



final report

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Value chain models for the 'top five' bioactives

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SUMMARY¹

This report describes the findings and recommendations of a project carried out for MLA by Occum Enterprises Pty Ltd from June 2011 to February 2012. As described in the research agreement between the two organisations, the objectives of the project were to:

- Perform a detailed analysis of the domestic and international markets for the top four blood derived bioactives (BSA, haemoglobin, IgG, and prothrombin) and chondroitin sulphate (CS) derived from beef cattle processing;
- Determine the proportion of the total global market (volume and value) of each of the five bioactives that could be satisfied by the Australian red meat bioactives industry (in terms of raw material available);
- Perform analysis around selected product market segments and processes, mapping out the selected value chains and quantifying the value add created during that process;
- Determine what value is added along the supply chain – qualitatively and financially;
- Identify global and local companies involved in the supply chain (where possible); and
- Carry out a SWOT analysis.

These objectives have been accomplished, and the results are presented here, although for the sake of logical flow the objectives are presented in this report in a different order than in the research agreement.

MLA has sponsored considerable previous research on red-meat based bioactives. This report builds on that base and adds to it by including more recent estimates of market sizes, prices, and other data, and more importantly by describing the dramatic rise of China and India as global competitors in some bioactives markets. In addition, this report includes information gained from more than 20 interviews and site visits with active participants in the Australian and New Zealand bioactives sectors. The report thus combines quantitative and qualitative information in describing the current situation and in making recommendations for the future.

This report is structured somewhat differently than previous reports, based on the observation that from an industrial economics perspective the blood-based bioactives are quite similar to each other, and as a group quite different to CS. The table on the next page describes the bases for this observation. The report therefore considers CS separately, and the four blood-based bioactives as a group, although separate market information is provided for each of the four.

Overall, the report concludes that CS is unlikely to be manufactured in Australia without support from MLA, governments, or other outside organisations. Overseas manufacturing, particularly in China, has a very large cost advantage due to efficiencies of scale and lower labour costs, and while there is much talk about market niches for CS from BSE-free sources, there is little evidence for the current existence or future viability of such niches. On the other hand, blood-based bioactives are likely to continue to be manufactured in Australia, perhaps in larger volumes than at present, based on the ability of Australian bioactives companies to identify local markets and other quality-sensitive niches for their products. However, it is important to note that the *specific* blood-based bioactives studied in this report may not continue to be the mainstay of Australian production. There are already recombinant forms of BSA on the market, for example, and the FDA has shown concern about the use of bovine-based prothrombin in medical devices no matter what the country of origin. In order to prosper over the long term, bioactives companies, like all science-based organisations, must have an eye on the future needs of the market and the ways in which they can respond to, and ideally even anticipate, those needs.

¹ For ease of reading, this section is presented without footnotes. Findings and recommendations are described in detail in the body of the report, and references are provided there as well.

Comparison of blood-based bioactives and chondroitin sulphate

Factor	Blood-based bioactives	CS
Raw material	Bovine blood is the largest source by volume; blood from other mammals can be used to produce the same products, but blood from different species is not mixed	Bovine tissue is an important source, but tissue from other mammals, and from birds, fish, and molluscs, can also be used, and raw materials from different sources can be mixed together
Global manufacturing	Includes some large companies in US, Europe, China, and South America, but many smaller, privately-held companies as well; factories can often produce multiple bioactives	Volume predominantly from very large factories in China and large factories in India, Europe, and South America; factories are dedicated to CS production
Australian manufacturing	A number of small players, some well-established and others newer, all highly entrepreneurial, most exporting at least part of their production, many looking for new bioactives opportunities	None
Product form	Generally fluid, requiring refrigeration and other special handling; limited storage lifetime and expensive to ship	Dry powder, easy to store and easy to ship
Intermediate buyer	Typically either a research-based organisation that will consume the product in its own processes, or a device or diagnostic manufacturer that will incorporate the bioactive into its own products.	Typically a nutraceutical manufacturer who combines CS with other ingredients, forms the mixture into tablets, and bottles the result.
Intermediate buying factors	Quality (bioactive is typically a very small proportion of the cost of the final product); traceability (for devices and diagnostics); price (for some research uses)	Price, quality (for some buyers)
End-user buyer	Generally an organisation, buying a technical product that is tightly specified, including the origin and quality of materials used	Generally a consumer, buying a nutraceutical product of unproven efficacy and often containing ingredients of unknown origin
End-user buying factors	Quality, reliability, availability	Brand, retail recommendation, and price (order will differ from buyer to buyer)

Given this situation, the recommendations for MLA include working with the Australian red-meat based bioactives industry both to promote existing products and to develop new products. MLA has already had some success with the latter, and there are precedents for the former in the broader biotechnology sector. It is acknowledged that these recommendations are different in approach to those in previous reports, which typically focussed on working directly with abattoirs. The findings of this report, particularly the interviews and visits to abattoirs and bioactives manufacturing facilities, lead to the proposition that, although very little value is currently being extracted by abattoirs within the bioactive supply chain, it is unlikely that any Australian abattoir will enter directly into bioactives manufacturing. The less direct, but arguably more promising, path proposed here is to work with intermediaries, on the basis that their success will lead to success for the abattoirs and thus for Australian producers as well.

PRODUCT END USE APPLICATIONS

The following tables outline the range of applications for each of the top five bioactives along with sample uses and end user companies.

Chondroitin Sulphate (not necessarily bovine source)

Use	Why used	End-user Companies	Australian end-user companies
Nutraceutical – humans	Joint pain	Cenovis (US), GNC (US)	Blackmores, Herron Pharmaceuticals
Nutraceutical – animals	Joint pain	Innovet (Italy), Nutri-Vet (US), Ceva Santé Animale (France), Natura Pet Products (US, owned by Procter & Gamble)	Biocel Australia, Technyflex, Vetalogica, Eukanuba Australia
Cosmetic	Skin conditioning	L’Oreal (global), Avon (global)	Paula’s Choice

BSA

Use	Why used	End-user Companies	Australian end-user companies
Animal feed – fish, shellfish, swine, poultry, ruminants	Source of protein	APC (US)	None found
Pet food	Colouring agent	APC (US)	Cool Off (NSW) (intermediary selling to Pet Food manufacturers)
Research	Tissue growth medium and other applications	Proliant (US), Akron Biotech (US)	Serana (WA), Bovogen (Vic)
Vaccines	Large scale cell culture	Vaccine manufacturers	CSL

Haemoglobin

Use	Why Used	End-user Companies	Australian end-user companies
Animal feed – fish, shellfish, swine, poultry, ruminants	Source of protein	Veos (Belgium), APC (US)	None found
Pet food	Colouring agent	Wecia SA (Argentina), Veos (Belgium), VION (Holland)	Cool Off (NSW) (intermediary selling to Pet Food manufacturers)
Laboratory	Microbiological culture media	Neogen (US), Becton, Dickinson (US), Sigma Aldrich (Switzerland)	None found
Nutraceutical	Supplement for iron deficiency	Colorado Biolabs (US), Sunmoon Biotech (China)	None found

IgG

Use	Why Used	End-User Companies	Australian end-user companies
Food ingredient	Nutritional supplement	NOW Foods (US)	None found
Laboratory	Widely used as a reagent in diagnostic testing in humans and animals	Zymogenetics (US), Agrisera (Sweden), Fitzgerald Industries (US), Equitech Bio (US), Sigma Aldrich (global)	None found
Veterinary	Nutritional supplement, especially for beef and dairy cattle	APC (US)	None found

Prothrombin

Use	Why Used	End-User Companies	Australian end-user companies
Treatment after surgery or trauma	Wound sealant – stops blood oozing	King Pharmaceuticals (now part of Pfizer), Pfizer, Gen Trac	None found (for bovine-sourced prothrombin)
Coagulation diagnostic	Test for diagnosing bleeding disorders	Grifols (Spain), MP Biomedicals (US)	None found (for bovine-sourced prothrombin)

INDUSTRY ANALYSES

Chondroitin Sulphate industry analysis

- **Estimated market²**

Use	Global demand (T)	Australian price (per kg)
Nutraceutical (human)	Around 4,000	At retail, \$100-\$300/kg and around \$1,000/kg for BSE free
Cosmetic	unknown ³	unknown
Pet and racing animal nutraceutical	1,750	\$20 - \$170 (imported from China)
Total	4,750 – 5,000 T	

- **Demand conditions.** Demand for chondroitin sulphate (CS) has slowed. Recent reports have questioned the efficacy of CS as a pain relief treatment (generally combined with glucosamine) for arthritis, both in humans and in animals. For example, the Glucosamine/chondroitin Arthritis Intervention Trial (GAIT) study showed no difference over two years between treatment with glucosamine and chondroitin sulphate (CS), alone or in combination, and treatment with a placebo.⁴ In animals, the best study done to state similarly shows no effect of glucosamine and CS on dogs with osteoarthritis.⁵ The lack of efficacy data does not, of course, mean that people will stop buying CS, but it does open the door for alternatives to take its place in the treatment of arthritic pain, and raise questions about future growth rates.
- **Structure.** Chinese companies dominate the manufacture of chondroitin sulphate. Some manufacture exists in Spain (Bioiberica) and Argentina (Inter Farma), but an estimated 85% – 90% of the CS sold for human consumption is produced in China. Some Chinese-manufactured CS is

² *Bioactive opportunities for the Australian red meat industry* (MLA, January 2011) and Source One <http://www.source-1-global.com> Market information for 2007 unless otherwise noted.

³ Chondroitin sulphate is used in a wide range of cosmetics, including hair and skin conditioners. However, the amount used is generally very small. For example, Derma Silk Miracle Cream is sold in 0.5 fluid ounce bottles for about US\$35 retail. Chondroitin sulphate is 27th on the list, in order of volume, of the 43 ingredients in this product. This usage pattern makes it quite difficult to estimate the amount of CS used in cosmetics applications, but it would be reasonable to assume that this amount is very small in comparison to the nutraceutical applications.

⁴ Sawitze AD et al, "Clinical efficacy and safety of glucosamine, chondroitin sulphate, their combination, celecoxib or placebo taken to treat osteoarthritis of the knee: 2-year results from GAIT", *Ann Rheum Dis*. 2010 Aug; 69(8):1459-64.

⁵ Aragon CL et al, "Systematic review of clinical trials of treatments for osteoarthritis in dogs", *J Am Vet Med Assoc*. 2007 Feb 15; 230(4):514-21.

labelled as produced from Australian-source material; anecdotally, much of the product so labelled is in fact produced from Chinese material and in addition is sometimes adulterated with caregenan, maltodextrin, or other ingredients. Some suppliers, for example Source One in America, offer complete traceability, but the bulk of the market seems unconcerned about the source of the CS it consumes or the conditions under which that CS was produced. We were not able to locate any CS end products (as opposed to raw CS to be used as an ingredient) that are advertised as being sourced from NZ or Australia. Field trips to three shops specialising in nutritional supplements revealed that CS/glucosamine tablets are typically not labelled with regard to country of origin, and nor are staff generally aware of the source of the material.

There are currently no known manufacturers of CS in Australia. In New Zealand, NZ Pharmaceuticals Ltd⁶ oversee quality control of the manufacture of CS, but the actual manufacturing happens in China. In the US, Chinese imports dominate the market but some US manufacturing still takes place. Sioux Pharm Inc’s chondroitin sulfate (Chondropure™), US manufactured, is the only chondroitin with a Drug Master File registered with the FDA⁷. Pure Bulk⁸ also offer US-manufactured CS (\$93/kg), as well as China-manufactured CS (\$178/kg); the source of the raw material is not disclosed. Indian CS manufacturers, for example Bayir Chemicals⁹, are emerging as major players. In Australia, Bio Active Pharmaceuticals Australia (BAPA), founded in Cootamundra NSW, was planning to manufacture CS in Australia, but appears to have given up on this plan. Cartilage from Australia is being purchased by European companies and shipped to Asia and Europe to be made into CS. South American sourced and manufactured CS dominates the vet market.

- **Major companies.** Among the largest manufacturers of Chondroitin Sulphate are CAMB (Hong Kong) Company Limited (China)¹⁰, Yantai Kangde Biochemical Products (China), Inter Farma (Argentina), and Bioiberica (Spain).

Prices and Performance. As noted in the table above, prices vary significantly depending on the quality and intended end-use application. It must also be noted that there are significant issues with mislabelling and adulteration of CS products. For example, one source notes, “Low-cost chondroitin products ... seem to contain little chondroitin, but some higher-priced products may

⁶ www.nzp.co.nz

⁷ www.siouxpharm.com

⁸ www.purebulk.com

⁹ http://www.bayirextracts.com/bayir_chemicals.html

¹⁰ This company claims to have built a cGMP CS plant of 700T capacity in China in 2008. <http://www.cambhk.com/product.asp?id=162&sortpath=0,109>, visited 2 January 2012.

also contain less chondroitin than claimed.”¹¹ These issues make comparisons across uses and countries problematic. However, for the sake of this analysis, we will assume that raw material is sourced in Australia and is converted into CS for human or animal use. To begin, we note that bovine trachea sell for about \$0.70 per kg.¹² Conversion processes struggle to achieve a 4% yield, but if we optimistically assume 4% then 25 kg of trachea are required to make 1kg of CS. That is, the CS manufacturer pays \$17.50 for the raw material required to produce 1kg of CS, plus reagents, labour, and overheads. These additional costs are estimated to be at least \$7/kg, giving a total direct cost of \$24.50 per kg.¹³ “Medicine grade” CS is available from Chinese manufacturers for as little as \$10 kg in large quantities,¹⁴ and from cGMP manufacturers for \$60/kg.¹⁵ Bulk CS is then formulated, almost always with glucosamine and often with other ingredients as well, and sold in tablet form to arthritis sufferers, body builders, pet owners, and others concerned about joint pain. There are some pure CS consumer products on the market; one such is from Source Naturals. A bottle of 120 tablets, each containing 600mg of CS, has a suggested retail price of \$37.50 and can be found on the internet for \$20.81¹⁶. The source of the CS is not disclosed. Assuming a wholesale price of \$20, this equates to \$280 per kilogram of CS. These rough numbers suggest that bovine trachea purchased for \$17.50 could be converted into CS tablets worth \$280 at wholesale; obviously there are many additional costs along the way. We did find evidence of higher prices being charged for CS advertised as BSE-free but it is not clear how much of this type of CS is being sold.

The question of how much revenue and profit are obtained from the production and sale of CS is a difficult one. Even restricting the question to the first step in the chain – the conversion of bovine trachea into bulk CS – still requires dealing with the dearth of information from companies that are privately held or the highly aggregated information from public companies that are so diversified that identifying results from CS alone becomes impossible. The Value Chain Analysis section below addresses this issue.

- **Buying factors.** The human CS market does not yet appear to be particularly discerning with respect to the source and quality of tablet form CS (whether alone or in combination with

¹¹ <http://www.webmd.com/vitamins-supplements/ingredientmono-744-Chondroitin%20%28CHONDROITIN%20SULFATE%29.aspx?activeIngredientId=744&activeIngredientName=Chondroitin%20%28CHONDROITIN%20SULFATE%29> visited 11 December 2011

¹² Interview with Dean Schiller, Fayman International. All figures are in Australian dollars.

¹³ Interview with Dean Schiller. This assumes a factory capable of producing a minimum of 20T of CS per year.

¹⁴ http://www.alibaba.com/product-gs/450865518/Chondroitin_Sulfate.html?s=p visited 11 December 2011

¹⁵ http://www.alibaba.com/product-gs/491810478/GMP_Factory_Chondroitin_Sulfate_95_Min.html visited 11 December 2011

¹⁶ http://www.luckyvitamin.com/p-19045-source-naturals-chondroitin-sulfate-600-mg-120-tablets?utm_source=sortprice&utm_medium=frl&utm_term=SourceNaturalsChondroitinSulfate600mg120Tablets&utm_content=68159&utm_campaign=sortprice&site=www.sortprice.com& visited 11 December 2011

glucosamine). For example, the website of the “Arthritis and Glucosamine Information Center” lists and evaluates many products containing chondroitin sulphate, but does not include the country of origin of the raw material as a purchasing criterion.¹⁷ Price is the major buying factor in this market. For example, Puritan’s Pride, a large on-line seller of nutritional products, offers many variations of chondroitin sulphate, but focuses on price without mention of country of origin.¹⁸ Some customers are reportedly concerned with the sustainability of CS sourced from shark cartilage, and thus have a preference for bovine-sourced products.

The veterinary market is claimed to be more careful with respect to product quality, with some manufacturers said to be paying a premium for CS from known BSE-free countries and traceable suppliers, but there is no solid evidence for this. Indeed, an Internet search found numerous veterinary products containing CS, almost none of which revealed the source of the material or made any statement about BSE. The only exception was a product containing CS made from New Zealand green-lipped mussels, which was significantly less expensive than the competing products. As noted above, there is significant uncertainty in the veterinary market about the overall effectiveness of CS in any form, a typical comment being “The benefits of chondroitin are much less clear [than the benefits of glucosamine]. It is a large molecule and poorly absorbed when taken by mouth. Most glucosamine and chondroitin formulas are probably useful only because of the glucosamine.”¹⁹

- **Role for Australian companies.** It is not clear whether Australian companies can compete in the market for CS given the very large price differential between Australian and Chinese manufacturing conditions. Certainly, attempts to do so to date have been unsuccessful. BAPA was established with a view to manufacturing CS in Australia, but has not yet commenced commercial production and may never do so. This situation would appear to offer rich opportunities for learning about the realities of the opportunity for CS production in Australia. Peter Riikonen, General Manager, New Products Development (Brisbane), has been trying to improve the extraction process for CS (scientific work done by Research Directions), but is having difficulty sourcing sufficient material to run a minimum-scale plant (20 T annual capacity) at an economically viable price. Peter believes that there would be ready markets for both human and vet CS produced from Australian material, but this has not been tested in any meaningful way. A telephone interview with a major manufacturer and distributor of natural health products revealed that there is very little perceived consumer interest in, or concern about, the source of raw materials used in chondroitin sulphate. This company is therefore unlikely to pay any significant price premium for bovine raw material

¹⁷ <http://www.glucosamine-arthritis.org/glucosamine/glucosamine-product-guide.html> visited 7 December 2011

¹⁸ <http://www.puritanspride.com.au> visited 7 December 2011

¹⁹ <http://www.placervillevet.com> visited 7 December 2011

from BSE-free countries. They believe that the situation in the veterinary market is very much the same – no consumer concern, and therefore no premium. The absence of any demonstrable premium for any CS product in any market must be kept in mind in considering the opportunities listed below.

Some possible opportunities do appear to exist, but need further investigation:

1. CSIRO has developed and commercialised cost-effective advanced separation technologies such as simulated moving bed chromatography and membrane technology in dairy applications at Murray Goulburn Cooperative Co. These technologies represents non-organic solvent based manufacturing processes that are safe and may provide a lower cost base, but further investment in scaling up and validating the technology for bovine products is needed. CSIRO has developed applications of these new technologies for separation of bioactives such as glycosaminoglycans (e.g., dermatan sulphate and chondroitin sulphate), but the economics of applying this technology to chondroitin sulphate at larger scale needs further investigation.

2. Supply of the vet market represents a possible opportunity for an Australian CS manufacturer. According to some anecdotal reports, which could not be verified, this market may be willing to pay a higher market price for BSE-free CS. Inter Farma, for example, is branding its Argentinian bovine-sourced chondroitin sulphate as Dynatin CS, and is marketing it on the dual platforms of US Pharmacopoeia certification and hailing from a BSE-free country.²⁰ It should be noted, however, that Inter Farma is an ingredient producer, not an end product producer, and that no end product that claimed to include Dynatin CS could be located. Inter Farma has abandoned the Dynatin CS trademark in the United States,²¹ suggesting that it did not find much value in promoting an ingredient based on BSE-free sourcing and USP certification. No data could be located on the price of Dynatin CS relative to other CS.

3. An emerging trend in nutraceutical markets appears to be the marketing and branding of higher quality ingredients. For example, Blackmores have begun advertising high quality liquid fish oil. The advertising behind this product suggests both a higher dose but also higher quality through an improved purification process. Wellnessnetworks.net offers a

²⁰ <http://www.inter-farma.com/dynatin.htm> visited 2 January 2012

²¹ <http://tarr.uspto.gov/servlet/tarr?regser=serial&entry=77057469> viewed 2 January 2012

BSE free CS capsule for humans, manufactured by the US company Karuna, at a retail price that works out to US\$867/kg for the CS content.²² The same website offers CS from PhysioLogics, source unstated, for the equivalent of US\$700/kg; from Douglas Laboratories, “bovine source” CS for US\$1,100/kg; and from Vital Nutrients, source unstated, for US\$900/kg. CS tablets can be obtained inexpensively; 120 tablets containing 600mg of CS each, source unstated but said to be manufactured in GMP conditions, can be gotten for the CS content equivalent of US\$310/kg.²³ However, there is typically great variation in price across a given website or retail outlet, and the four examples given above suggest that BSE-free sourcing does not always lead to higher prices. Visits to three retail nutritional supplement stores in a Melbourne suburb suggested that staff are generally unaware of the source of the CS that they are selling, and are sometimes mystified by questions about the source. So while the marketplace may be starting to become more aware of the importance of knowing the source and the quality of nutraceuticals in general, and while poor quality products and inadequate testing procedures for CS coming out of China have been reported recently²⁴, the market may not be ready to support a premium for BSE-free sourcing.

4. Collagen type II is a by-product of CS manufacture. In recent trials collagen type II had a significant impact on arthritic conditions²⁵, and is also reportedly a successful anti-ageing nutraceutical. This product may represent a potential growth area for Australian companies. Retail prices for collagen type II in capsule form are in the range of A\$1,000/kg. However, as with CS, collagen type II is readily available from Chinese sources at low prices, and the market does not appear to be particularly discerning with regard to the source of the material.

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http://www.karunahealth.com/index.php?page=shop.product_details&flypage=KARUNA_flypage.tpl&product_id=89&category_id=15&option=com_virtuemart&Itemid=60 visited 7 December 2011. Price of US\$20.80 for a bottle of 60 tablets, each containing 400 mg of CS from BSE-free sources, taken from <http://www.wellnessworks.net/page/WW/CTGY/KAR> visited 2 January 2012; all other prices are from this same website, and product information is from the manufacturers’ websites.

²³ <http://www.evitamins.com/chondroitin-sulfate-600-m-now-9021> visited 2 January 2012

²⁴ Chondroitin remains one the ‘most adulterated supplements in the market’, Elaine Watson, Nutraingredients-usa.com, April 19, 2011

²⁵ Crowley, Lau et al, “Safety and efficacy of undenatured type II collagen in the treatment of osteoarthritis of the knee: a clinical trial”, *Int J Med Sci* 2009; 6:312-321

Blood products industry analysis

This analysis includes all four blood-derived bioactives – BSA, Haemoglobin, IgG, and Prothrombin. While end product markets can be different, many manufacturers have the capability to produce most or all of the four listed bioactives, and can switch among them to respond to market conditions. It therefore makes sense to analyse the four blood-derived bioactives together.

▪ Estimated markets

Estimated global annual sales in millions of Australian dollars²⁶

Use	BSA	Haemoglobin	IgG	Prothrombin
Total	190	40	50	50

- **Demand conditions.** Demand for BSA and the other blood-derived bioactives studied is expected to increase at rates of less than 5% p.a. in all markets (research, pharmaceuticals, food ingredient, and supplement). This is consistent with the growth rate of a major US player – SeraCare. The company’s revenues (for all products) increased at 4% p.a. from \$48 million in 2008 to just over \$50 million in 2010²⁷. In some cases, the US FDA is actively discouraging the use of bovine sourced material²⁸. Some new markets however for the products are emerging. For example, bovine sourced IgG is included in nutritional supplements such as Immune Advantage (NOW Foods), ImmunoLin (GNC), ImmunoSmart (NutraSense), and others based on a product from Proliant that has received a Generally Recognised as Safe (GRAS) rating from the FDA²⁹.
- **Structure.** In Australia, a number of small manufacturers produce blood-related technical products. These include AusgeneX (Brisbane), Bovogen (Victoria), Maverick Biosciences (NSW), Moregate (Queensland), Selborne Biological Services (Tasmania), and Serana (Bunbury WA).
- **Major companies.** SeraCare is one of the major US manufacturers and distributors of BSA and related blood products for diagnostic and research uses. APC Inc, part of The Lauridsen Group (LGI), is a privately-owned company based in Iowa that manufactures products based on bovine blood (<http://www.functionalproteins.com>). Proliant Biologicals, also a part of LGI with operations in

²⁶ Sources: CSIRO, MLA, Occum judgement

²⁷ However, SeraCare’s revenues fell to \$43.5 million in 2011, and its shares have significantly underperformed both the NASDAQ as a whole and the NASDAQ Biotechnology Index.

²⁸ For example, the FDA has had extended interaction with King Pharmaceuticals (now owned by Pfizer) about the labelling and marketing of its product THROMBIN-JMI, which is used to control bleeding during and after surgery but has caused severe bleeding and thrombosis in patients who have antibodies against bovine thrombin.

²⁹ <http://www.immunolin.com/article.aspx?id=1&ImmunoLin+Receives+GRAS+Recognition> visited 20 December 2011. Proliant says that its product is produced in cGMP facilities but makes no statement about the source of the material used.

Iowa and Spain, is another major US manufacturer of BSA and blood related products for the diagnostic, life science research, biopharmaceutical, and veterinary vaccine industries with reported sales of between US\$20 million and US\$50 million in 2010³⁰. Akron Biotech, based in Boca Raton Florida, manufactures BSA and other products for use in tissue growth media, vaccine production, and diagnostics. In China, a number of manufacturers exist including Sinopharm Chemical Reagent Company and Jinan Great Chemical Industry Company. Shanghai Genon Biotech Company Limited manufacture haemoglobin for animal feed markets. In India, MP Bio manufacture BSA, IgG, and thrombin. These large manufacturers effectively dominate the global blood products industry.

- **Prices and Performance.** Companies that compete in this space generally report significant gross margins. Sigma-Aldrich operated in 2010 with a 52.7% gross margin and a 24.2% operating margin. SeraCare operated in 2010 with a 41.2% gross margin and a 13% operating margin. Life Technologies had revenues of US\$3.3b in 2010 with a gross margin of 66.3% and an operating margin of 26.6%. There is evidence of consolidation in the sector. For example, Invitrogen purchased Life Technologies in November 2008, Merck purchased Millipore in July 2010, and Pfizer purchased King Pharmaceuticals in March 2011.

Prices can vary significantly depending on the quality and end-use application. Food ingredient prices are generally lower than research grade which in turn are lower than technical grade prices.

BSA

Application	Product	Price/kg	Source
Research	BSA powder pH7	US\$325	Equitech Bio
Research	BSA reagent grade	US\$450	Equitech Bio
Pharmaceutical	BSA Fraction V	US\$578	Equitech Bio ³¹

³⁰ www.manta.com www.proliantinc.com

³¹ <https://www.equitech-bio.com/Fraction-V-30-BSA-solution.html?mode=add&page=> visited 19 December 2011 for all three products. BSA is of US origin.

Haemoglobin (bovine source)

Application	Product	Price	Source
Nutraceutical	Proferrin ES®	US\$54.75 for 90 tablets, each containing 12mg of elemental iron	Colorado Biolabs ³²
Research	Haemoglobin	US\$51 for 1g	Sigma Aldrich ³³

IgG (bovine source)

Application	Product	Price	Source
Nutraceutical	Immune Advantage (Now Foods)	US\$4,800/kg ³⁴	www.healthsuperstore.com
Research	Reagent grade	A\$433 for 100g	Sigma Aldrich ³⁵
Research	Technical grade	A\$201 for 100g	Sigma Aldrich

ProThrombin (bovine source)

Application	Product	Price/kg	Source
Wound sealant	THROMBIN-JMI®	US\$82 for 5,000 IU ³⁶	Pfizer
Coagulation diagnostic	DG-TT	unavailable	Grifols

- **Buying factors.** BSE free sources of BSA and other blood products are said to be attractive to customers, as are lower contaminant levels. However, it is more difficult to demonstrate a premium for source than for purity; some customers are clearly willing to pay higher prices for products with greater purity, but it is not easy to identify customers who are willing to pay more simply for Australian sourced material. The market however does recognise that Australian-sourced material will in general have lower contaminant levels and thus should be willing to pay a premium assuming other factors (e.g reliability and consistency of supply) are equal.

³² <https://www.proferrin.com/proferrin-es.php> visited 19 December 2011

³³

http://www.sigmaaldrich.com/catalog/ProductDetail.do?D7=0&N5=SEARCH_CONCAT_PNO%7CBRAND_KEY&N4=H2500%7CSIGMA&N25=0&QS=ON&F=SPEC visited 6 January 2012

³⁴ Based on US\$8.27 for 90 tablets with 180mg IgG per tablet

³⁵

http://www.sigmaaldrich.com/catalog/Lookup.do?N5=All&N3=mode+matchpartialmax&N4=IgG&D7=0&D10=IgG&N1=S_ID&ST=RS&N25=0&F=PR visited 19 December 2011 (for both products)

³⁶ http://healthcare.utah.edu/pharmacy/bulletins/NDB_156.pdf visited 19 December 2011

- **Role for Australian companies.** There is said to be a definite perceived advantage in the pharmaceutical and research sector to sourcing Australian blood derived bioactives, but as noted above this advantage is difficult to demonstrate, and in some cases products from New Zealand are said to be at least as good as those from Australia. In the pharmaceutical space, if a bioactive product is used in trials, and the drug gets approval and becomes successful, this can mean significant demand for the bioactive from the same supplier. Prices achieved whilst in trial phase however may not be high as this stage of the market is more price sensitive. Ways to further support, promote and stimulate blood-derived bioactives are contained in the recommendations section below.

PROPORTION OF GLOBAL DEMAND THAT AUSTRALIA COULD SATISFY

This section presents the results of an analysis that is based on many assumptions, both about the sizes of global markets and about the amount of raw material available in Australia³⁷. In addition, the analysis does not consider cost, quality, existing supply relationships, or any of the other factors that may influence a decision to purchase from a particular source. It does, however, provide a basis for understanding the potential role of Australia in manufacturing various bioactives.

Bioactive	Number of known current manufacturers in Australia (from bovine sources)	Global Market (T)	Tonnes Australia could produce	Proportion that Australia could supply
CS	0	4,000	216	5%
BSA	6	770	240	31%
Haemoglobin	3	2	3	>100%
IgG	3	55	501	>100%
Prothrombin	2	10	1,001	>100%

The proportion that could be supplied is calculated on the assumption that ALL tissue or blood from cattle slaughtered in Australia is used to produce the given bioactive.

The spreadsheet used to produce the following results will be provided to MLA in electronic form. It contains references for the many assumptions required to calculate the proportions in the table. The table is done on a volume basis; additional assumptions would be required to calculate proportions on a dollar basis, and the results of the calculations would be difficult to interpret. For example, the estimated global market for BSA consists of BSA sold for technical and diagnostic use (200 tonnes) and BSA sold for other uses (500 tonnes). Clearly the former carries a higher price than the latter. It could be assumed that Australian-produced BSA would all sell at the higher price, but there is little justification for this assumption.

³⁷ These assumptions include the number of animals slaughtered, the proportion slaughtered by traditional methods and by halal methods, the average weight of the animals and the average amount of blood recovered in the two slaughtering techniques, the amount of bioactive in the blood, and so on. All of these assumptions can be changed in the model.

SWOT ANALYSIS

A SWOT analysis is typically done for a given organisation or industry, recognising that the latter must be carried out at a higher level of abstraction than the former. In the case of the top five bioactives, it is appropriate to carry out two analyses, one for the (potential) bovine tissue-based CS industry in Australia, and the other for the bovine blood-based bioactives industry. The latter analysis is not limited to the four blood-based bioactives that are considered in detail in this report.

Bovine tissue-based Chondroitin Sulphate

Strengths

- The industry does not currently exist in Australia. See “Opportunities” below

Weaknesses

- History of lack of success (BAPA and others) would have to be overcome
- Bovine source not considered particularly safe compared to fish and molluscs³⁸
- Consistency of Australian-sourced trachea supply is reportedly an issue for potential manufacturers, with a reluctance among suppliers to establish contracts longer than one year.

Opportunities

- A vertically-integrated company based on Australian ingredients, quality certified and from a BSE-free country, might be created, including a consumer brand. Significant capital would be needed.
- CSIRO-developed separation technologies could be applied to improve yields and reduce costs for CS from bovine trachea.
- An increase in awareness of the importance of quality and source of nutraceutical ingredients may improve the market for Australian-sourced and manufactured CS.

Threats

- Market demand for “quality” CS may be scattered geographically and low overall
- Allegations of widespread product counterfeiting and document forgery with regard to CS may cause the public to lose confidence in veracity of claims to “quality”
- Continued research finding no evidence for the effectiveness of CS may penetrate the public’s consciousness, reducing demand for CS regardless of quality
- The next miracle substance may be discovered, pushing CS down into the ruck of vitamins, minerals, and other supplements contending for the consumer’s attention and pocketbook

Bovine blood-based bioactives

Strengths

- The presence of a number of well-established, apparently successful firms
- Success at developing new products and new markets
- Some “success stories” in collaboration between intermediaries and abattoirs (but not all of the experiences have been successful)

³⁸ ‘There is some concern about the safety of chondroitin sulfate because it comes from animal sources. Some people are worried that unsafe manufacturing practices might lead to contamination of chondroitin products with diseased animal tissues, including those that might transmit bovine spongiform encephalopathy (mad cow disease).’ Sourced from the NIH’s Medline Plus (<http://www.nlm.nih.gov/medlineplus/druginfo/natural/744.html>)

- “Clean, green” image of Australia among customers for blood products (but New Zealand’s image is apparently better)³⁹
- Ability to trace final product to the farm and animal level

Weaknesses

- Existing companies are small and typically lack resources for product development
- The major markets are overseas, and it is expensive and time-consuming to explore them
- Shipping and customs issues are prevalent
- Move to halal slaughter is reducing quantity and quality of available blood
- A number of companies have left the industry, and a number of abattoirs have stopped collecting blood, even after investing substantial amounts in blood collection equipment. This does not encourage other abattoirs to consider blood collection.

Opportunities

- Companies could, perhaps in partnership with universities or CSIRO, develop new bioactives and new ways of manufacturing existing bioactives
- MLA, State governments, and other organisations could support the creation and promotion of a “clean, green” brand for Australian blood-based bioactives
- CSIRO separation technologies could be leveraged to extract bioactives from blood
- Expected future food shortages may increase the demand for bioactives to assist with high value food protein sources (such as haemoglobin).
- The recent reduction in Indonesian demand for Australian live cattle may cause producers in some parts of Australia to become more interested in on-shore processing, which could in turn increase the supply of blood available from processors who will be keen to maximise revenue per animal

Threats

- If BSE is found in Australia, one of the major selling points for Australian-sourced bovine-blood bioactives will disappear
- The New Zealand industry is very export-focused and has a number of intermediaries active in this space. It may continue to capture market share⁴⁰
- China could improve its manufacturing credibility to the point that it can produce bioactives using imported blood from Australian cattle, as it does now in using imported trachea to produce CS; Chinese companies already produce bovine-blood based bioactives using locally-sourced raw material
- Recombinant products are likely to grow in use as their costs decrease and fears of BSE and of reactions to bovine antibodies increase (smaller, niche bioactive markets may be the exception here as economies of scale are required).

³⁹ Spooncer, Bill, “Blood Processing Capability Analysis,” MLA, February 2011, page 23

⁴⁰ Spooncer, *loc cit*

KEY COMPANIES LIST

The tables below contain basic information about some manufacturers of the top five bioactives. Companies were chosen on the basis of size and, for blood products, on the basis of location. Particularly for blood products, many of the companies are privately owned, and financial information is generally not available.

Chondroitin Sulphate

Company	Location	Estimated Annual CS Sales and Production	Company website	Notes
Biolberica	Spain (and 30 other countries)	200 T (US\$5m – US\$10m)	www.bioiberica.com	Humans, cats, and dogs
Inter Farma	Argentina (and US)	360 T (revenues of <US\$500,000 in the US)	www.inter-farma.com	Nutraceutical, pharmaceutical, and veterinary; BSE-free
TSI Health Sciences	US/Global	Estimated US\$75m	www.tsiinc.com	Purchased NPD in Brisbane. Nutraceutical and pharmaceutical, using many animal sources, Asian and non-Asian
Yantai Kangde Biochemical Products	China	360 T/ reported revenues A\$15-\$50m	www.yangtai-kangde.com	This is stated CS capacity on their web site

Blood products

Company	Location	Financials (where available)	Company website	Products
AusgeneX	Australia		www.ausgenex.com	BSA (Australian and NZ sourced)
Bovogen	Australia		www.bovogen.com	BSA, IgG, haemoglobin, prothrombin
Maverick Biosciences	Australia		www.maverickbio.com	BSA, haemoglobin
Moregate Biotech	Australia		www.moregatebiotech.com	BSA
Selborne Biological Services	Australia, UK, US		www.selborne.com.au	BSA, haemoglobin, IgG, prothrombin

Serana	Australia		www.serana-australia.com	BSA, IgG
Shanghai Genon Biological Product Company Limited	China		www.cnngenon.com	IgG (porcine), haemoglobin (porcine)
Akron Biotech	US		www.akronbiotech.com	BSA
Bethyl Laboratories	US		www.bethyl.com	IgG (bovine, caprine, ovine)
Biocell Laboratories	US		www.biocell.com	BSA
Life Technologies (formerly Invitrogen)	US	Have an estimated 18% share of the serum market	www.invitrogen.com	BSA, IgG (not bovine sourced), haemoglobin, prothrombin (not bovine sourced)
Millipore Corporation	US	2011 sales US\$771 m (now part of Merck)	www.millipore.com	BSA, IgG (not bovine sourced), haemoglobin (bovine erythrocytes), prothrombin (not bovine sourced)
Pel-Freez Bio	US		www.pelfreez-bio.com	BSA, IgG
Proliant Biologicals (has a strategic partnership with Lampire Biological Laboratories)	US	Estimated annual sales US\$5m to US\$10m	www.proliantinc.com	BSA, IgG
SeraCare Life Sciences	US	2011 sales US\$43.5 m	www.seracare.com	BSA, IgG (not bovine sourced)
MP Bio	US/Global	Estimate of \$75 m (<\$1m in Australia)	www.mpbio.com	BSA, IgG (not bovine sourced), haemoglobin, prothrombin (not bovine sourced)

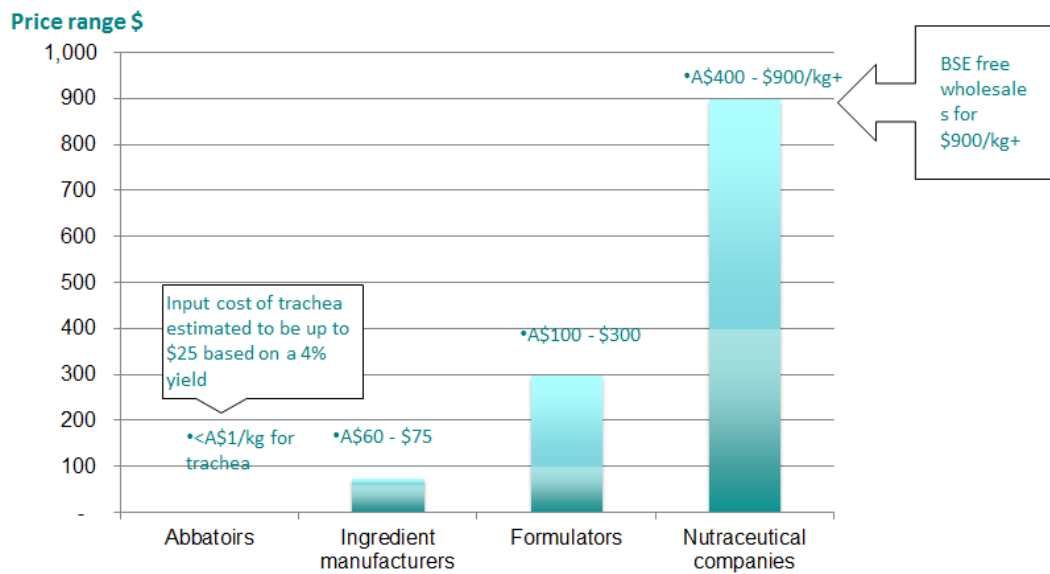
Sources: wikinvest; Hoovers; manta; company websites

VALUE CHAIN ANALYSIS

(c) Occum Enterprises 2011

CHONDROITIN SULPHATE

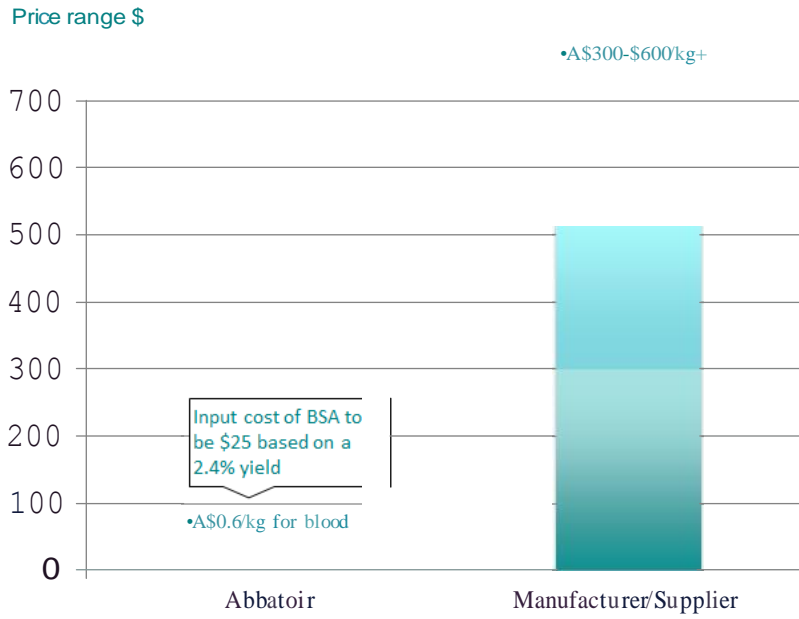
Prices along the value chain



Source: Interviews; wholesale prices from company websites

BSA- Diagnostic Grade

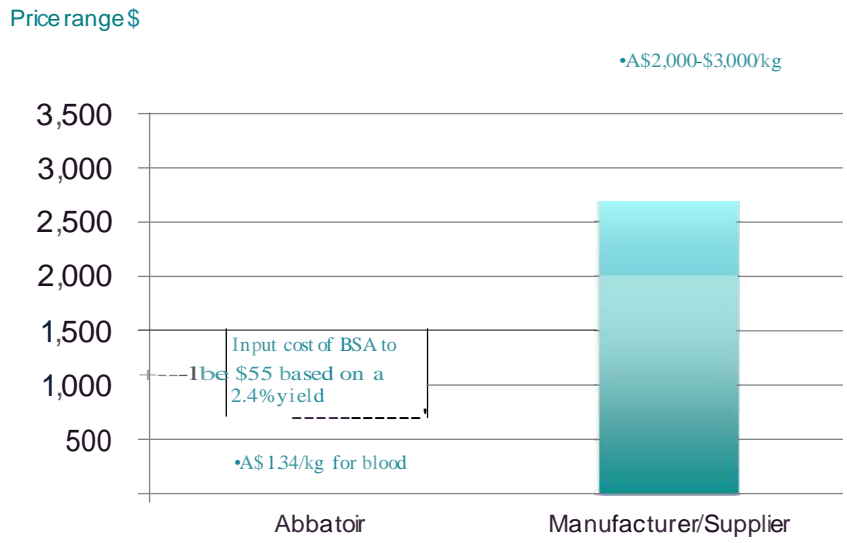
Prices along the value chain



Source: Interviews; Bill Spooner report 'Blood processing capability analysis' June 2011; prices from company websites

BSA-Pharmaceutical Grade

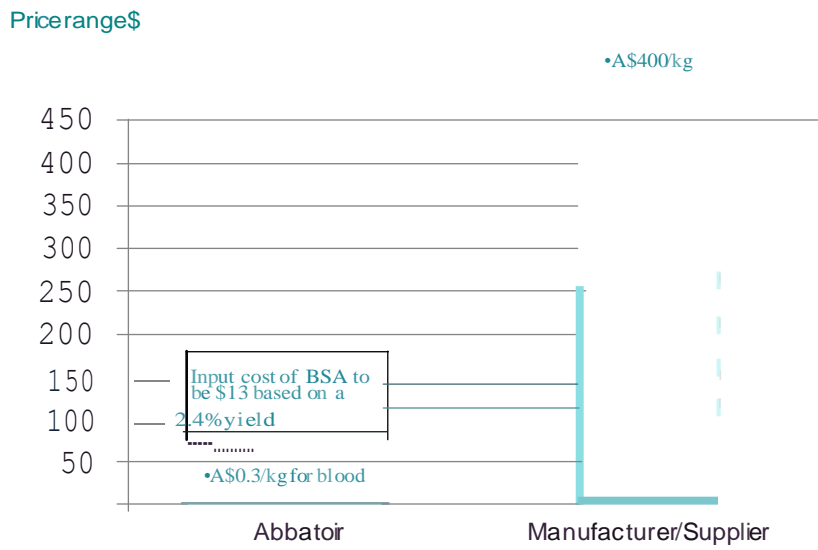
Prices along the value chain



Source: [InteiViews](#); Bill Spooner report 'Blood processing capability analysis' June 2011; prices from company websites

BSA- Food Grade

Prices along the value chain

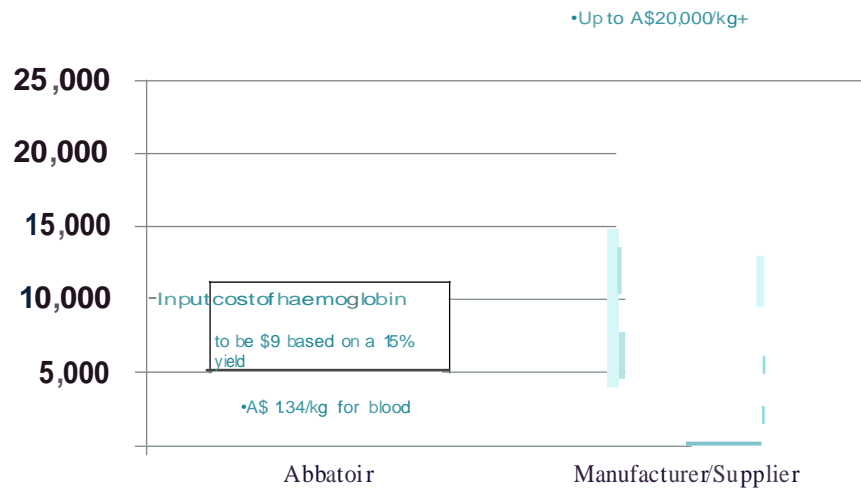


Source Interviews; Bill Spooner report 'Blood processing capability analysis' June 2011; prices from company websites

HAEMOGLOBIN- Research grade

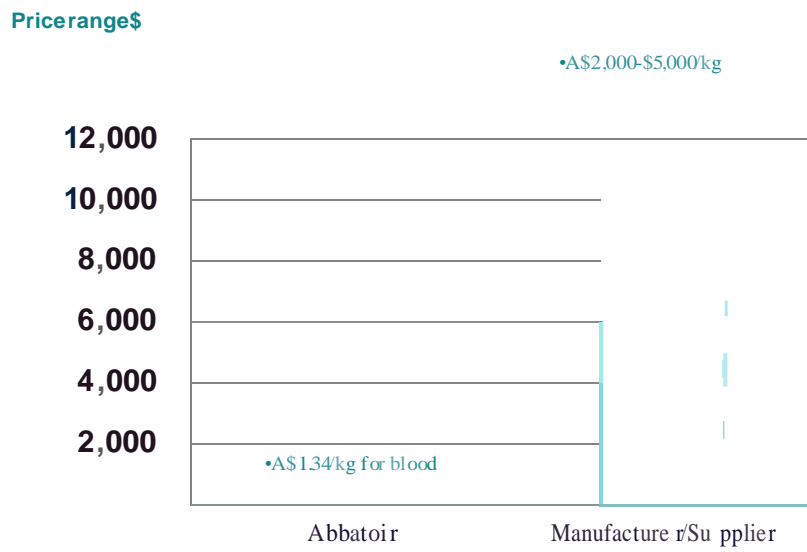
Prices along the value chain

Price range \$



Source: Interviews; Bill Spooner report 'Blood processing capability analysis' June 2011; MLA bioactives compendium; prices from company websites

Prices along the value chain

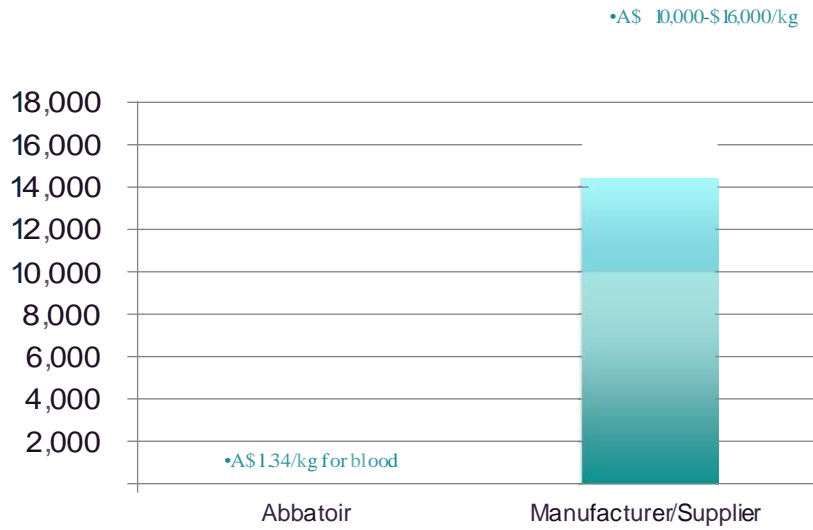


Source: Interviews; Bill Spooner report 'Blood processing capability analysis' June 2011; prices from company websites

PROTHROMBIN

Prices along the value chain

Price range \$



Source: Interviews; MLA [bioactives](#) compendium; Bill [Seoanzer](#) report 'Blood processing capability analysis' June 2011; prices from company websites

SUGGESTED NEXT STEPS FOR AUSTRALIA TO CREATE AND CAPTURE GREATER VALUE FROM BIOACTIVES

As the analysis above demonstrates, the markets for the top five bioactives are global and fiercely competitive. While Australian-sourced products are said to command a price advantage, this is difficult to demonstrate and will be increasingly difficult to maintain in the face of competition from other BSE-free environments and dramatic cost advantages in China and India. While the top five will continue to be produced in Australia, under current circumstances there is unlikely to be significant growth in either volume or revenue. The following suggestions are offered as avenues for expanding sales of both the top five and of other bovine-based bioactives.

Recognise chondroitin sulphate as a separate issue and develop an action plan specifically for that product. CS is different to blood-based bioactives in several ways. It can be produced from a wide variety of sources (shark, seafood, chicken, etc) in addition to bovine sources. Its overwhelming use is as an OTC nutritional supplement of uncertain advantage; gaining a premium on the basis of origin of material and mode of manufacture requires educating a very large retail market, which producers and distributors may prefer to keep uninformed. There is widespread suspicion of mislabelling and adulteration, which again will require substantial effort to overcome. The apparent failure of BAPA to enter the CS market is a cautionary tale which should be explored further as part of the creation of an action plan for CS production in Australia and CS production overseas using Australian sourced material.

Develop and publicise the economics of blood collection (in collaboration with intermediaries). Although some abattoirs are collecting blood, many are not, and the decision about collecting generally does not appear to be based on a clear economic analysis. Such analysis makes sense only in the context of a buyer who is willing to pay the prices on which the analysis is based. An MLA-endorsed analysis framework that could be adopted by intermediaries in their discussions with abattoirs would be a step towards increasing the level of blood collection, and therefore the value gained per animal.

Develop ways of guaranteeing label integrity. Collecting blood is only the first step. Bioactives must be produced, packaged, and sold, and for many buyers traceability and integrity along this chain is of great importance. The Australian NLIS system is a great advantage in this regard, but concerns have arisen about mislabelling of products produced outside of Australia or from non-Australian source ingredients. An investigation into these concerns, and an action plan, could be of significant help to the overall market.

Promote the Australian bioactives industry at trade fairs, conferences, etc. As described above, the Australian bioactives sector consists of small, privately-owned companies that generally lack the resources to visit trade fairs and other industry events. An MLA-sponsored stand at selected events, similar to the stand sponsored by AusBiotech at the annual BIO conference, could be shared among companies under a “clean, green” banner, exposing Australian bioactives to a broad audience of interested buyers. MLA could also offer support for intermediary companies to travel to conferences for the purpose of raising awareness of their products and of Australian bioactives generally.

Support the development of new bioactives. Finally, but perhaps most importantly, it should be acknowledged that Australia’s “top five” are the top five around the world, and therefore are subject to relentless competition on the basis of price, quality, and availability. High-volume customers for these bioactives are generally global companies with enormous purchasing power and complicated procurement processes, creating challenges for selling to them from Australia. The suggestions above are aimed at making the sales process more effective, but it will never be easy. Developing new and improved bioactives, as has been done successfully with MLA support in the past, is another way forward, which may well be the better path to a sustainable future for bioactives from Australian cattle and sheep.

INTERVIEWEES

Interviews Held		
Company	Person	Date
Aspen By-Products	Dean Schiller	31/08/11
Blackmores	Sarah Gould	22/02/12
Bovogen Biologicals	Rick Clements	28/07/11
CSIRO	Bruce Lee	21/07/11
CSIRO	Kirthi Desilva	23/06/11
CSIRO	Andrew Chalmers	22/07/11
Industrial Research Ltd	Tom Nicole	27/07/11
JBS	Garry King	15/09/11
Luttick Pty Ltd	Bill Luttick	03/08/11
Maverick Biosciences	Cameron Crawley	09/09/11
MG Nutritionals	Ken Thomas	26/08/08
Moregate	James Dunster	08/09/11
Northern Co-op	Garry Burridge	23/08/11
NPD	Peter Riikonen	23/08/11
NZ Pharmaceuticals	Selwyn Yorke	22/07/11
O'Connor Beef Pty Ltd	Tim O'Connor	16/08/11
PAA	Rainer Waldmann	08/09/11
Research Directions Pty Ltd	Stephanie Smith	21/07/11 & 17/08/11
Selborne Biological Services (Launceston)	Neville Pope	18/08/11
Selborne Biological Services (Taree) Nippon Beef abattoir visit	Ian Clingo	01/09/11
Serana	Tamara Gahr	23/08/11
Sigma Aldrich Australia	Ben Perrin	08/08/11
Southern Lights Biomaterials	Peter F Mayer	22/07/11
Waitaki Bio	Steve Coulton	12/08/11