conference promotion will be essential marketing tools.

Based on a plant processing 120,000 head per year, then by the fifth year of operation):

Payback	< 2 years (based on net profit before tax)
Capital cost	$650,000 (all used equipment, including blood separation equipment)
Sales price	$150AUD/kg
Market share	5% fifth year

- Net benefit per head of pTH (barium salt) sales is ~$10.9 (excluding sales of surplus plasma and red cells).*

** Calculated as Net Profit Before Tax in year five by 120,000 head. Number of head required to produce bioactoive product is less.*

26 Assumptions based on USD72 per 5000 IU Thrombin – 2.7 IU/mg therefore 5000 IU = 1.8 mg thus $USD40/mg sales price. 20-30% API cost of sales price.

The value of the surplus plasma and red blood cells is not presented within the model outputs, however based on the plant scale in the underlying assumptions at the current market price this could add (if all product were sold as liquid plasma @ $1.20/L and red blood cells @ $0.90/L) approximately $500,000 to revenue. This would improve the payback and net benefit per head.

A revenue model was also prepared assuming the combined production of BSA, Immunoglobulin, Thrombin and Haemoglobin. Greater revenue and product offering could be considered by combining production of up to four blood derived bioactives in the one plant.

Any processor interested in taking the next step should contact MLA to receive more detailed information and to discuss it further.

4.10 Potential processor benefits

- net benefit per head of pTH (barium salt) sales is attractive
- decreased waste burden (and cost) by value adding the waste stream
- adding greater value to blood waste stream than currently available
- access to a non food markets thus differentiating existing business product mix
- adding further to revenue
- potential to add other bioactive products with adaptive modification to existing plant

Partnerships

MLA has access to research and development partners who can provide development of pilot scale plants and process development and scale up. MLA is also able to provide funding support through its donor funding company on a dollar for dollar basis for suitable projects.

Further Information

MLA has assembled an information package with revenue modeling based on recently collected data. Any processor interested in taking the next step should contact MLA to receive this information and discuss the opportunity further.

Section 5 Haemoglobin (Hb)

Haemoglobin is a protein in red blood cells that carries oxygen.

5.1 Markets

The major market application for haemoglobin is as a spray-dried product in veterinary/animal and pet feed applications.

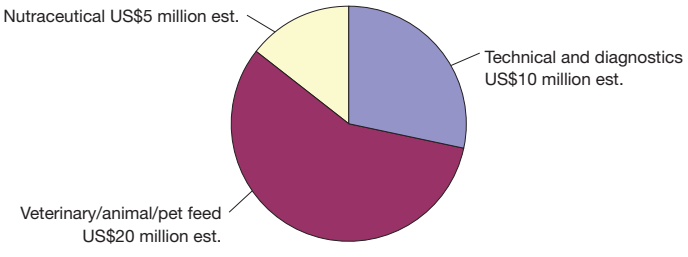
The bulk use of haemoglobin is in animal feed (the trade price suggested is US$5-10/kg for food grade) and it also has niche veterinary therapeutic applications, for example Oxyglobin™. Biopure introduced Oxyglobin™ in 1998 to treat anaemia in canines and reported sales of US$2.6million in 2008.

In the animal feed market Hb is a palatable source of protein for aquaculture, swine, poultry and ruminants. Haemoglobin is also used as a colouring agent for pet food.

Hb is sold into the Technical and Diagnostics market for use in research as a protease substrate, as an ingredient in agar and a sizable market exists for the diagnosis and manufacture of haem-dependent bacterial vaccines such as *Haemophilus influenzae* b.

Hb also has applications in the therapeutics market as a blood substitute in blood transfusions. There are also nutraceutical applications for Hb as a supplement for groups of the population who suffer from iron deficiency.

Figure 8: Estimated market segmentation of haemoglobin applications



5.2 Global trends

The traditional market of haemoglobin is as a spray dried product used in microbiological media culture formulation and as a functional protein ingredient in animal feed and pet food formulation.

High end technical products such as Oxyglobin®,Hemopure® and HemoTech™ with therapeutic uses as tissue oxygenation and blood substitutes are very encouraging since there is a demand for a safe and non toxic blood substitute due to chronic human blood donation shortages.

In line with consumers' acceptance of dietary supplements and functional foods, an increase in animal derived heme products (from APC Europe – AproFER) incorporated into dietary and functional foods anticipated.

Key market drivers:

- as per purchasing requirements, distributors need access to secondary suppliers in alternate geographical regions to mitigate risk
- market growth potential as an alternate protein source for feed or food
- novel biotechnological applications

5.3 Overview of Hb supply chain

Table 7: A general overview of the haemoglobin supply chain (see Appendix G for details of the companies)

	Manufacturer	Distributor	User
Sigma Aldrich		✔	
BioSynth AG (Hematin)	✔		
Calbiochem		✔	
USB Corp		✔	
Becton Dickinson		✔	✔
Neogen Corporation		✔	✔
Worthing Biochemical Corp		✔	
Proliant Inc	✔		
APC Inc	✔		
Biopure Corp			✔
Bovogen Biologicals	✔		
HemaTech Inc			✔
Marcor		✔	
Calzyme Laboratories Inc	✔		
Daka Proteins (porcine)	✔		
Voigt Global Distribution		✔	✔

The major suppliers of Hb are APC Inc and Proliant. APC Inc supplies AP301 for animal feed and AP720 for pet food.

5.4 Competitive landscape

A number of companies compete in the market; however competitively priced Australian product may find favor with respect to quality and safety.

In particular, competition is high at the low end market; however, a local supplier with low transport costs may be at an advantage.

Section 5 Haemoglobin (Hb)

5.5 Customers

The following points describe the points of value to potential customers of Hb:

Cost (pricing) Drivers:

- Production efficiencies by having the bioactive production plant along side the primary meat processing plant sharing common utilities, infrastructures and processes.
- The product pricing is influenced and dependent on the production scale and raw material internal transfer pricing, both of which are controlled by the processor.

Quality and Safety Drivers:

- a strong focus on quality
- manufactured in the country of animal origin
- geographical Bovine Spongiform Encephalopathy (BSE) Risk category 1 (lowest risk) country status

5.6 Product specifications

Typical product specifications are given in Table 8 below.

Table 8: Haemoglobin specifications

	Calzyme Laboratories Inc	Bovogen Biologicals	Sigma- Aldrich
Product	Bovine Erythocytes	Bovine Haemoglobin Powder	Haemoglobin from bovine blood
Description	Freeze-dried powder	Fine, dark-red powder	Brown powder
Pack sizes	US$4/g	500-1000kg	H2625 1Kg
Protein	~100%	≥85%	n/a
Moisture	n/a	≤8.0%	8%
Ash	n/a	≤6%	n/a
Fat	n/a	≤2%	n/a
Solubility	Distilled water/buffer	90%	1 part in 7 water
Comments		Approved for human consumption	Suitable for use as a protease substrate

5.7 Manufacturing considerations

Haemoglobin is usually prepared by separating red blood cells from the lighter plasma component by centrifugation. Ether (or water) is added to the red blood cells paste causing it to burst before being further centrifuged to remove the ruptured cell envelopes in order to leave a clear red solution of haemoglobin[27]. The flow diagram in Appendix H details the processing steps.

In the animal feed market, haemoglobin (red blood cells) is spray dried to give a dark reddish brown colour with high digestible protein and a palatable source of protein.

The red blood cell concentrate can be further processed to yield the following useful bioactives:

- amino acids (lysine, histidine, phenylalanine)
- hematin/hemin and
- sphingomyelin.

5.8 Regulatory considerations

Haemoglobin that is aimed at the global market place should meet the following regulatory accreditation:

- Processed from AQIS inspected and passed bovine red cell fraction deemed edible.
- AQIS Registered for shipment to the EU/USA.
- Manufactured to an auditable food grade standard under a HACCP program.

27 Merck Index, 12th Edition. S.Budavari. Ed., pg 794, #4682 (1996)

Section 5 Haemoglobin (Hb)

5.9 Revenue model

A revenue model was developed assuming wholesale manufacturing of Hb. Under this model processors would create a business unit for bioactives and drive business development activities under the unit's banner. Sales are derived from direct sales or tenders to bulk end users, distributors or channel partners/agents who may re-label or sell on directly.

Website information and trade conference promotion will be essential marketing tools.

Based on a plant processing 120,000 head per year, then by the 5th year of operation:

Payback	< 2 years (based on net profit before tax)
Capital cost	$800,000 (all used equipment, including blood separation equipment)
Sales price	$15AUD/kg
Market share	2.5% fifth year

- Net benefit per head of Hb sales is ~$10.9 (excluding sales of surplus plasma and red cells).*

The value of plasma as a by-product is not presented in the model outputs. Based on the proposed plant scale in the underlying assumptions sales of plasma could add (given plasma is sold at $1.20/L) more than $1,000,000 to revenue ($1,296,000 from 1,080,000 L plasma at $1.20/L.)

A revenue model was also prepared assuming the combined production of BSA, Immunoglobulin, Thrombin and Haemoglobin. Greater revenue and product offering could be considered by combining production of up to 4 blood derived bioactives in the one plant.

Any processor interested in taking the next step should contact MLA to receive this information and discuss in further detail.

5.10 Potential Processor Benefits

- net benefit per head of Hb sales is attractive
- decreased waste burden (and cost) by value adding the waste stream
- adding greater value to blood waste stream than currently available
- access to a non meat markets thus differentiating existing business product mix
- adding further to revenue
- potential to add other bioactive products with adaptive modification to existing plant

Partnerships

MLA has access to research and development partners who can provide development of pilot scale plants and process development and scale up. MLA is also able to provide funding support through its donor funding company on a dollar for dollar basis for suitable projects.

Further Information

MLA has assembled an information package with revenue modeling based on recently collected data. Any processor interested in taking the next step should contact MLA to receive this information and discuss the opportunity further.

** Calculated as Net Profit Before Tax in year five by 120,000 head. Number of head required to produce bioactoive product is less.*

Section 6 Appendix A – participants in the BSA supply chain

The following is a survey of the companies that are making an impact in the BSA supply globally. These companies are manufacturers of technical quality BSA ranging from standard grade to cell culture grade and are suppliers to end users such as pharmaceutical (vaccine) production, in vitro diagnostic manufacturers, laboratory researchers etc. Food grade manufacturers are not surveyed in this section, which is not to say that these manufacturers are not also suppliers of BSA for functional foods (for example Proliant Inc).

6.1 Bovogen Biologicals Pty Ltd – Australia www.bovogen.com

Bovogen Biologicals Pty Ltd is an Australian privately owned company located in Melbourne. Bovogen manufacture and supply highly purified bovine serum albumin (BSA), purified animal proteins and animal serum products. Bovogen assures full traceability with its products with GMP manufacturing certification and sources raw materials from only Australian or New Zealand export abattoirs, USDA and EU approved establishments or donor animal herds. Bovogen Biologicals has Certification of Suitability from European Directorate of Quality Medicines for its range of bovine serum albumin products. This certification meets the criteria described in the current version of the monograph "Products with Risk of Transmitting Agents of Animal Spongiform Encephalopathies" No. 1483 of the European Pharmacopoeia.

Bovogen Biologicals was awarded the Australian Red Meat Industry Award for Innovation in 2006 for its BovoLep BSA. Bovogen is an established company with a cohesive range of animal-derived products and is a main player in the BSA manufacture in Australia. Bovogen continues to build and innovate by expansion of business opportunities such as the formation of Biovine Biologicals with focus on the development and supply of ovine proteins and related products for the life science industries.

Bovogen Biologicals Pty Ltd
Head Office
71 Ogilvie St
Essendon VIC

Phone: +613 9336-3622
Fax: +613 9336 3644
info@bovogen.com

6.2 Moregate Biotech – Australia and New Zealand www.moregatebiotech.com

Moregate BioTech is recognised as foremost producers of high quality Australian and New Zealand Animal Sera, Protein and by-products supplying leading international pharmaceutical groups and major research organisations. Founded in 1975 with its core business of supplying foetal serum into Europe and today have offices and distribution channels globally.

Morgate Biotech has two manufacturing sites designed to meet cGMP manufacturing in Brisbane, Australia and Hamilton, New Zealand and only sourcing its raw materials from Australian and New Zealand. In 1995, Morgate manufactured its first large scale Bovine Serum Albumin batch produced across its operations. Morgate Biotech then received a Certificate of Suitability from European Directorate of Quality Medicines New Zealand and Australia. Since then, Moregate have upgraded the Bovine Albumin facility and increased the production of a range of Bovine Serum Albumin products. Morgate Biotech company diversification includes world market accessibility via global distribution chains with sales people positioned internationally, a cohesive range of bovine derived products, multiple cGMP manufacturing sites and are now engaging into research and commercial enzymes production.

Moregate Biotech
54-56 Banya Street
PO Box 654
Bulimba QLD 4171
Australia

Phone: +61 7 3399 7000
Fax: +61 7 3399 5578
moregate@moregatebiotech.com

6.3 Millipore Corporation – US www.millipore.com

Millipore is a leading provider of products and services that improve productivity in biopharmaceutical manufacturing and in clinical, analytical and research laboratories via its two operating divisions of Bioprocessing and Bioscience. Incorporated in 1954, Millipore emerge as a leader in membrane technology providing tools not only to researchers but also used by medical schools, hospitals and dialysis centres, and many industries – including the pharmaceutical, chemical, plastics, food and beverage, and microelectronics industries. In 2006, Millipore Corporation acquire Serologicals Corporation with businesses such as Chemicon, Upstate, Linco, Celliance. By incorporating Serologicals' product and services, Millipore offers both upstream cell culture and downstream separation for biopharmaceutical production. Celliance then moved all manufacturing of cell culture products including EX-CYTE®, the largest selling, cell-growth supplement; Probumin™, a proprietary line of bovine albumin; and Incelligent™, the Company's recombinant human insulin from Toronto, Canada to Kankakee, Illinois in 2006.

Millipore 2008 revenue was U$1.6 billion with 5% derived from upstream cell culture of its Bioprocessing Division. The company is part of the S&P 500 index and employs approximately 5,800 employees in more than 47 offices worldwide.

Corporate Headquarters
Millipore Corporation
290 Concord Road
Billerica, MA 01821

Phone: 978-715-4321

Section 6 Appendix A – participants in the BSA supply chain

6.4 SAFC – Sigma Aldrich

SigmaAldrich is a leading Life Science and High Technology company. The company operates 4 business units of Research Biotechnology, Research Specialties, Research Essentials and SAFC. Sigma Aldrich 2008 Revenue is USD2.2 billion with 28% derived from SAFC activities. Through its SAFC company, SAFC Biosciences in 2005 acquired JRH Biosciences (Lenexa, Kansas) and further upgraded the facility to manufactureserum (sterile filtration and packaging) and dry powder media (continuous pin milling technology). Information obtained from annual reports and website suggests that the serum is sourced from production of serum and serum products derived from US, Canada and Australia. As the largest serum processor in Australia, SAFC Biosciences- Asia Pacific operation is based in Brooklyn, Victoria, Australia where animal serum is processed and manufactured (filtered and packaged) as well as another serum facility located in Brisbane, Queensland. Sigma-Aldrich operates in 37 countries and has over 8,000 employees providing excellent service worldwide.

Sigma-Aldrich Corp.
St. Louis, MO, USA

Phone: 314-771-5765
Fax: 314-771-5757
Email: OC_DOM_HC@sial.com

SAFC Lenaxa US
13804 W. 107th Street
Lenexa, Kansas 66215
Phone: 913-469-5580

SAFC – Australia
18-20 Export Dr
Brooklyn Victoria 3025
Phone: +61 3 9362 4500

6.5 Invitrogen Corporation – US (Life Technologies)

Invitrogen Corporation and Applied Biosystems Inc merger formed a new premier life science company Life Technologies in November 2008 with revenue of U$3.14 billion. Under the brand name of Gibco®, Invitrogen offers an extensive range of cell culturing products for research and manufacturing. AlbuMax® range of BSA chromatographically purified by Invitrogen proprietary methods using bovine serum sourced from New Zealand. Invitrogen have four cGMP manufacturing sites with two being in New Zealand (Auckland & Christchurch) Grand Island NY USA and in 2005 a facility in Newcastle Australia. New Zealand facilities have capabilities to manufacture both sera and protein products sourced from New Zealand herds. Invitrogen have 18% share of the serum market and 8% share for cell media market[28], hence the strategic manufacturing sites in both Australia and New Zealand for clean health (BSE-free status). Gibco products generated 24% (U$303 million) of Invitrogen total revenue of USD1.263 billion in 2006.

Invitrogen Corporation
3175 Stanley Rd
Grand Island NY 14072

Phone: 1800 955 6288
Fax: 1800 331 2286

Invitrogen New Zealand Ltd
18-24 Botha Road
Penrose Auckland 1006
Canterbury 8042

Invitrogen New Zealand Ltd
7 Brixton Street
Islington,
Christchurch City

6.6 Proliant Inc – US www.proliantinc.com

Proliant manufactures and markets protein products for the food, nutrition, human health, nutraceutical, diagnostic, life science research, biopharmaceutical and veterinary vaccine industries. Proliant operates under 4 business units of Meat, Dairy, Health and Biologicals. Proliant Biologicals manufacture a range of BSA, growth factors concentrate and lipoproteins for research and diagnostics market. The Proliant BSA story began back in the 1990's when there was a shortage of BSA supplies when Centeon was shut down and Intergen and Pentex were acquired by Serologicals, which again have reduced BSA production capacity when acquired by Millipore in 2006. Proliant purpose built a manufacturing facility and now claim to have the Proliant BSA 'Closed Loop' Manufacturing to produce albumin at high consistency, of low protease, low endotoxin and essentially fatty-acid and IgG free. Proliant improves further with process innovations by sterile bag in-tray system and all stainless steel chambers in the largest and most efficient freeze driers in the world. Proliant supply over 50% of BSA products used around the world[29]. The Iowa Workforce Development published that the export revenues for Albumins; Modified Starch; Glue for the year 2008 was approximately U$105 million.[30]

2425 SE Oak Tree Court
Ankeny, Iowa 50021-7102 USA

Phone: 515 289 7600
Fax: 515 289 4369

Proliant – Boone Facility
2020 Lakewood Drive
Boone, IA 50036

28 www.wikinvest.com/stock/Invitrogen_(IVGN) 2006

29 A Proliant White Paper: How Proliant's "Closed Loop" Has Revolutionized BSA Manufacturing

30 www.iowaworkforce.org/trends/exports.html

Section 6 Appendix A – participants in the BSA supply chain

6.7 Equitech – Bio, Inc
www.equitech-bio.com

Located in Kerville Taxas, Equitech manufacture BSA along with serum products in its cGMP facility utilising heat-shock and cold ethanol extraction methods. A range of grades of BSA are available ranging from microbial grade, reagent, standard, diagnostics etc to suits the specific applications. Equitech received its Certificate of Suitability with the European Directorate for the Quality of Medicines for Bovine Serum Albumin products. Its European importer is Europa Bioproducts. Equitech is a private company with annual sale in the range of USD30 million.

Equitech-Bio, Inc.
512 Cotton Gin Lane
Kerrville, TX 78028

Phone: 1.830.257.0005
Ordering: 1.800.259.0591
Fax: 1.830.257.0006
Email: info@equitech-bio.com

6.8 Biocell Laboratories Inc
www.biocell.com

Biocell laboratories was founded over 25 years ago by scientists to meet a low cost and high quality defibrinating plasma and sera for diagnostics applications. Today Biocell offers a range of human and animal protein fractions, tissue culture sera, and bulk human and animal sera. Biocell have been making and market bovine serum albumin since 1982 and believed to be the few manufacturers using the Cohn Cold Ethanol extraction method. Biocell's BSA is manufacture in compliance with USDA and EU regulations and received "Certificate of Suitability for TSE" from the European Directorate for the Quality of Medicine for BSA. Biocell BSA customers include the United States, Europe and Asia.

2001 University Drive
Rancho Dominguez, CA 90220

Phone: 310-537-3300
Fax: 310-637-3927

6.9 SeraCare Life Sciences
www.seracare.com

SeraCare have been serving the global life sciences market for 25 years. SeraCare business includes blood testing and donor screening, clinical trials and research, drug and vaccine research and manufacturing, in vitro diagnostics research and manufacturing and sample storage and management. SeraCare manufacture bovine serum albumin in their Milford, Massachesetts facility with-state-of-the art facility with full cGMP compliance with its recent upgrade in 2008. The company has an alliance with Proliant for the supply of plasma[31]. Some of SeraCare valued customers in the in vitro diagnostics manufacturers are BioRad, Beckman Coulter,Thermo Scientific and cell culture company such PAA.

SeraCare revenue for its Diagnostics and Biopharmaceutical Products division for 2008 was USD35 million[32] which includes bovine serum albumin in the product portfolio.

SeraCare Life Sciences, Inc.
800.676.1881
37 Birch Street
Milford, MA 01757

Toll free (US only):
Phone: 508.244.6400
Fax: 508.634.3394

6.10 AusGeneX Pty Ltd
www.ausgenex.com

AusGenex located in Gold Coast Australia is a manufacturer and supplier of animal derived sera and proteins. AusGeneX supplies Australian sourced bovine serum albumin via distributors around the world and in particular Asia. AusgeneX animal derived products are sourced from Australian and New Zealand export abattoirs with USDA and EU approval.

Contact Lee Sandes
Unit 8, 36-38 Newheath Dve
Arundel, QLD 4214
Australia

Phone: +61 7 5580 6009
Fax: 61 7 5580 4009
Email: sales@ausgenex.com

6.11 ICPbio International Ltd
www.icpbio.com

ICPbio is a manufacturer of bovine serum albumin, transferring, IgG and thrombin in their state of the art chromatographic processes. Their target customer included biopharmaceutical, diagnostics and researchers. ICPbio sourced their plasma in New Zealand from USDA and EU approved abattoirs to ensure complete traceability.

ICPbio supply BSA products through a distribution network distributors such as VWR International in US and Shigematsu-bio in Japan with pack sizes 10g – 1kg selling for U$35 –U$700 respectively. ICPbio (ICP Biotechnology) reported revenue of $4.7 million for 2007 and information suggested that the company is now privately owned since its receivership in Aug 2008 when it was part of ICP International which includes veterinary embryo transfer units.

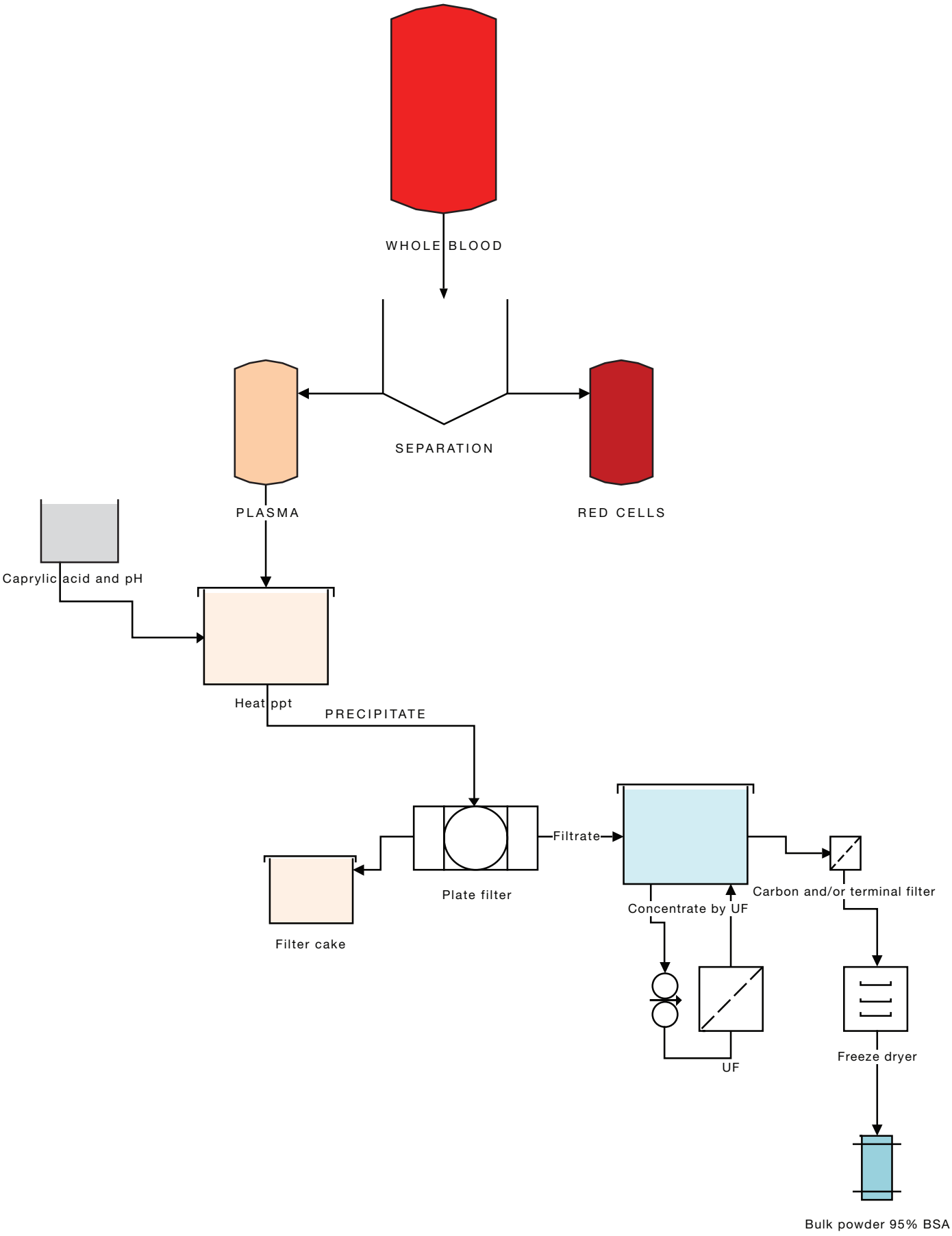
37-39 Waipareira Avenue
Henderson, Auckland
New Zealand

Phone: +64 9 9122460
Fax: +64 9 8384209

31 MLA Bioactive Market Investigational Tour Report Jun 2004 Geoff Keipert

32 SeraCare Life Science Annual Report 2008 pg28

Section 7 Appendix B – process flow diagram for BSA



Section 8 Appendix C – participants in the IgG supply chain

8.1 APC Inc
www.americanprotein.com

Since 1981, American Protein Corporation (APC) has been recognized as the global leader in plasma protein fractionation and applications research for feed and industrial use. APC is an LGI company which is in the same group as Proliant Inc. Both companies have very similar raw product ingredients that are formulated and registered from different market. APC targets the animal feed market with their range of plasma products and and Proliant Inc targets the technical and function and dietary supplements for human consumption. APC's LifeLine made from bovine serum concentrate used as a colostrum supplement designed for calfs in the first 24 hours. Gammulin (IgG and vitamins) enhances the nutrition of animals in 2-15 days and improve immunity during stress and infection from viral, bacterial and protozoan sources.

2425 SE Oak Tree Court **Phone: 515 289 7600**
Ankeny, IA 500021 **Fax: 515 289 4360**

8.2 Mach One Corporation
www.machonecorp.com

Mach One Corporation is a biotech company with a focus on providing wellness solutions and on human nutrition in the long term. Mach One offers a range of IgG products derived from bovine serum in the Bridge™ range of products as immune support during the many stages of animal life from colostrum replacement (1st- Bridge) to RP-Bridge which help with challenges related with birth, weaning, shipping and receiving. Mach One recently acquired Ceres Organic Harvest with plans to coat with IgG and market as an immune booster in sick animals and Pacific Rims Food to gain market presence in Asia and in particular China.

974 Silver Beach Road **Phone: 888 400 7179**
Belgium WI 53004 **Fax: 262 285 7179**

8.3 Proliant Inc
www.proliantinc.com

Proliant manufactures and markets protein products for the food, nutrition, human health, nutraceutical, diagnostic, life science research, biopharmaceutical and veterinary vaccine industries. Proliant operates under 4 business units of Meat, Dairy, Health and Biologicals. Proliant Biologicals manufacture a range of BSA, growth factors concentrate and lipoproteins for research and diagnostics market. Proliant lead the way in the introduction of NutraGammax™ and Immunolin™ into the functional food category in the early 2000. As an ingredient, NutraGammax is supplied as an ingredient used in sport nutrition as a powder form or in snack bar format.

ImmunoLin with GRAS (Generally Recognised as Safe) status have seen a higher price tag and has been used in brands such as Zymogen, Nutraplete (dietary supplement for AIDS/ HIV patients), Extreme Immunity.

Proliant Health & Biologicals **Phone: 515 289 7600**
2425 SE Oak Tree Court **Fax 515 289 4369**
Ankeny, Iowa 50021-7102 USA

Proliant – Boone Facility
2020 Lakewood Drive
Boone, IA 50036

8.4 ICPbio International Ltd
www.icpbio.com

ICPbio is a manufacturer of bovine serum albumin, transferrin, IgG and thrombin in their state of the art chromatographic processes. Their target customers include biopharmaceutical and diagnostics manufacturers and researchers. ICPbio source their plasma in New Zealand from USDA and EU approved abattoirs to ensure complete traceability.

ICPbio supply IgG products through a distribution network distributors such as VWR International in US and Shigematsu-bio in Japan with pack sizes 10g- 100g selling for U$259–U$880 respectively. ICPbio (ICP Biotechnology) reported revenue of $4.7 million for 2007 and information suggest that the company is now privately owned since its receivership in Aug 2008 when it was part of ICP International which includes veterinary embryo transfer units.

37-39 Waipareira Avenue **Phone: +64 9 9122460**
Henderson **Fax: +64 9 8384209**
Auckland New Zealand

8.5 Bovogen Biologicals Pty Ltd – Australia
www.bovogen.com

Bovogen Biologicals Pty Ltd is an Australian privately owned company located in Melbourne. Bovogen manufacture and supplies highly purified bovine serum albumin (BSA), purified animal proteins and animal serum products. Bovogen assures full traceability with its products with GMP manufacturing certification and sources raw materials from only Australian or New Zealand export abattoirs, USDA and EU approved establishments or donor animal herds.

Bovogen continues to build and innovate by expansion of business opportunities such as the formation of Biovine Biologicals with focus on the development and supply of ovine proteins and related products for the life science industries.

Bovogen Biologicals Pty Ltd **Phone: +613 9336-3622**
Head Office **Fax: +613 9336 3644**
71 Ogilvie Street **info@bovogen.com**
Essendon VIC

Section 8 Appendix C – participants in the IgG supply chain

8.6 Murray Goulburn

Murray Goulburn (MG) Co-operative was established in 1950 and today is Australia largest manufacturer of diary products with 2900 supplier/shareholders. MG has nine manufacturing sites throughout Victoria and Tasmania with 3.3 billion litres of milk intake and exporting 375,000 metric tonnes in 2006/7 to over 100 countries. In 2008, MG reported revenue of A$2.6 billion with a diverse business units of MG Ingredients, Nutrition, Farm & Hardware Supplies and functional food companies/brand such as Ascend (sport nutrition), Proform (meal replacements) and Liddell (lactose-free milk). Interestingly, in MG 2008 annual report, it announced that it has stopped the manufacturing of whey protein isolate and concentrate, except as required by MG Nutritions for their range of proprietary Ascend brand products.

140 Dawson St
Brunswick VIC 3056
Australia

Phone: 61 3 9398 6400
Fax: 61 3 9387 5741

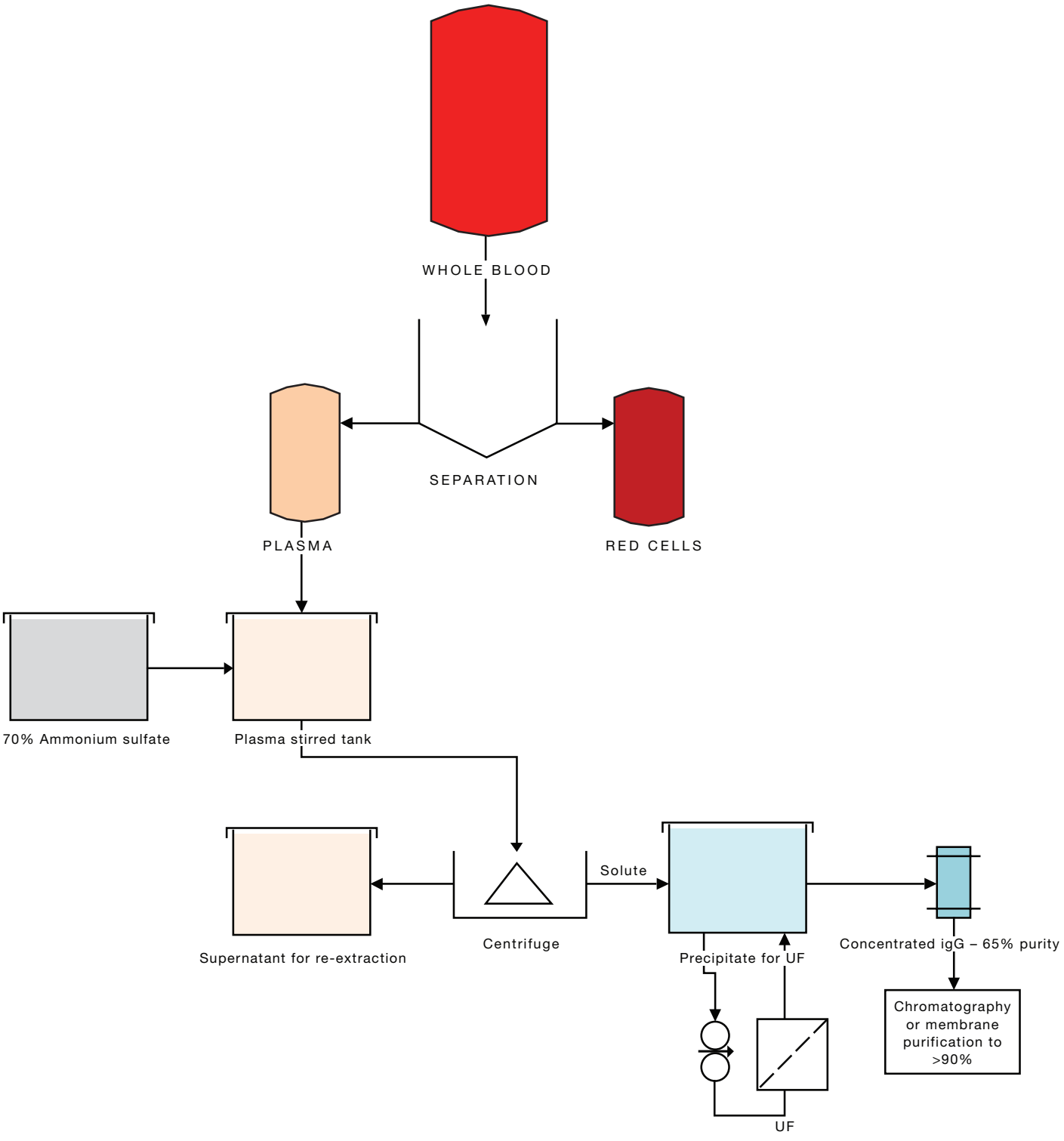
8.7 Fonterra

Fonterra is the 6th largest exporter of dairy products and has 1/3 of market share of dairy products. Fonterra was founded in 2001 with the merger of New Zealand Diary Cooperatives and New Zealand Dairy Board and it also have operations in Australia, US and China. The revenue for 2008 was reported to be NZ$19.5 billion, from sales of 2.63 million metric tonnes exporting to 140 countries with Krafts Food Inc and General Mills Inc. Fontera recently launched whey protein isolate ClearProtein™ used bottled water by Coca-Cola. Fontera is a global company with a range of innovative whey protein products such as the ProteinPower (whey and milk proteins) for use in snack bars. The company also invests in biofuel made from waste whey products.

Fonterra Ingredients
Private Bag32
032 Auckland New Zealand

Phone: 64 9 374 9000
Fax: 64 9 374 9001

Section 9 Appendix D – process flow diagram for IgG



Section 10 Appendix E – participants in the TH supply chain

10.1 ZymoGenetics Inc www.zymogenetics.com

Zymogenetics focus is on the discovery, development and manufacture and commercialization of therapeutic proteins for the treatment of human diseases with specific target on hemostasis, inflammatory and autoimmune diseases. Their first internally developed product candidate RECOTHROM® was approved by the US FDA in January 2008 for use as a topical haemostat. Recothrom is a recombinant thrombin that used to control moderate bleeding during surgical procedure. Recothrom is claimed to have benefits over bovine derived thrombin for patients which may experience allergic reactions to plasma derived thrombin and potential risk of transmitting infectious and others diseases from human derived thrombin.

ZymoGenetics and Bayer Healthcare have a global collaboration and will co promote of Recothrom in the US in the next three years. ZymoGenetics receives US$40 million milestone payment from Bayer since FDA approval in January 2008. Sales of Recothrom were reported to be US$ 8.8 million for 2008. Recothrom is distributed via wholesalers AmerisourceBergen Corporation, Cardinal Health Inc and McKesson.

Zymogenetic Inc
1201 Eastlake Avenue
Seattle, Washington 98102
Phone: (206) 442 6600
Fax: (206) 442 6608

10.2 King Pharmaceuticals Inc www.kingpharma.com

King Pharmaceuticals Inc was incorporated in 1993 with wholly owned subsidiaries Alpharma Inc, Meridian Medical Technologies, Monarch Pharmaceuticals, King Pharmaceuticals Research and Development inc, Parkedale Pharmaceuticals Inc and Monarch Pharmaceuticals Ireland Ltd. King's revenue for 2008 was US$ 1.565 billion with Thrombin JMI® accounted for 16.3 % which is US$254 million. Thrombin JMI® (bovine thrombin) have been in the market since the early 90's and have proven efficacy as a homostat agent and at times being tested for its adverse events due to patients developing bovine allergic reactions. Since the outbreak of bovine spongiform encephalopathy (BSE) in the late 1990's in US and Canada, King Pharmaceutical are vigilant and have a risk minimisation strategy to source their raw materials from two approved vendors and only of United States origin. Thrombin JMI® comes from bovine plasma and lung tissue from US FDA approved sources and from cattle of 18 months or less. Further, in protecting the market position of Thrombin JMI, an upgraded facility and FDA validated manufacturing process assure the removal of viral contaminants. King's understand that there are high levels of global public concern about BSE and that Physicians could determine not to administer Thrombin JMI® because of the perceived risk.

King Pharmaceutical hemostasis product includes Thrombin JMI- Epistaxis kit, Thrombi-Gel™ (thrombin/gelatine foam haemostat) and Thrombi-Pad™ 3x3 Hemostatic pad which are manufactured by Vascular Solutions Inc with exclusive license to King Pharmaceuticals.

King Pharmaceuticals Inc
501 Fifth St, Bristol
Tennessee USA
Phone: 1800 776 3637
Fax: (423) 989 8000

10.3 Johnson & Johnson – Ethicon

Ethicon Inc is a (Johnson & Johnson company) global medical device company specialising in surgical sutures for more than 100 years. In 2007 it acquired a human thrombin product, Evithrom, from Omrix Pharmaceuticals which was approved by the FDA as a topical thrombin in late 2007 for use as a hemostatic agent. FDA news release noted that Evithrom is the first human thrombin approved since 1954 and is the only product currently licensed. It is intended to provide an alternative to bovine-derived products that carry a risk of immunogenetic response and associated complications such as severe bleeding, thrombosis, and anaphylactic shock. The estimated sale of Evithrom for 2008 was ~US$20 million and it has a strong position being distributed globally by Johnson and Johnson wound management division. Ethicom Company Group Chairman's Alex Gorsky predicted that Ethicon would be world's no 1 in 2007 with US$3.6 billion sales with 75% of global sutures market share. Ethicon ambitiously predicted 18% annual growth and 2 billion revenue for its Biosurgicals for Hemostasis products by 2012.[33]

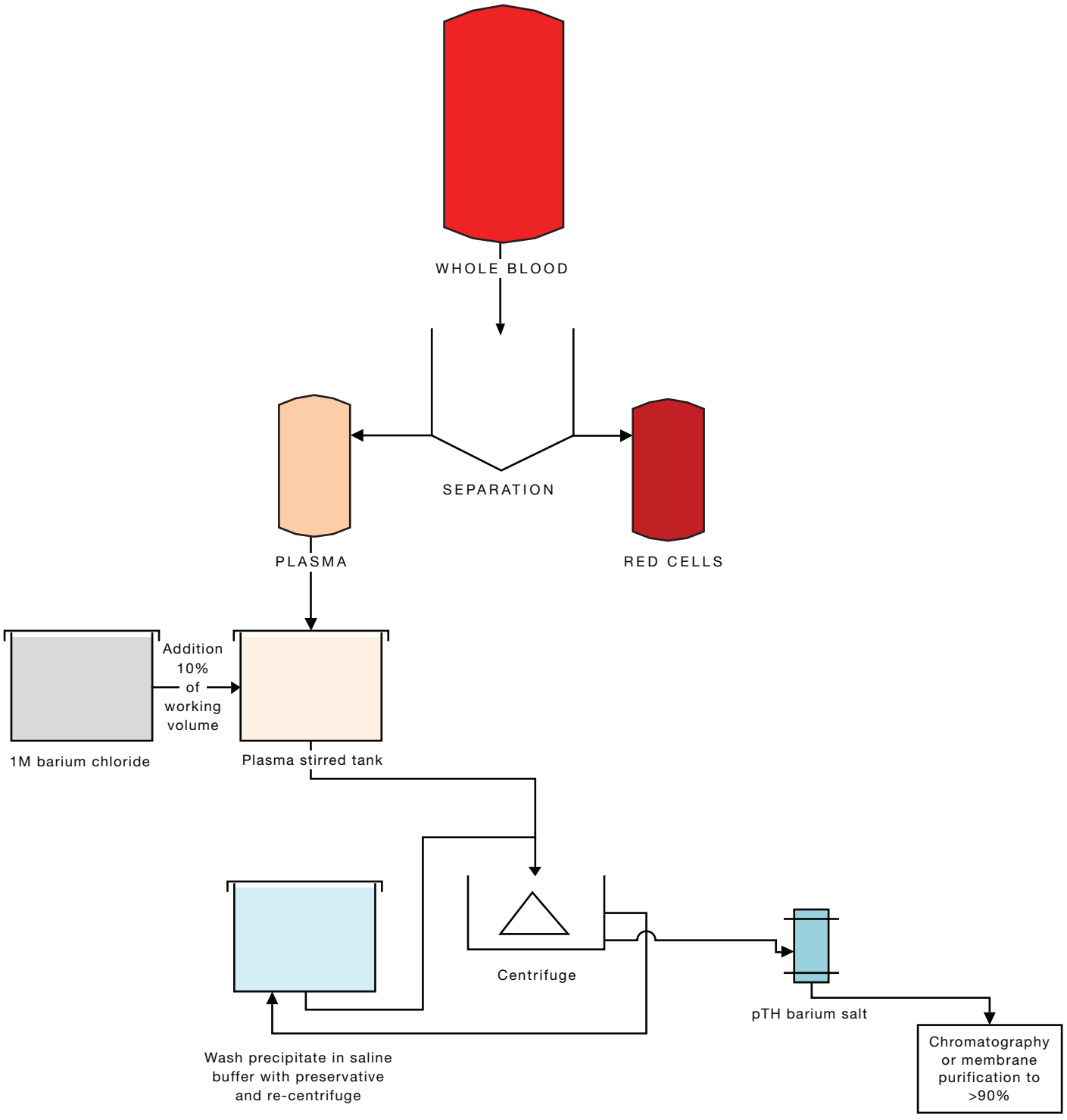
10.4 Baxter Healthcare www.baxter.com

Baxter is a global healthcare company with 2008 annual revenue of US12.3 billion. Baxter Biosurgery products reported to have good growth with approvals of their core product Tisseel in Europe, Latin America and Asia and is working by adding more products in their biosurgery portfolio such as Artiss and Tochosil. The net sales of Bioscience divison increases by 14% for 2008 to US5.3 billion. The Regenerative Medicine product line which principally, includes products derived from plasma proteins includes hemostasis products such as FloSeal, CoSeal and Tisseel reported combine sales of US408 million. Baxter FloSeal haemostasis products used both human derived thrombin (US market) and bovine-derived (Japan market). FloSeal was initially made by Fusion Medical Technologies and in 2002 was purchased by Baxter. The bovine thrombin reagent of FloSeal is King's Thrombin JMI.

Baxter Healthcare Pharmaceutical
1 Baxter Parkway
Deerfield Illinois 60015 4624
Phone: (847) 948 2000
Fax: (847) 948 3642

33 Presentation notes of Alex Gorsky Ethicon Company Group Chairman – December 2007

Section 11 Appendix F – process flow diagram for pTH (barium salt)



Section 12 Appendix G – participants in the Hb supply chain

12.1 Bovogen Biologicals Pty Ltd-Australia www.bovogen.com

Bovogen Biologicals Pty Ltd is an Australian privately owned company located in Melbourne. Bovogen manufacture and supplied bovine Haemoglobin powder in premium grade in pack size 500-1000kg. Bovogen's bovine haemoglobin has been approved for human consumption and manufacture from the blood of 100% Australian cows.

Bovogen continues to build and innovate by expansion of business opportunities such as the formation of Biovine Biologicals with focus on the development and supply of ovine proteins and related products for the life science industries.

Bovogen Biologicals Pty Ltd
71 Ogilvie St, Essendon Vic
Phone: +613 9336-3622
Fax: +613 9336 3644
info@bovogen.com

12.2 APC Inc www.americanprotein.com

Since 1981, American Protein Corporation (APC) has been recognized as the global leader in plasma protein fractionation and applications research for feed and industrial use. APC is an LGI company which is in the same group as Proliant Inc. Both companies have very similar raw product ingredients that are formulated and registered from different market. APC targets the animal feed market with their range of plasma products and Proliant Inc targets the technical and function and dietary supplements for human consumption. APC has two product derived from haemoglobin AP301, used in animal feed and AP720, used as an ingredient in pet food.

APC, Inc.
2425 SE Oak Tree Court
Ankeny, IA 50021
Phone: 800-513-8755 / 515-289-7600
Fax: 515-289-4360
Email: info@functionalproteins.com

12.3 Proliant Meat Ingredients http://eu.proliantmeatingredients.com/en/

Proliant Meat Ingredients, formed in 1981, is part of a global family of privately-held companies owned by the Lauridsen Group, Inc. (LGI). Today, Proliant Meat Ingredients, is a global leader in the manufacture of a range of products for the meat, savoury and prepared food markets which includes stock, broths, flavours, fats and functional proteins.

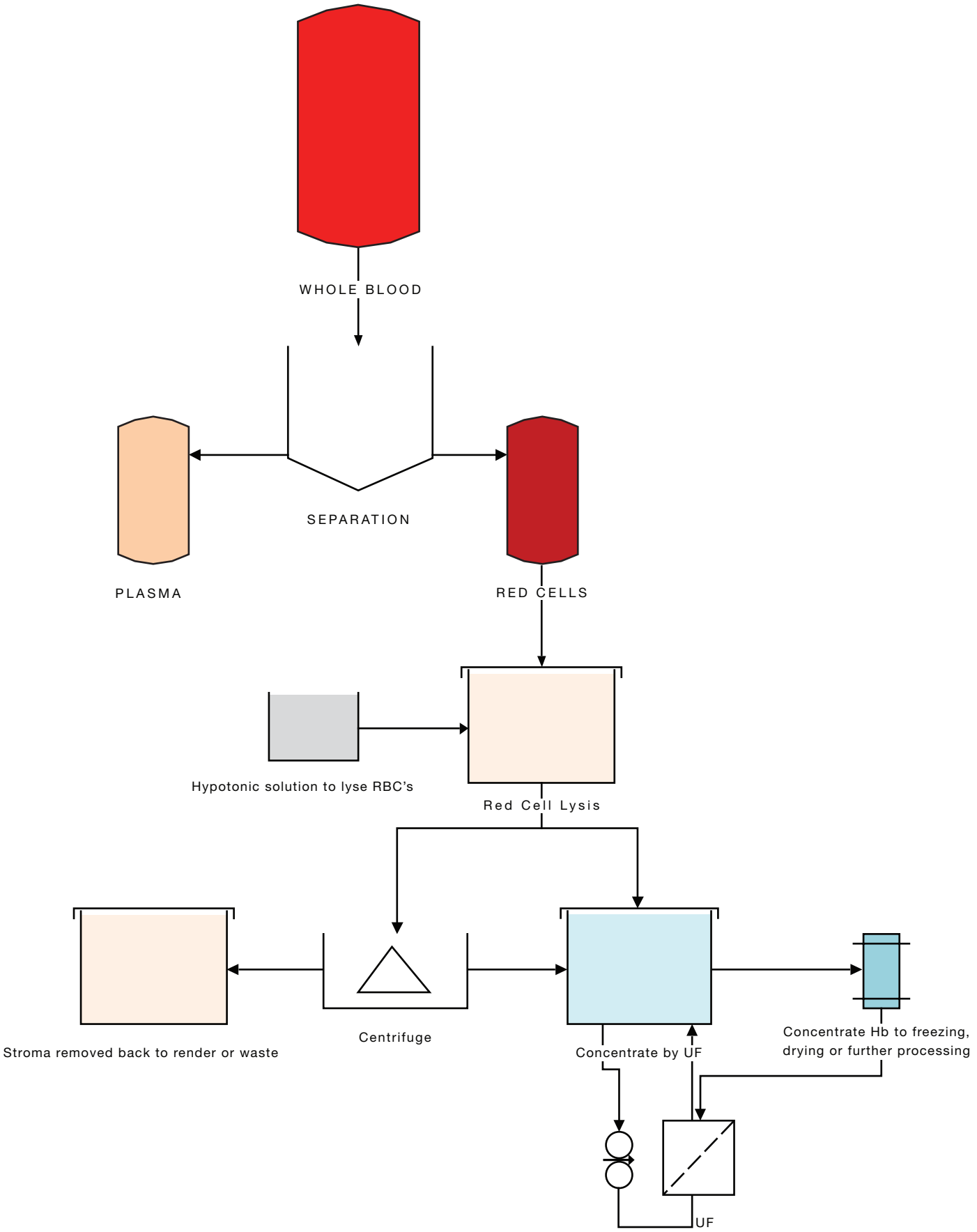
Specializing in the development and production of ingredients for animal and human health and nutrition, LGI has formed a global presence in a number of markets and industries. Proliant Meat Ingredients' sister companies include APC, Inc., BHJ (Denmark), the Boyer Valley Company, Proliant Biologicals, Proliant Dairy Ingredients and Proliant Health Ingredients.

Proliant's is marketing a product under the brand AprFER 1000 a heme iron concentrate for use as a iron supplement for oral administration in dietary supplement, food or beverages.

U.S. Office
2425 SE Oak Tree Court
Ankeny, IA 50021 USA
Phone (Toll Free): 800.466.7317
Phone: 515.289.5100
Fax: 515.289.5110

Europe Office
Polígono Industrial Congost
Adva. San Julián, 246-258
08403 – Granollers, Spain
Phone: +34 93 861 52 87
Fax: +34 93 849 59 83

Section 13 Appendix H – process flow diagram for Hb



Meat & Livestock Australia

Level 1, 165 Walker Street, North Sydney NSW 2060
Postal address: Locked Bag 991, North Sydney NSW 2059

Phone: 02 9463 9333
Fax: 02 9463 9393
Email: info@mla.com.au

MEAT & LIVESTOCK AUSTRALIA