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Chondroitin Sulphate: A Market Review

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1 Background

Chondroitin sulphate (CS) has an established global market as a nutraceutical addressing issues of joint health, with claims to benefit joint health, osteoarthritis treatment and pain management. However, the clinical literature supporting these claims is diffuse. Furthermore, the uniformity and quality of existing commercial products are ill-defined and uncertain. Chondroitin sulphate is predominately manufactured in China from animal sources which range from chicken and fish waste to cattle cartilage. Most Australian trachea (a source of chondroitin sulphate) is currently exported to China for CS extraction. This report details the opportunity to capture a portion of the growing CS market by manufacturing this product in Australia. In addition, this report assesses the potential for manufacturing CS as a nutraceutical with a defined set of health benefit claims, backed by clinical research, in a consistent and high quality form from Australia's red meat industry.

Together with CSIRO, MLA has adapted an aqueous extraction process for chondroitin sulphate manufacture, which is organic solvent-free and has significantly reduced costs of production. To date, the process has been developed to laboratory scale and requires further confirmation of market opportunities before increasing to pilot, and ultimately, commercial scale.

This report sets out to provide additional information to support a definitive decision on the commerciality of bovine/ovine-extracted chondroitin sulphate as a nutraceutical supporting joint health. That input is specifically concerned with the market size, the clinical efficacy of chondroitin sulphate in managing joint health, and the key points of difference between bovine/ovine-extracted and fish-extracted chondroitin sulphate. As a consequence, MLA seeks to provide market information to its stakeholders from Australian red meat industry on the commerciality (or otherwise) of bovine/ovine-extracted chondroitin sulphate as a nutraceutical supporting joint health.

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2 Executive Summary

2.1 Key findings

- The market for chondroitin sulphate (CS) as a nutraceutical for use in joint health for humans and companion animals is substantial, global and growing. There may be additional global market opportunity in industrial animal and fish feed industries and in pet foods and supplements.

- The market for CS is predominantly supplied by product manufactured in China, which is reported by the international nutraceutical industry to be of low and variable quality and purity, low and variable concentration, unknown bioactivity, of ill-defined or unknown animal origin, and subject to intentional adulteration.

- Therefore, there is a substantial opportunity for Australian meat processors to supply an international market with a reliable source of high and uniform quality and concentration CS at demonstrable bioactivity from a defined and sustainable animal source, by means of a transparent and auditable supply chain.

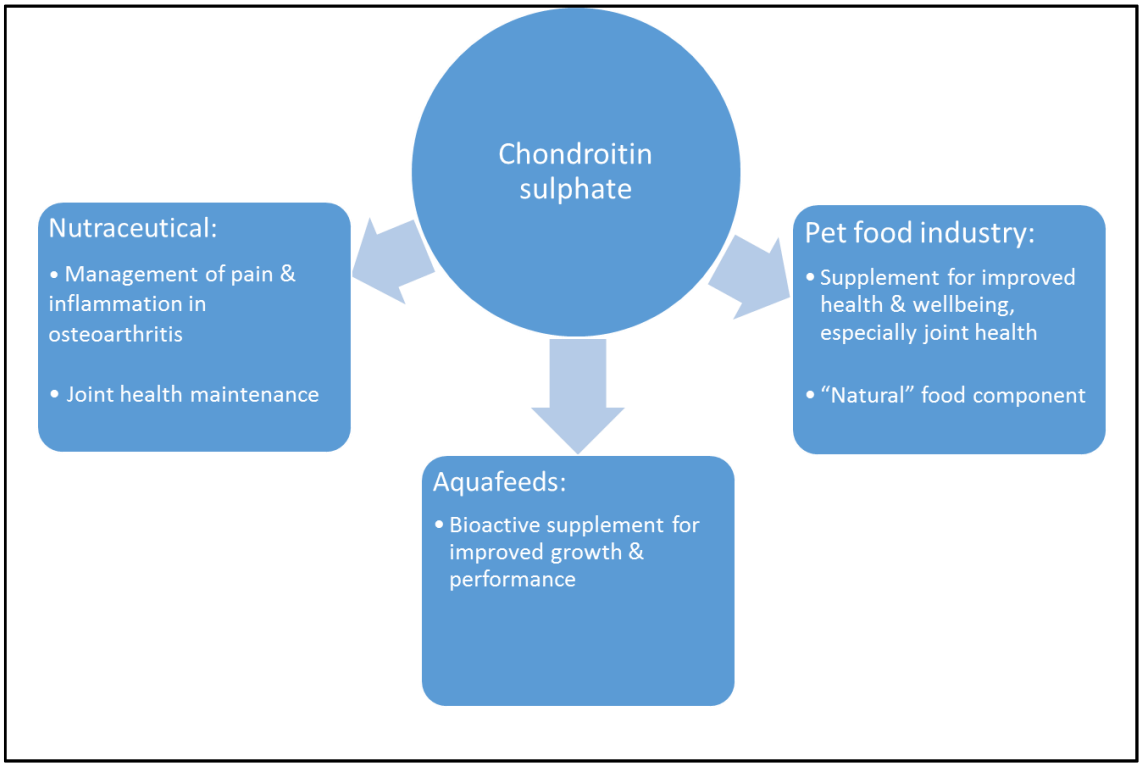

Figure 1: Opportunities within the nutraceutical, pet food and aquafeeds markets for chondroitin sulphate as a value added product derived from meat processing.

2.1.1 Market opportunity

- The global market for nutraceutical ingredients is predicted to generate revenues of ~US$24 billion in 2015, with annual growth of ~15%. The joint health ingredients market is the largest and most rapidly growing subset within the nutraceuticals ingredients market globally, with US$584.2 million in retail sales generated within the US and Europe alone during 2012. In Japan, bone and joint support has the fifth

largest market share of that nation's bioactive food and beverage market and is estimated to be worth ~A$1.7 billion[1].

- The ingredients which dominate this market segment are glucosamine and chondroitin sulphate.

- The volumes of consumption of chondroitin sulphate are substantial: the US imports the majority of its chondroitin sulphate: reportedly ~3500 tonnes of chondroitin sulphate was imported for product formulation in 2012, valued at around US$210 million to US$350 million[2]

- An estimate for annual global market for chondroitin sulphate as a nutraceutical ingredient ranges from US$420 million to US$1 billion.

- The market driver for chondroitin sulphate consumption in joint health is largely osteoarthritis (OA), which is increasing in association with the burgeoning global trend of an ageing and obese population. The joint health market is also supported by health-conscious 'baby boomers' and 'Gen-X' consumers who wish to maintain joint health to proactively maintain quality of life.

- In the US veterinary dietary supplements market, joint heath is the leading supplement category, with a 4% growth rate and sales of US$690 million, or 45% of total sector sales. Chondroitin sulphate is among the established bioactive supplements in the pet industry that have substantiating evidence to support health benefit claims. The trend in the pet industry is in preventative health for a growing population of ageing, overweight dogs, treated by their owners as family members.

- In the animal market, the aquafeed industry maintains a watching brief on potential bioactive ingredients, such as chondroitin, to add to fish feeds to improve growth performance and animal health. The global market for aquafeeds was estimated to be worth US$106 billion in 2009 and is growing at the CAGR[3] of 12.1% from 2013 to 2018. By 2020, global aquaculture is expected to contribute about 120–130 million tonnes of fish to meet projected demands; the current demand for fish is estimated at 68 million tonnes pa. The total global industrial compound aquafeed production is estimated at ~ 39.6 million tonnes; the Australian aquafeeds industry produces ~ 40,000 to 45,000 tpa of compound feed annually, and growth promoters are added at a rate between 0.001% and 5%. At this inclusion rate, the uptake for chondrotin sulphate as a growth enhancer may be as high as 2,250 tpa within the local market alone.

- In general, chondroitin is acknowledged by the nutraceutical industry in particular as one of the "most adulterated supplements in the market". The existing supply chain for animal-derived chondroitin sulphate is negatively impacted by both poor process control and intentional adulteration by raw material processors. This then represents an opportunity for the Australian red meat industry to establish an international business based on the processing and supply of high quality, food-grade, bovine-derived chondroitin sulphate.

[1] Bioactives include biological compounds which have a stimulatory or otherwise beneficial effect on animal wellbeing, independent of any nutritional benefit. Examples of bioactives include antibiotics and probiotics. Compounds with a solely nutritional benefit include proteins, carbohydrates and sugars, and fats and lipids.
[2] Wholesale prices from company websites and Vitale 2012.
[3] CAGR is the growth rate of a business averaged over a period of several years (typically the last five). In this way, CAGR provides a better indication of the growth trend within a business, than does reflection on one year's growth rate.

- From a survey of a limited number of nutraceutical industry respondents, there was a substantial level of interest in a high quality, bovine-derived chondroitin sulphate product. The leading drivers for change of CS supply were identified as (i) the quality of chondroitin sulphate evidenced by its measurable purity using international standard methods of analysis, (ii) price, and (iii) evidence of efficacy. For many respondents, price would determine their volumetric uptake of this ingredient.

- CS may be supplied to the end-user either as an ingredient ready for incorporation into the end-user's products, or as a partially purified ingredient or slurry, ready for further purification by the end-user to meet their product requirements. The extent of purification by the CS refiner will need to be determined and customised for each end-user.

From a survey of nutraceutical industry respondents, there was a substantial level of interest in a high quality, bovine-derived chondroitin sulphate product. The leading drivers for change of supply of chondroitin sulphate are the quality of chondroitin sulphate evidenced by its measurable purity using international standard methods of analysis, followed by price, and evidence of efficacy. For many respondents, price would determine their volumetric uptake of this ingredient.

2.1.2 Clinical effectiveness

- Chondroitin sulphate is one of the symptomatic slow-acting drugs for osteoarthritis (SYSADOAs) used to provide relief from the pain and inflammation associated with joint degeneration. CS is recommended by the European League Against Rheumatism and the Osteoarthritis Research Society International as a SYSADOA in Europe in the treatment of knee and hand osteoarthritis.

- The clinical benefits of CS have been established by a large number of human trials and studies. Depending on the design of the trial and the manner in which data is reviewed, the results may appear contradictory. However, overall, these studies characterise CS with respect to:
    - Safety and tolerability: In contrast with conventional pharmaceutical treatments, CS has an excellent safety and tolerability profile which justifies long term administration for OA and joint health. CS can be taken for extended periods and improves patient quality of life.
    - No drug interactions: Unlike other conventional pharmaceutical treatments, CS can be taken by aged OA patients whose diminished health may require the use of other medications.
    - Pain relief is a measurable benefit of long term CS use. Pain relief from CS has a slow onset of response, but an enduring beneficial effect.
    - Inflammation reduction is a measurable benefit of long term CS use.

- The majority of evidence of the biological function of CS is based on bovine and shark-derived products. Bovine-derived CS is considered by industry to deliver the greatest benefit in knee and hip OA. This is significant as the knee is the dominant joint affected by OA on a population basis.

- The dominant animal source of pharmaceutical grade CS in the international market is influenced by jurisdiction. Based on their experience with BSE[4], Europe prefers shark-derived CS, whereas the US and Australian markets prefers bovine-derived, due to a social reluctance to support the harvesting of sharks.

2.1.3 The Refining Process

- CS currently supplied to the market is extracted from cartilaginous feedstocks using organic solvents, usually ethanol. This well-established extraction methodology underpins a low technology operation, is non-specific for CS, is amenable to small to medium scales of operation, and provides product at a low cost-of-goods.

- As one technology option, MLA has contracted the development of a continuous chromatography protocol (CSEP[5]) for CS extraction. This innovative methodology specifically extracts CS away from other biological materials in the feedstock, and has the potential for the production of high and uniform quality, bioactive CS at a consistently high concentration from animal feedstocks.

- CSEP has an established track record of industrial application in the food and beverage industries globally at commercial scale, and has been adapted in Australia by MLA and CSIRO, its research collaborator, for specific application in the meat industry. CSEP has most recently been adapted elsewhere for specific extraction of bioactive compounds from dairy feedstocks, also at commercial scale.

- CSEP technology, as a commercial scale extraction protocol, has considerable prospective operational advantages for the extraction of a high quality, bioactive CS for use in the nutraceutical and feed industries. Indicative costings of CS production using the CSEP process at laboratory scale are in a range consistent with the low end of the current CS price scale, and therefore CSEP delivers a nutraceutical product which compares well with its commercial competitors. This suggests that the CSEP process may deliver a cost-effective CS product in a cost-sensitive market.

- To date, the use of CSEP technologies for meat industry applications has been demonstrated at laboratory scale only. Further work is required, for example by CSIRO, before a decision for commercial scale rollout can be made by stakeholders within the Australian meat industry. Such decisions need to be supported by process efficiency and economics data from pilot scale operation, and by quality analysis of the CS produced, in comparison with that produced by conventional organic solvent protocols.

- Volumetric productivity: With shorter processing throughput time for hydrolysed feedstock, CSEP may have the potential to increase annual feedstock processing capacity, delivering improved volumetric productivity with additional economic benefits to the CS refiner.

- This report suggests that initial work to scale up the CSEP process to refine CS from hydrolysed cartilage, as well as the commissioning of a commercial scale plant, may be eligible for the R&D tax incentive scheme[6] for those organisations that fund that effort.

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[4] Bovine spongiform encephalopathy or mad cow disease, is a fatal neurodegenerative disease in cattle that is transmissible to humans via consumption of contaminated bovine products.

[5] CSEP or *Chromatographic Separation* is a continuous (rather than batch) process for the separation and recovery of specific components (such as chondroitin sulphate) from a feedstock, such as cartilage.

[6] http://www.business.gov.au/grants-and-assistance/innovation-rd/RD-TaxIncentive/Pages/default.aspx

- Quality: Persistent, recalcitrant problems of CS quality within the nutraceutical and animal feeds industries provides the Australian meat processors with an opportunity not only to provide high quality, high concentration CS from BSE-free feedstocks to national and international industries, but potentially to reframe the quality metrics achievable for CS.

Based on the molecular specificity of the separation technology and the mild conditions of operation, the CSEP process may present the opportunity for the Australian meat industry to redefine the gold standard in bioactive polymers in the global market, particularly for chondroitin sulphate, for the nutraceutical and potentially the animal and pet feed markets. CSEP-extracted bovine-derived CS reliably produced at consistent and high concentration by a cost-effective process from sustainable meat industry feedstocks with a transparent supply chain may have significant competitive advantages over existing competitor products.

2.2 Next steps

There is an opportunity to establish a CS refining business using a staged approach (Implementation Strategy), overseen by a dedicated implementation team. The staged approach provides time for development of a full scale manufacturing process from the CSEP technology, potentially by CSIRO, and for assessment of the market opportunity for the product. The value of the staged approach for both operational deployment as well as product rollout are comparable: there is time allowed to develop the commercial scale refining technologies; to prepare for commercial release of CS into target markets, and to integrate the new value-adding refining technology into existing operations.

Implementation strategy: To access this market opportunity for CS, the Australian meat industry needs further investment to establish and evidence the production of bovine-derived CS, with:

- Scalable manufacturing processes;
- Sustainable production from a transparent and auditable supply chain;
- Qualified raw material, i.e. specified animal source;
- Reliable product supply at appropriate volumes to meet end-user needs;
- Price targets; and
- Product specifications, such as concentration and purity of 90% or 95%.

The prioritised first target market is in the human nutraceutical and veterinary dietary supplements markets.

The Implementation Strategy is a risk management framework of sequential stage gates that allows the meat industry to assemble the data necessary to make an operational decision regarding the establishment of industrial production of CS. Each stage gate provides a ‘go/no go’ decision point for the progression (or otherwise) of the CS production venture. Those stage gates are:

- **Stage Gate 1**: Define and demonstrate the product; estimate industry uptake
- **Stage Gate 2:** Establish a collaborative partnership or joint venture
- **Stage Gate 3:** Define the supply chain: consider a *hub and spoke precinct model* for feedstock processing within the meat producing regions, with the refining hub at the centre of the spokes of meat processors.

- **Stage Gate 4:** Define the business structures to achieve: feedstock aggregation, technology deployment and end-user alliances.
- **Stage Gate 5:** Staged technology rollout, and secure or outsource the skill sets needed to operate the refining operation, for full scale commercial manufacturing.

Implementation Team: An implementation team will support the staged roll out strategy and be responsible for

- Strategic partnerships: Identification of strategic partners, and the development and management of relationships, on behalf of the meat processors and the refining venture. Strategic relationships are as essential as supply chain optimisation to minimising risks, and overcoming the barriers and uncertainties that the meat industry may face in developing a sustainable and competitive value-adding venture;
- Product assessment: confirming the market readiness of the CS product refined from Australian meat processing by-products by potential end-users within the human nutraceutical and pet foods and supplements industries; and
- Strategic modelling: Project management of the financial modelling needed to assist the meat processing industry to define and initiate a successful CS refining venture, with input from all partners and end-users. In particular, the financial modelling would be valuable in supporting commercial decision making by the meat processing industry and understanding the time to pay-back on capital expenditure.

CHONDROITIN SULPHATE: STAGED IMPLEMENTATION STRATEGY

Target market: human nutraceutical market, driven by the current issues of poor quality and inconsistent concentration CS supply; and the pet food and supplement markets, driven by the demand for "natural" bioactives or cereal-free ingredients to improve pet health and wellbeing.

Stage Gate 1: Define & demonstrate the product; estimate industry uptake

Stage Gate 2: Establish a collaborative partnership or joint venture

Stage Gate 3: Define the supply chain: consider a *hub and spoke precinct model* for feedstock processing within the meat producing regions, with the refining hub at the centre of the spokes of meat processors.

Stage Gate 4: Define the business structures to achieve: feedstock aggregation, technology deployment and end-user alliances

Stage Gate 5: Staged technology rollout, and to secure or outsource the skill sets needed to operate the refining operation, for full scale commercial manufacturing.

3 Market for Chondroitin Sulphate

3.1 Market opportunity and size

Chondroitin sulphate is a key component found naturally in the extracellular matrix of the connective tissues of animals, with a critical role in the function and elasticity of the joint (articular) cartilage, inflammation, and other processes [3].

Recently, the scope of potential commercial applications for extracted chondroitin sulphate has expanded, based on the compound's high biocompatibility, to areas of biological tissue engineering of bone repair, cartilage and cutaneous wound [4]. In addition, other applications have been proposed: as a potent antiviral [5], and partially-purified CS as a food preservative with emulsifying properties [4].

However, the largest market opportunity for chondroitin sulphate, by volume and value, is the well-established one in joint health in both the human nutraceutical and pet supplement markets, and as a potential bioactive ingredient in animal feeds. To date, chondroitin sulphate has been used to address joint health largely in the context of osteoarthritis, with a body of evidence describing effects on cartilage regeneration, joint inflammation and pain.

3.1.1 Nutraceutical Market

The nutraceutical market is made up of foods and beverages, ingredients and supplements that offer health benefits to the consumer. As heathcare costs continue to rise and the population ages, individuals increasingly focus on preventative care and self management by means of nutraceuticals to maintain their health and wellness.

The total nutraceuticals market was estimated at US$346 billion in 2012, of which the retail nutraceuticals supplements segment represent 28%, or US$96 billion in sales, and projected to exceed $104 billion globally in 2021 [6].

Within the broader nutraceuticals industry, the global market for nutraceutical ingredients is predicted to generate revenues of almost US$24 billion in 2015, with annual growth of ~15%. The greatest growth is expected from those ingredients which have clinically confirmed health benefits, for application within a range of dietary supplements, drinks, foods, and nutritional preparations for both children and adults, particularly older adults.

In terms of the nutraceutical market structure, the key jurisdictions currently are the US, EU and Japan, although analysts expect growth in the consumption and production of nutraceutical ingredients within developing nations to exceed that in developed nations [7]. In the European region are some of the largest and most well-established product and ingredient manufacturers in the global nutraceutical industry. Furthermore, Europe has seen the greatest focus on innovation and new product development. The US nutraceutical market is considered by some observers as the most advanced in terms of product offerings and market penetration, and consumer acceptability of newly introduced nutraceutical products. In addition, new opportunities exist within the Asian region: India is considered a key new market for entry of nutraceutical product and ingredient manufacturers, with an expected growth in this sector of 16% pa [8].

3.1.1.1 The Joint Health Market

The joint health ingredients market is the largest and most rapidly growing subset within the nutraceuticals ingredients market globally. The ingredients which dominate this market segment are glucosamine and chondroitin sulphate [9-11]. Chondroitin-containing supplement products are in the top five best-selling dietary supplements, with reported annual sales of about $1 billion globally [11]. The joint health ingredients market in the

United States and Europe earnt $584.2 million in retail sales during 2012 [10]. Chondroitin is also frequently complemented with other ingredients including collagen, methylsulfonylmethane (MSM), and hyaluronic acid. The joint health ingredients market targets general joint health but specifically osteoarthritis, and therefore this disease, as well as conditions which affect the onset of the disease such as aging, are major drivers for the joint health market.

Joint health supplement use is considered a top priority for nutraceutical companies, enforced by demand from both baby boomers to maintain joint health, and the aged market to manage joint dysfunction. With the goal of maintaining or increasing market share, manufacturers strive for further differentiated products, for example, by means of new or improved ingredients, formulations, or delivery technologies [12].

In the US, chondroitin sulphate sold is predominantly imported: ~3500 tonnes of CS was reportedly imported in 2012 and 3000 tonnes in 2011 [11]. At US$60-100/kg [13], this may represent an annual US wholesale market for chondroitin sulphate of US$210 million to US$350 million. While accurate figures for the total CS maket are difficult to find, the US market may represent between 33% to 50% of the international ingredients market – therefore this US uptake suggests that an annual global market for chondroitin sulphate as a nutraceutical ingredient may range from US$420 million to US$1 billion.

Japan is the world's third largest bioactive food and beverage market, valued at ¥1.77 trillion (~A$ 20 billion[7]) in 2011, driven by a rapidly ageing society, an increase in Western lifestyle-related diseases, and a proactive interest in health [14]. Japan's Consumer Affairs Agency (CAA) makes provision for a class of nutraceutical-type food products, Food for Specified Health Use or FOSHU, with an estimated market size of ¥517.5 billion (A$5.9 billion) in 2011 [14]. Within the bioactive food and beverage market in Japan, bone and joint support has the fifth largest market share at 8.3%, estimated to be worth ¥146 billion (A$1.7 billion) in 2011. Glucosamine, chondroitin and calcium are the key ingredients, with consumption of glucosamine leading market growth [14].

In Australia, the complementary medicine (CM) industry is comprised of 254 companies generating around A$2.3 billion in annual revenues. Australia has a reasonable capability in production of CMs, with 59 TGA-approved manufacturing facilities nationwide. Australian companies export around A$200 million in complementary medicines to more than 20 countries in South-East Asia, Europe and the Americas, with exports growing at a higher rate than domestic consumption [15].

3.1.1.2 ***Osteoarthritis***

A major driver of the chondroitin sulphate market is the incidence of osteoarthritis. Osteoarthritis, the most common form of arthritis [16], is a degenerative joint disease, which mainly affects the cartilage in the joint (i.e. articular cartilage). The disease commonly impacts joints which have been continually stressed, especially the knees, hips, fingers, and lower spine [17], leading to pain and loss of function [18].

Osteoarthritis is recognised as one of the ten most disabling diseases in developed countries [17], and is the fourth leading cause of disability, most of which is attributable to the involvement of the hips or knees.

Worldwide estimates are that almost 10% of men and 18% of women aged over 60 years have symptomatic osteoarthritis. Of those affected, 80% will have limitations in movement, and 25% cannot perform major daily activities [17, 18]. Nearly 1 in 2 people may develop

[7] Historical exchange rate of AUD0.011419/JPY

symptomatic knee osteoarthritis by age 85 years; and 1 in 4 people may develop painful hip arthritis in their lifetime [16].

Osteoarthritis is more prevalent in Europe and the USA than in other parts of the world. In Europe, an estimated 15 million active people aged 40-65 suffer from joint pain; in the US, this figure reaches 19 million. Furthermore, according to the WHO, osteoarthritis will become the fourth most common cause of disability in the world by 2020 because of the progressive ageing of the population [18].

The risk factors for osteoarthritis are ageing, female gender, obesity, joint injury and heavy physical occupational activity. Osteoarthritis is strongly associated with ageing . Australia's population will age dramatically over the coming years, with evidence already of an increase in the median age and a doubling of the number of individuals over 85 years of age [19]. These trends in ageing are global, enduring and pervasive, with the proportion of older persons (60 years or older) increasing from 8% in 1950 to 10% in 2000, and projected to reach 21% in 2050 [20].

The burgeoning incidence of osteoarthritis is a major driver for the uptake of joint health supplements. With ageing, obese and osteoarthritis-affected populations, there is a growing demand for anti-inflammatory supplements as well as so-called "chondroprotective" or joint health supplements to stimulate the production of cartilage tissue. In addition, the nutraceutical industry recognises an increasing demand for these supplements from so-called 'Gen-X' and 'baby boomer' consumers to maintain wellbeing and support an active lifestyle. Therefore, the market for chondroitin sulphate and glucosamine, current leaders in joint care ingredients, continues to grow, despite a crowded health supplement landscape and pressure on prices [12].

Nutraceutical Market: Leading player

Bioiberica, S.A.

Bioiberica, S.A. is a privately held company founded in 1975 and based in Barcelona, Spain. As of February 10, 2012, Bioiberica, S.A. operates as a joint venture between Teeuwissen Holding B.V. and SARIA Bio-Industries International GmbH. Bioiberica specializes in research, manufacture and marketing of biomolecules for the pharmaceutical and nutrition industries, especially chondroitin sulphate, hyaluronic acid and glucosamine [1].

Bioiberica manufactures ingredients and finished products targeting the pharmaceutical, veterinary, and agricultural industries. Within the veterinary and agricultural sectors, the company offers products for a pet's joints and digestive system; and ingredients for feed and veterinarian medicines for farm animals and pets. For the pharmaceutical and nutrition industries, the company provides ingredients and finished products for joint disorders ranging from prevention and early detection to pharmacological and personalized treatments, including osteoarthritis therapies and heparin molecules; and nutritional supplements for athlete joints. The company also provides bioactive ingredients for the food supplement and functional foods industry [1].

Bioiberica actively invests in the development of new and novel ingredients and formulations of joint health products. In December 2013, Bioiberica launched a new functional food based on rooster comb extract (trademarked as Mobilee), the first such product to be approved as a food ingredient by the European Commission for use in the European Union (and, in fact, globally). As a source of chondroitin, rooster comb extract is an ingredient considered useful in preserving joint health and is the first ingredient to be approved for addition to dairy products such as milk, yoghurt or cheese for everyday consumption. The product launch was a consequence of five years of clinical and analytical testing to establish efficacy, stability, security and toxicity [2]. The source of the raw material was not reported.

3.1.2 Pet food and veterinary supplements

Market size

The US market for natural and organic pet food, supplements (for dogs, cats, horses and other small companion animals) and natural & organic pet supplies was US$3.2 billion in 2010, and is expected to rise to US$5.5 billion globally in 2014. Most US households reported at least one dog or cat as a pet in 2009-10, with the pet dog population at more than 67 million and the pet cat population at more than 83 million, consuming more than 8 million tonnes pa of pet food [21]. Similarly, the pet market in Japan is stable but "lavish" and is valued at A$4 billion in 2012, including A$2.9 billion in pet food, particularly high quality premium foods, specialised food and health supplements [22]. Expenditure on pet dietary supplements in 2009 in Australia was A$21.4 million [23].

The US is also a major exporter of pet foods, with sales of ~US$1.1 billion in 2009 to Japan, Canada, Mexico, and the European Union [21].

In the US, more than 500 ingredients are sold as animal health supplements according to the National Animal Supplement Council [24], including probiotics, nutraceuticals, vitamins, antioxidants, fatty acids, and supplements for arthritic joints. Industry observers consider the pet food and supplements industry in the US as "recession resistant" [25] .

Pet Feed market: Leading players

Market leaders in pet food ingredients and supplements include DSM (natural vitamins and carotenoids), Martek (microbial docosahexaenoic acid (DHA) and arachidonic acid (ARA)), Vitatene (natural carotenoids), Verenium (food enzymes and technology), Ocean Nutrition Canada (fish-derived omega-3 fatty acids), and Tortuga (animal dietary supplements). Recently, Tortuga was acquired by DSM, to gain entry into the animal nutrition market in Latin America and extend DSM's nutritional range to include organic trace minerals. This acquisition completes a €1.8 billion portfolio of acquisitions in nutrition for DSM.

Drivers

While the trend in the pet industry is for natural and bioactive products for preventative health, it is health supplements that drive growth within the pet market.

The pet market is underpinned by a growing population of ageing, overweight dogs, an expanding pet population and consumer attitudes such that owners treat their pets as companions or family members. Pet owners now place significant value on the health and wellbeing of their pets, despite the statistics which record rates of obesity and diabetes in pets trend in concert with that of their owners [23]. Consumer concern about ingredient quality is evidenced by a US$15 billion spike in one year's sales, and subsequent continued 20% growth of "natural and holistic" pet foods reached after the pet food recall triggered by melamine contamination[8] [25].

Pet health concerns are addressed by both premium and super-premium pet foods and breed-specific specialty food mixtures, and by nutritional supplements [21].

In the US market, the top-selling pet supplement category is joint heath, with a 4% growth rate and sales of US$690 million, or 45% of total sector sales. By comparison, the dental category grew almost 7% to reach $20 million; skin and coat supplements grew 8% and accounted for 10% of sales. A recent industry survey conducted by Nestle Purina Petcare found that 40% of dog owners and 50% of cat owners expressed interest in purchasing veterinary medications, foods or supplements to address their pet's gastrointestinal condition. Multivitamin sales continue to decline as consumers prefer more condition-specific supplements, and pet food manufacturers aim to meet this demand with bioactive ingredients. Consequently, there are a number of bioactive ingredients for use in the pet

[8] In 2007, Chinese wheat gluten intentionally adulterated with melamine was imported into the US for use in pet foods. Melamine and related products cause kidney failure in cats and dogs, as well as cancer and birth defects in humans. The tainted pet food products subsequently sickened a reported 9,000 pets and killed at least 13,000. The pet food industry paid around US$32 million in damages to pet owners. Significantly, consumer concern about pet food quality consequently stimulated a rapid 20% growth in sales of natural and holistic pet food to US$15 billion by 2008, while other pet food segments stagnated. The melamine event has embedded natural pet foods within the competitive western pet food market.

25. Phillips Brown, L. *State of the Pet Supplement Industry. www.nutraceuticalsworld.com/issues/2012-03/view_features/state-of-the-pet-supplement-industry/*. Nutraceuticals World, 2012, 26. Schmidt, J., *Tainted pet food suit settled for $24 million. http://usatoday30.usatoday.com/money/industries/2008-05-22-petfood-lawsuit-settled_N.htm.* 2008,
27. Food and Drug Administration, *Melamine Pet Food Recall of 2007. www.fda.gov/AnimalVeterinary/SafetyHealth/RecallsWithdrawals/ucm129575.htm>*. 2007.

industry that have reported substantiating evidence: prebiotics, probiotics, glucosamine and chondroitin, antioxidants such as vitamins C and E, and zinc and other trace elements [25].

3.1.3 Aquafeed market

The global market for aquafeeds was estimated to be worth US$106 billion in 2009 and is growing at the CAGR of 12.1% from 2013 to 2018. Currently, the total global industrial compound aquafeed production is estimated at approximately 39.6 million tonnes pa [28]. By 2020, global aquaculture is expected to contribute about 120–130 million tonnes of fish to meet projected demand; current estimations of global demand are 68 million tonnes. The market for aquafeeds is well-established in North Europe and in Asia, and growth is particularly high in countries such as China, Vietnam, and Ecuador, due to an increasing awareness of the impact of quality aquafeeds on fish yield and production efficiency [29, 30] as producers strive to meet the burgeoning demand for quality, high protein table foods.

Europe and Asia Pacific are the major aquafeed-consuming regions followed by North America. Moreover, the animal feed industries are expanding their domains to meet the requirements of a growing aquafeeds market, and are tailoring feed composition to the demands of the distinctly different varieties of fish cultivated in those two (or three?) jurisdictions [29].

3.1.3.1 ***Bioactives in aquafeeds***

The aquafeeds industry maintains a watching brief on potential bioactive ingredients, such as chondroitin, for aquafeeds which improve growth performance and animal health. Of particular interest are those compounds that improve the resilience of the animals to intensive farming practices, such as pre-and probiotics and antivirals, and modifiers of mineral deposition, osmoregulation and blood cell count. Currently, bioactives are added to aquafeeds at inclusion rates which vary from 10 grams/tonne to 5% of feeds, depending on potency of the additive. Industry needs to see evidence which substantiates health and/or performance claims for new bioactive ingredients such as CS, but may work directly with the ingredient supplier to build the evidence dossier, using relevant fish models such as the commonly farmed barramundi [31].

The Australian aquafeeds industry produces around 40,000 to 45,000 tpa of compound feed annually, and, at inclusion rates of 0.001% and 5%, the potential uptake for chondrotin sulphate as a growth enhancer in the local aquafeeds industry may vary from 40 tpa to as high as 2,250 tpa [30].

Palatability is a critical hurdle for new aquafeed ingredients to meet fish growth performance metrics. In addition, the cost of aquafeed additives is also constrained: raw material ingredient costs can account for 75% of feed production costs; additional costs of raw materials are borne by the aquafeed manufacturer [29, 32]. However, animal feed compounders may consider paying a premium price for nutritional and/or bioactive proteins if one supplier provided all the requirements for bioactive components as a single high quality and secure supply [31].

While this animal feed market is a substantial and growing one, for the Australian meat industry to consider aquafeed manufacturing as a customerof its animal-derived products for use as bioactive and/or nutritional ingredients, further investment in research is needed to demonstrate to industry the comparable advantage of these products as aquafeed components.

3.2 Challenges

3.2.1 New Joint Health Ingredients

In human healthcare, glucosamine and chondroitin are well-recognised as having captured the predominant market share in the nutraceutical joint health category and to continue to hold this position. However, the nutraceutical and veterinary dietary supplements consumer markets are fad-driven [33]. New ingredients within these markets readily grab the attention of consumers, particularly with reportedly comparable safety and efficacy profiles and with consumer-friendly delivery formats. Recent market entrants include: MSM (methylsulfonylmethane), NEM (natural eggshell membrane), UC-II (undenatured type II collagen), curcumin, soy phospholipids, and resin extracted from the herb *Boswellia serrata* (or Indian frankincense) [12].

These new ingredients will undoubtedly have an impact on the chondroitin sulphate market share, the magnitude of which will depend on demonstrated health benefits, price, and how regulatory hurdles are addressed by the new ingredients. Recently, the regulatory requirements in the US and Europe have become more stringent, requiring nutraceutical companies to evidence the efficacy and health claims of new bone and joint ingredients. As a consequence, manufacturers are increasing their investment in research and development to substantiate efficacy, as well as marketing to spread awareness among consumers. Overall, the demand for new joint supplement ingredients is expected to increase, but the uptake of the new ingredients will require acceptance by consumers and validation by the manufacturers of scientific evidence of efficacy, formulations that are easy to use (e.g. liquids), and the offer of additional benefits that go beyond the need for enhanced health and wellness [10]. Industry respondents do not consider this will happen with any speed, despite consumer appetite for novelty in this market [31].

3.2.2 Adulteration of chondroitin sulphate

Chondroitin is now acknowledged within the nutraceuticals industry as one of the "most adulterated supplements in the market" [9], a problem which is widespread, deteriorating and on-going. Furthermore, the extent of adulteration is probably underestimated, with much of the adulteration going undetected, encouraged and abetted by the lack of industry-wide validation methods [9, 34]. One industry trend which drives adulteration is price pressure, resulting in inferior quality ingredients which “win price battles” [12]: low quality chondroitin sulphate is very cheap[9]. The majority (80-90%) of the chondroitin sulphate supply to the US and Europe originates from China and it is the Chinese-dominated supply which raises adulteration concerns. The problem is not considered to be the source material, which originates from Australia, New Zealand, Vietnam and India [9, 34] but rather later process. Some dietary supplement products contain less than the claimed amount of chondroitin sulphate, in some cases as little as 10% [35].

The contamination and adulteration of chondroitin sulphate is significant within the nutraceutical industry, as the molecular structure of chondroitin sulphate depends on the source, and biological function as a nutraceutical varies with structure. Chondroitin sulphate can be contaminated as a consequence of the extraction process or it can be intentionally adulterated. Contaminants which arise as a consequence of the extraction process include proteins from the source tissue, organic solvents used in downstream processes, and small organic molecules and surfactants from the adjuvant used in the purification process [35].

Intentional adulteration of chondroitin persists because pricing pressure pushes the nutraceutical manufacturer to minimize ingredient costs by using substandard sourcing

[9] Industry respondent: response to US$10-60/kg was anger at the “bastardisation” of the CS market by deliberately adulterated product – “at this price there was likely to be no useful CS present”

practices. Chondroitin sulphate is adulterated with cheaper polysaccharides (such as the algal polymer carrageenan) and keratin sulphate [34, 35], amongst others.

3.3 Drivers for Change

What will make industry customers adopt a new, potentially higher quality CS product produced by the Australian meat industry? Within the nutraceutical, veterinary dietary supplements and animal feeds industries, the drivers for change of supply of chondroitin sulphate are the quality of chondroitin sulphate as demonstrated by its measured purity and concentration, followed by the evidence of efficacy, and price. For many industry respondents, price would determine their volumetric uptake of chondroitin sulphate as an ingredient in their manufactured product or feed.

Despite how long chondroitin sulphate has been on the market for joint health and the competition presented by newer ingredients, industry respondents indicated that there continues to be an increasing demand for chondroitin sulphate and glucosamine products. For existing customers of CS, the change to a new supplier of chondroitin sulphate would be advantaged if the CS was derived from a fully qualified raw material stream and transparent downstream processing operation.

Respondents from the nutraceutical industry indicated interest in significant volumetric quantities of Australian animal-based chondroitin sulphate, on the condition that it meets such product criteria as:

- Transparent and qualified supply chain;
- Traceability;
- Availability of volumetric supply; and
- Product specifications, such as concentration and purity of 90% or 95%.

Potential client companies would need to audit the Australian supplier and processor before any supply deal is considered.

Price remains a key issue for some industry representatives and volumes purchased would depend entirely on a competitive price or on some other efficiency or bioactivity advantage. Australian animal products are acknowledged by international respondents to be “very expensive”, based on the pressure on the raw materials. However, the Australian meat industry should recognise that segregation of premium nutraceutical products occurs within the ingredients market, such that the price for Australian-derived chondroitin sulphate may have market uptake as a premium ingredient.

Individual nutraceutical industry respondents indicated an interest in volumetric provision of chondroitin sulphate, with an indicative volume of ~1-10 metrics tonnes of chondroitin sulphate per year, or higher. Although other respondents were not aware of their company’s volumetric uptake of ingredients, they considered that joint health is their biggest seller so the quantities of chondroitin sulphate would be consumed in “significant volumes”. In the aquafeed industry, no specified rate of inclusion of chondroitin sulphate has been determined as yet: however, based on the rate of inclusion of other bioactive ingredients between 10 grams/tonne to 5% of the feeds, the demand for chondroitin sulphate by one compounder may be between 400 kilograms pa to multiple tonnes pa. In addition, animal feed compounders may consider the purchase of their entire requirement for an ingredient from one qualified supplier warrants a “premium price” [31]. However, the uptake of CS by the aquafeeds industry will need further investigation to introduce what is essentially a new feed ingredient. Therefore, the volumes of CS required by all potential end-users would need further clarification before a commercial decision is made on the venture by the Australian meat industry.

3.3.1 Evidence

The use of CS as a human nutraceutical supplement is well-established. Industry respondents indicated satisfaction with the level of clinical data already available in peer-reviewed literature for the use of chondroitin sulphate as a human nutraceutical. In addition, some nutraceutical companies have built their own proprietary portfolio of clinical evidence for their products. Other respondents, however, indicated that in order to justify a change of suppliers, “the data for (the Australian meat industry’s source of) chondroitin sulphate needs to be impressive” particularly human studies of the bio-availability profile of chondroitin sulphate, and its effect on inflammation and/or pain.

As CS has less of a history as a feed additive, animal feed compounders are insistent on the need for data in the target species. Therefore, exactly what evidence is required by specific end-users of chondroitin sulphate would need further clarification before further investment in product development.

4 Efficacy and analysis

The structure of chondroitin sulphate (CS) is well understood, as is the structural differences between CS from different animal sources, particularly those used in commercial production. The biosynthesis of endogenous CS has been established, although insight into the pathways for the breakdown of this polymer in the body is incomplete.

Analysis of CS is readily achieved using well-established laboratory techniques, particularly those of HPLC[10] and electrophoresis. These techniques can distinguish CS derived from different animal or marine sources based on disaccharide content, patterns of sulphation and molecular size of the polymer. This means that the analytical techniques needed by the Australian meat industry to evidence the bovine source of the CS produced are readily available.

The majority of evidence on the biological function of CS as a supplement in the body has been built around bovine- and shark-derived product, with some work in porcine and avian CS. There are no reported studies in ovine CS. However, studies of the efficacy for avian-derived CS have been sponsored by the producer of the product, and avian-derived CS is held now by researchers in the field to be less efficacious than bovine- and shark-derived CS. Shark-derived CS is considered by industry to deliver the greatest benefit to patients with hand OA, while bovine-derived CS delivers the greatest benefit in knee and hip OA [31]. The significance for the Australian meat industry is that knee OA is the dominant joint affected by OA on a population basis, and therefore represents a significant market opportunity.

The dominant animal source of pharmaceutical grade CS in the market is influenced by jurisdiction. Based on their experience with BSE, Europe prefers shark-derived CS, whereas the US and Australian markets prefers bovine-derived, based on consumer reluctance to support the harvesting of sharks.

From their publications of clinical trials with CS and glucosamine, there is a cohort of Australian medical researchers whom MLA may consider to undertake future research work on the CS project.

4.1 Industry guidelines

There are no accepted industry-wide guidelines to direct the quality assessment of industrial chondroitin sulphate preparations. Consequently, each company that uses chondroitin sulphate establishes (or does not establish) its own in-house testing procedures to direct CS preparation and ensure quality. CPC titration method is the most common industrial method used for analysis of chondroitin sulphate but is a non-specific method: that is, it is known to give false positive results for other GAGs as well as for adulterants e.g. carrageenan, proteins and surfactants. The testing regimens reportedly used by the major players within the nutraceutical industry, for example, are guided by the United States Pharmacopeia (USP) [36] and European Pharmacopoeia (EP) [37] methods. Both protocols use a variety of methods to determine the purity and quality of chondroitin sulphate against known standards. Near infrared (IR) scanning is also used by quality-focused companies to define the purity of chondroitin sulphate by identifying the presence of processing contaminants such as solvents used in extraction and any heavy metals [33].

Within the industrial landscape, the characterisation of chondroitin sulphate continues to be hampered by [38]:

[10] High performance liquid chromatography

- Lack of a simple, single, rapid and specific method of quantitative analysis of chondroitin sulphate or chondroitin sulphate/dermatan sulphate.
- The need for individual fractionation methods for each biological source of chondroitin sulphate, to obtain a fraction of high yield and purity.
- The need to use a combination of analytical methods to define the final fractionation product of. Such methods include chemical composition analysis, electrophoresis, chondroitinase digestion, and immunochemical reactions. Chondroitinase digests require further resolution using sophisticated techniques including HPLC, PAGE, FACE [11], capillary electrophoresis, mass spectroscopy, and nuclear magnetic resonance spectroscopy.

This lack of uniformity and clarity around the quality and origin of CS available commercially provides the Australian meat processors with the opportunity to establish a gold standard CS product, which is thoroughly defined and with a clear provenance, using existing analytical techniques.

This lack of uniformity and clarity around the quality and origin of CS available commercially provides the Australian meat processors with the opportunity to establish a gold standard CS product, which is thoroughly defined and with a clear provenance, using existing analytical techniques.

4.1.1 Clinical efficacy of Chondroitin Sulphate

The association of CS with the healthy joint has led to the administration of CS supplements to treat or manage diseased or damaged joints. The administered CS can be as a nutraceutical or food ingredient, or as a pharmaceutical. A leading cause of joint damage is osteoarthritis.

Chondroitin sulphate, taken with or without glucosamine, is regarded as one of the symptomatic slow-acting drugs for osteoarthritis (SYSADOAs) used to provide relief from the pain and inflammation associated with joint degeneration. Chondroitin sulphate is currently recommended by the European League Against Rheumatism (EULAR) and the Osteoarthritis Research Society International (OARSI) as a SYSADOA in Europe in the treatment of knee and hand osteoarthritis based on research evidence and meta-analysis of numerous clinical studies [39, 40].

CS is sold over the counter as a dietary supplement in North America, whereas CS and glucosamine are registered drugs in Europe [41].

Debate over the clinical efficacy of CS appears to continue in the literature, despite a long history of commercial production, consumer use, and publication of clinical trials and studies.

Recent scientific evidence suggests that proteoglycans, and their complex polysaccharides, are not only structural components within the cell, but are regulatory molecules with a profound influence over many cellular events and physiological processes [41, 42]. Recent evidence suggests that, in addition to an acknowledged structural role in cartilage within the joint, chondroitin sulphate polymers have biological roles in central nervous system development, wound repair, infection, growth factor signalling, as well as cell development, division, and migration. This broad portfolio of effects may support the use of bovine-derived CS in animal feeds and supplements, including for fish, as a bioactive.

[11] High performance liquid chromatography (HPLC), Polyacrylamide gel electrophoresis (PAGE) and Fluorophore assisted carbohydrate electrophoresis (FACE) are all well-established analytical technologies.

There are two grades of CS available commercially on the international market: nutraceutical (available in products sold over the counter) or pharmaceutical (available only on prescription).

Pharmaceutical-grade formulations of CS are reportedly of high and standardised quality, purity, and properties, due to the stricter regulations to which pharmaceutical drugs are subjected by national health institutes with respect to production and characteristics. The clinical trials considered most reputable by academic reviewers use pharmaceutical grade, hence bovine- or shark-derived CS. Consequently, many clinical studies of CS efficacy have been evaluated using a pure product with specific properties and physico-chemical characteristics. For example, a study to assess the long-term combined symptom and cartilage-modifying effects of CS used a highly purified preparation (≥95%) with a standardised structure produced from bovine cartilage [43].

Analysis of pharmaceutical and nutraceutical grades show that the quality and concentration of CS in pharmaceutical products is at a higher standard than that for nutraceutical products. In other words, the CS content in some nutraceuticals is a poorer quality CS which may further be non-compliant with the claims made on the label [44]. The biological activity of CS depends upon its structure and on other qualities such as polymer length and sulphation pattern [42, 44, 45]. Consequently, if CS in a nutraceutical product has a different or inconsistent physical composition and purity, there are questions of how likely it is to be able to exert comparable health benefits to those established for pharmaceutical-grade CS, as reported in clinical trial literature.

Recognising these confounders among others, the clinical benefits established by human trials for CS can be summarised as [41, 43, 46-52]:

- Safety and tolerability: In contrast with conventional pharmaceutical treatments, CS is widely accepted as having an excellent safety and tolerability profile which justifies long term administration of CS for OA and joint health. CS can be taken for extended periods, unlike other pain relief, and therefore provide a patient with improved quality of life;
- No drug interactions: the absence of drug interactions clearly distinguishes CS from other conventional pharmaceutical treatments. This means that CS can be taken by aged OA patients whose diminished health may require the use of other medications;
- Pain relief is a measurable benefit of CS administration over the longer time frame. CS does not provide the immediate pain relief of steroidal or non-steroidal medications or injections. However, the slower onset pain relief provided by CS has an enduring beneficial effect.
- Inflammation reduction is a measurable benefit of CS administration with longer term use. Inflammation is measured as a reduction in joint space width (or increase in joint space narrowing), and is characteristic of OA and other joint disease.

The clinical benefits for CS established by human trials can be summarised as:

- Safety and tolerability: CS is widely accepted as having an excellent safety and tolerability profile which justifies long term administration of CS for OA and joint health, in contrast with conventional pharmaceutical treatments;

- No drug interactions: The absence of drug interactions clearly distinguishes CS from other conventional pharmaceutical treatments. This means that CS can be taken by aged OA patients whose diminished health may require the use of other medications;

- Pain relief is a measurable benefit of CS administration over the longer time frame. CS does not provide the immediate pain relief of steroidal or non-steroidal medications or injections but has a slower onset with enduring effect.

- Inflammation reduction is a measurable benefit of CS administration over the longer time frame.

5 Refining Process

The majority of CS produced commercially to date is of low and variable concentration and poor quality. CS currently supplied to the market is extracted from cartilaginous feedstocks by means of an organic solvent protocol, largely based on ethanol. This well-established extraction methodology underpins a low technology operation, is amenable to small to medium scales of operation, provides product at a low cost-of-goods, but is non-specific for CS.

On behalf of the Australian meat industry, MLA has investigated the use of a continuous chromatography protocol for CS extraction as one extraction technology option. This methodology uses specific separation technologies to extract CS from other biological materials in the feedstock, and has the potential for the production of high and uniform quality, bioactive CS at a consistently high concentration from animal feedstocks.

That chromatography protocol (CSEP) has an established track record of industrial application in the food and beverage industries globally at commercial scale [53, 54], and has been adapted by MLA and its contractors for application in the meat industry. CSEP has most recently been adapted for specific extraction of bioactive compounds from dairy feedstocks, also at commercial scale.

CS may be supplied to the end-user either as an ingredient ready for incorporation into the end-user's products, or as a partially purified ingredient or slurry, ready for further purification by the end-user to meet their product requirements. The extent of purification by the CS refiner will need to be determined and customised for each end-user.

CSEP technology as a commercial scale extraction protocol has considerable operational advantages for the extraction of CS for use in the nutraceutical and feed industries:

- Use of non-organic solvents (such as water), which are low-cost consumables, and which eliminate the operational risk posed by large volumes of highly inflammable alcohols;
- Use of mild extraction conditions and aqueous solvents supports the retention of the structural integrity and biological activity by the polymers produced, including but not exclusively chondroitin sulphate;
- Is amenable to the production of valuable co-products, such as collagen, with minimal further investment, to improve overall process economics;
- Operates on a continuous basis with relatively efficient cycle times; and
- Has cost-effective process economics at laboratory scale, which support the extraction of a price-competitive product at commercial scale.

The use of CSEP technologies in the meat industry has been demonstrated to date at laboratory scale only. Further work is required before a decision for commercial scale rollout can be made by the meat industry. Such a decision needs to be supported by process efficiency and economics data from a larger pilot scale operation, and by quality analysis of the CS produced in direct comparison with conventional organic solvent protocols.

5.1 Process economics

Indicative costings of CS production using the CSEP process at laboratory scale are in a range consistent with the low end of the CS price scale, and therefore compare well with current commercial sources. This suggests that the CSEP process may deliver a cost-effective CS product into a cost-sensitive market.

The replacement of the organic solvent-based extraction protocol by CSEP has cost advantages in overall processing. This is particularly evident in the type of consumables and

hardware required: without organic solvents, there is no need for explosion-proof equipment, vessels, solvent storage, and wiring and lights. This cost saving may be significant: generally, the capital costs for any plant using flame and explosion proof material is accepted to be at least 2 to 3 times more expensive than the standard equipment required by a non-organic solvent-based process [55].

A cost estimate of CS production from commercial scale processing of feedstock of 13,500 animals/week has been calculated based on known costs at laboratory scale. From these cost calculations, an indicative production cost of CS by means of CSEP processing is A$33/kg (Table 3). An indicative price from the refiner (fractionator/value adder) to the compounder in this model is proposed as A$90/kg [56]. Direct cost comparison with other extraction technologies at any scale is limited at present.

Table 1: Indicative costings of annual production of bovine-based chondroitin sulphate using CSEP protocols at commercial scale.

Key feature	**Estimates**
Capital costs	A$3.95 million
Operating costs	A$1.9 million
Chondroitin Sulphate yield	56.5 tonnes pa
Cost of production of CS	A$33.17/kg
Wholesale price of CS	US$65/kg to S$150/kg

Source: [56]

A price estimate in this range is considered typical of CS produced by China-based manufacturers, who are currently responsible for more than 80% of CS product on the market. In contrast, CS prices of ~US$65/kg to US$150/kg are associated with higher quality material [57].

Therefore, the indicative costings of CS production using the CSEP process are in a range consistent of prices at the low end of the current scale, and therefore compare well with existing commercial sources (Table 3). This suggests that the CSEP process may deliver a cost-effective CS product into a cost-sensitive market.

Maintenance of these cost structures, or improvement of process economics for protocols developed at the current laboratory scale to translate to industrial scale production may be consistent with commercial viability of the process.

Table 2: Prices for chondroitin sulphate: comparison with proposed price from the CSEP process at scale.

Supplier	**Price/kg**	**Concentration**
Australian meat processor refining venture	A$90/kg	90%
Bioiberica	US$134/kg	≥ 90%
Redox, Australia	A$100/kg	unknown
Meitek	US$60/kg	85-90%

Sources: [56, 58].

5.2 Quality

Currently, global supplies of CS are predominantly provided by ethanol-based processes and are renowned for poor and inconsistent quality. Analysis of commercial supplies of CS reveals evidence of contamination by other biological materials from the original feedstock and by processing chemicals, as well as non-compliant concentrations. Using specific analytical methods such as HPLC, commercially available CS has been demonstrated as not only of lower concentration than specified by the manufacturer/refiner, but intentionally

contaminated with those molecules which may influence non-specific methods of CS quantitation, such as CPC[12], to give an artificially inflated estimate of CS concentration. The recognition of the extent of this recalcitrant problem by the nutraceutical and other industries provides the Australian meat processors with an opportunity not only to provide high quality, high concentration CS from BSE-free feedstocks to national and international nutraceutical and animal feeds industries, but potentially to reframe the quality metrics achievable for CS.

Consequently, a key selling point then is a CS product of high and consistent quality and concentration, both of which are likely outcomes of the CSEP process and its inherent chemical specificity. To date, only preliminary quality analysis of the product derived from the laboratory scale process has been completed [55]: however, this report recommends that an independent, appropriately certified third party be engaged to provide a detailed analytical profile of the following:

- Lab-scale CSEP-extracted product, especially of product from repeated cycles of the process; and
- Pilot-scale CSEP-extracted product, especially of product from repeated cycles of extraction.

The outcomes of this analysis should be benchmarked against a number of commercial CS products, and should make use of high specificity techniques such as HPLC and recognised commercial analytical standards.

5.3 Volumetric production

The organic solvent-free or CSEP process uses a single extraction step to recover CS from hydrolysed feedstock, and therefore the processing time from feedstock to CS is of shorter duration compared to alcohol-based processes. Therefore, with shorter processing throughput time for hydrolysed feedstock, CSEP may provide a larger capacity to contiuously process feedstock on an annual basis. The attribute of CSEP to deliver improved volumetric productivity may have additional economic benefits to the refiner, by processing additional quantities of feedstock per year compared to organic solvent extraction. At this stage in CSEP process development, the quantities of feedstock processed are estimates only, therefore this report recommends that further work be done at pilot scale to gauge the extent to which CSEP improves the volumes of feedstock processed and consequently the quantities of CS recovered per annum.

This report considers that initial work to scale up CSEP to refine CS from hydrolysed cartilage, as well as commissioning of a commercial scale plant, may be eligible for the R&D tax incentive scheme for the organisations that fund that effort.

Based on the molecular specificity of the separation technology and the mild conditions of operation, CSEP may present the opportunity for the Australian meat industry to redefine the gold standard in bioactive polymers in the market, particularly for chondroitin sulphate, reliably produced at consistent and high concentration by a cost-effective process from sustainable meat industry feedstocks with a transparent and auditable supply chain.

[12] Cetylpyridinium chloride is a quick and easy analytical method which is often used to measure CS but which is a non-specific method: it is known to give false positive results for molecules related to CS as well as for adulterants.

6 Conclusion

6.1 Target market

The most significant opportunities for the Australian meat industry's chondroitin sulphate on a volumetric basis are within the human nutraceutical ingredients and dietary supplements, and industrial and domestic animal sectors as animal feed, aquafeed and in veterinary dietary supplements. These opportunities are estimated based on both anticipated volume and/or value for chondroitin, the need for additional feed development, the demand for additional evidence of health benefits, and industry appetite for this ingredient.

The prospective applications identified for CS in this report (Figure 1) are based on a qualitative evaluation of the market opportunity for Australian bovine-derived chondroitin sulphate. This report recommends a detailed financial model in order to provide a firmer, quantitative evaluation of the relative commercial potential of each opportunity.

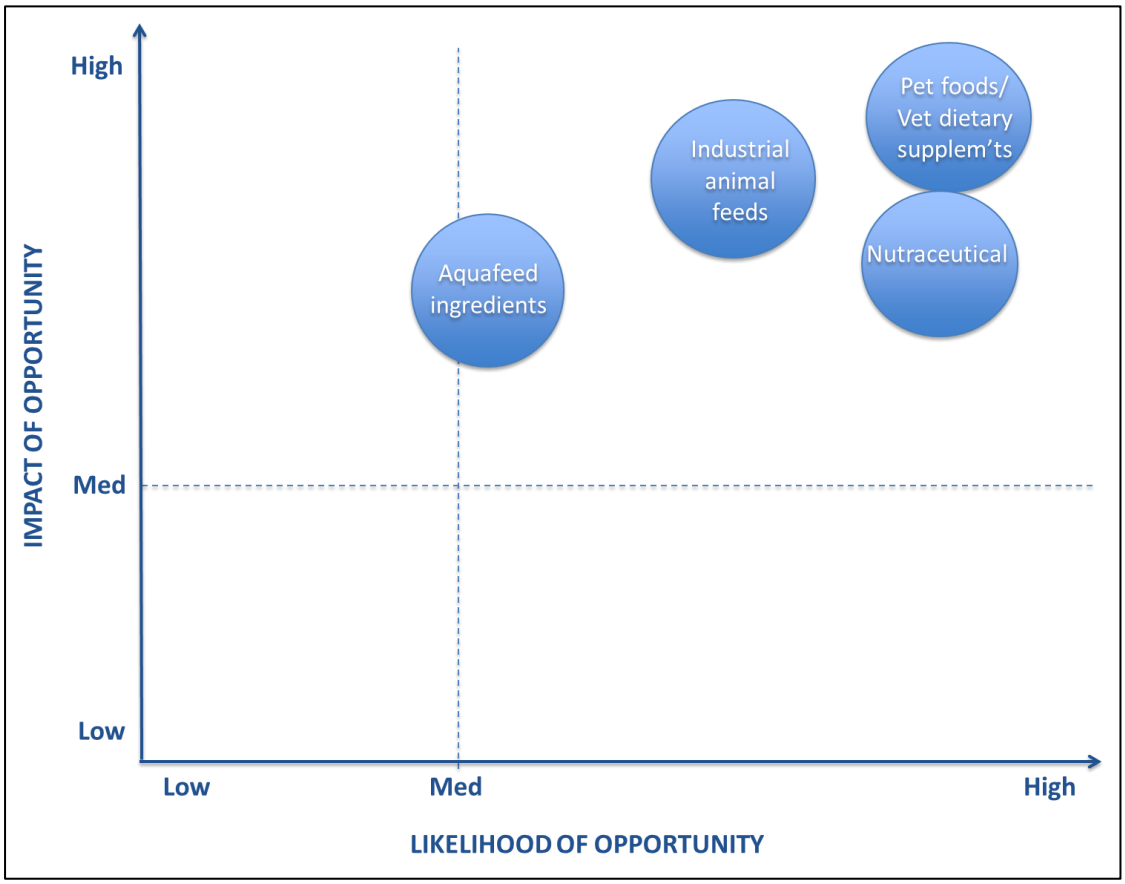

Figure 2: Market opportunity for chondroitin sulphate: an indicative view of the market opportunity for chondroitin sulphate as assessed from desk review and industry stakeholder interview (not drawn to scale).

CS has established markets within both the human and pet nutraceutical supplements sectors, and potential markets within the industrial animal feed sectors, particularly that for fish. The drivers within the nutraceutical and veterinary supplements markets are driven by the impact on joint health of osteoarthritis and ageing, and by the poor quality CS product currently available to supplements manufacturers. The drivers for potential uptake within the industrial animal feed markets are the demand for bioactives to improve growth and performance under conditions of intensive farming: for this market, efficacy in target animals needs to be demonstrated.

6.2 Redirect the supply chain

Development of a venture to refine cartilage from meat processing to extract CS may impact on the existing commercial supply chain for that product.

The current supply chain for the production of chondroitin sulphate from animal sources (bovine, ovine or porcine) is shown in Figure 3. The raw material from animal slaughter is sold to ingredient processors, commonly in China, for extraction and purification. Partly or fully purified chondroitin is then supplied globally by those refiners to end-users who are nutraceutical and feed ingredient compounders: to companies such as, Nature's Own, Nature's Way and Ridley Animal Feeds. In this way, animal-derived ingredients such as chondroitin sulphate are incorporated into products for the nutraceutical and veterinary dietary supplement markets, and into feeds for industrial animals (chickens, pigs, and fish).

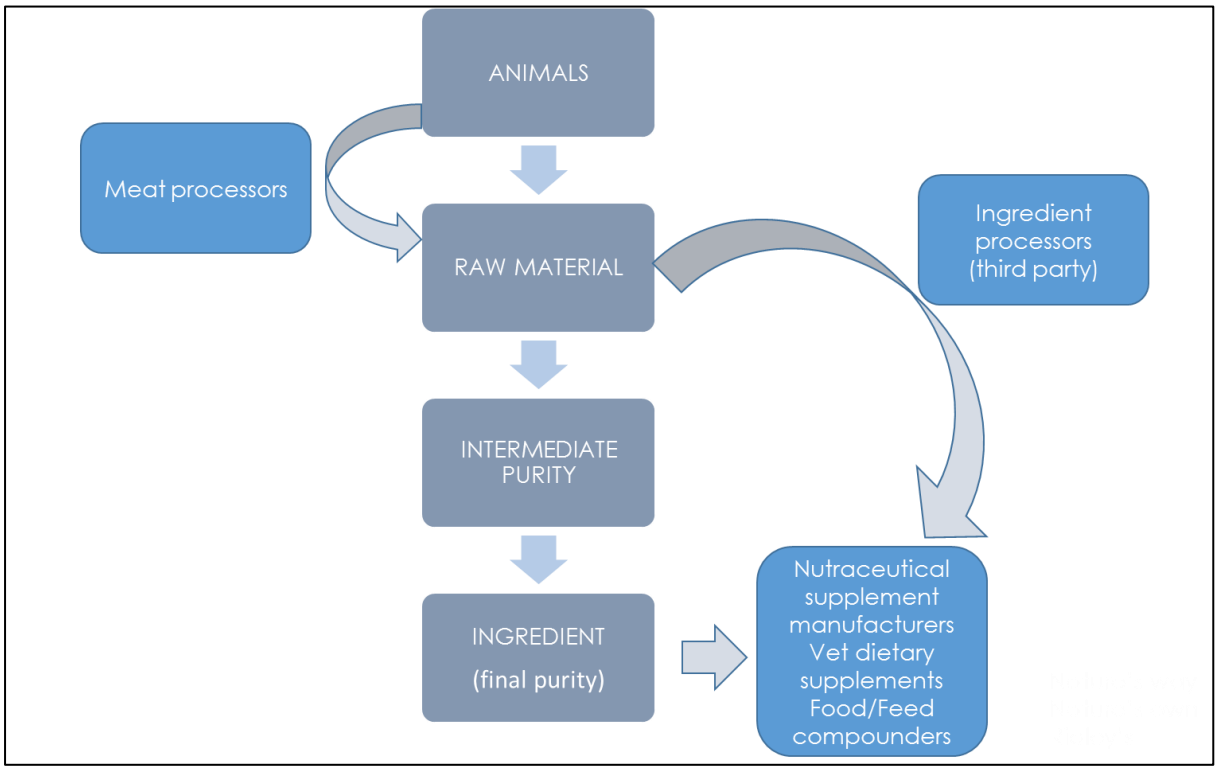

Figure 3: Supply chain for production of chondroitin sulphate: current

The recommended change to the supply chain for chondroitin sulphate derived from the Australian meat industry is outlined in Figure 4. This alteration provides the opportunity for the Australian meat industry to value-add animal-derived cartilage by controlling the extraction and refining of a valuable nutraceutical and feed ingredient for consumption within a large and steady global market.

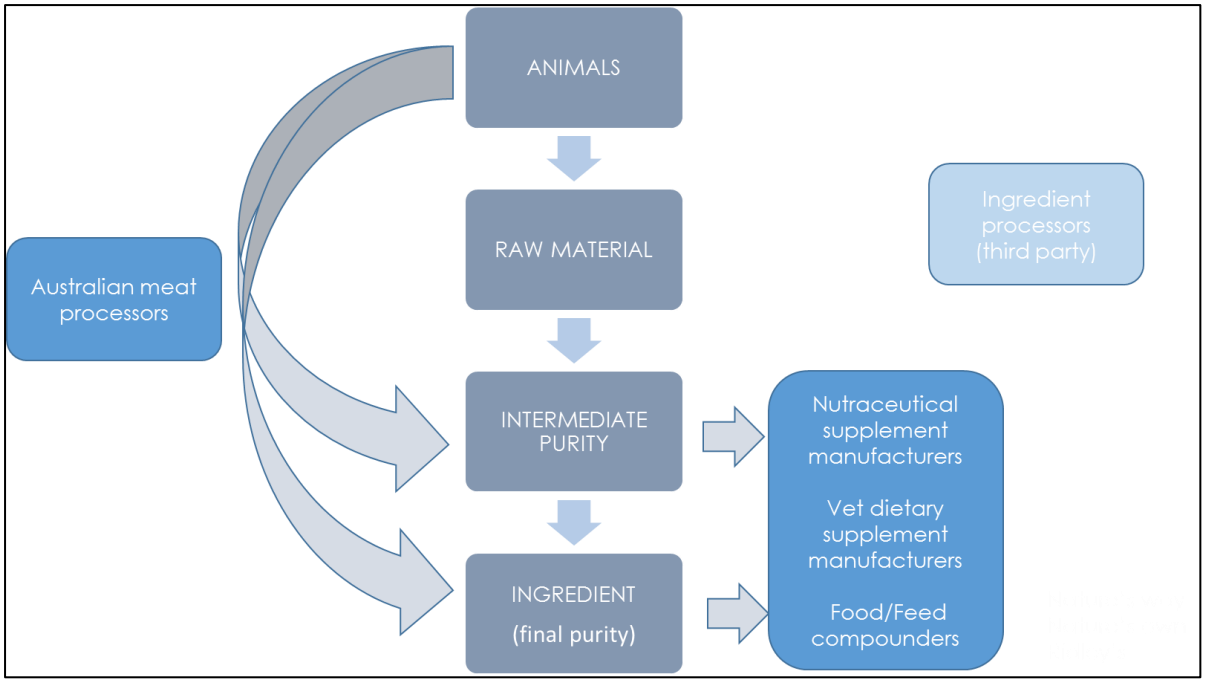

Figure 4: Supply chain for production of chondroitin sulphate: a prospective option for the Australian meat industry.

CS may be supplied to the end-user either as an ingredient ready for incorporation into the end-user's products, or as a partially purified ingredient or slurry, ready for further purification by the end-user to meet their product requirements. The extent of purification by the CS refiner will need to be determined and customised for each end-user.

The first potential strategy for local production of chondroitin sulphate requires investment in local centralised processing facilities for extraction of chondroitin sulphate from aggregated animal biomass (cartilage). The processing facility will need to have the appropriate analytical capability on-site for quality management of the extraction operation in order to meet the standards of major industry participants.

A second strategy locates extraction and purification operations overseas, with meat by-product refiners within the Australian meat industry maintaining ownership of the supply chain up to final product. Should the Australian meat industry intend to use a China-based processor, the recommended route would be firstly to source an existing, top quality factory[13], then secondly to establish and audit appropriate quality testing methods. For this approach, the Australian meat industry should seek expert advice to locate and audit a Chinese manufacturer: one industry respondent commented that both rents and salaries within the higher quality Chinese manufacturers are starting to rise, so an economic cost benefit assessment of this approach is recommended.

[13] For example, Yantai Dongcheng Biochemicals Co., Ltd., based in Yantai, China is GMP and ISO 9001-certified. It is also the first facility in China that is USP verified.

7 Next steps

This report recommends that the new chondroitin sulphate refining business be established using a staged approach (Implementation Strategy) supported by a dedicated implementation team.

The key to success of the staged approach is securing partners from within the supply chain or as end-users of CS. The roll out of the implementation strategy is best achieved through strategic relationships developed with partners who potentially participate anywhere along the supply chain from feedstock processing to final product manufacture, and which may include collaborative relationships or joint ventures. These relationships bring technology, manufacturing, marketing capacity and know-how to the venture, and in this way help to manage the risk of the new venture for the meat industry and potentially bridge capability gaps within the meat processing industry. In addition, the staged approach within a partnership framework rolls the project out to meet individual stage gates and "go/no go" points that provide a level of risk management to the new enterprise.

Overall, the staged approach provides the meat industry and its partners with opportunity to develop a full scale manufacturing process from proprietary technology and to assess the market readiness of the product. The value of the staged approach for both operational deployment as well as product rollout are comparable: there is time allowed to develop the market readiness of the bioactive products; to prepare for commercial release of the bioactive ingredients into their target markets, and to examine the options for business structures to support the CS enterprise, which may include integrating the new value-adding refining technology into existing operations.

The prioritised first target market is in the human nutraceutical and veterinary dietary supplements markets.

To access this market opportunity, the Australian meat industry and its partners need to establish the production of animal-derived CS, as one with:

- Scalable manufacturing processes;
- Sustainable production from a transparent and auditable supply chain;
- Reliable product supply at appropriate volume to meet end-user needs;
- Defined and consistent quality and purity standards
- Price targets; as well as
- Innovation in feed ingredient composition, with benefits substantiated by an evidence pack in target animals.

7.1 Implementation strategy

The Implementation Strategy is a suite of sequential stage gates that allows the meat industry to assemble the data necessary to make an operational decision regarding the use of CSEP for the industrial production of CS. Those stage gates provide 'go/no go'

A key issue for the Australian meat industry in the commercial decision-making process for a blood-based bioactives venture is whether demand by the feed or pet food industry will support the conversion of large volumes of by-product streams[14]. In contrast, the market uptake of CS within the human supplements sector, particularly in the US, appears substantial and consistent. However, details around the volumetric uptake by the market need to be confirmed as will the price.

[14] See MLA's "Blood-based proteins: A market review" A.BIM.0040, January 2015.

Therefore, an implementation strategy for the Australian meat industry and its partners to value-add meat processing by-product streams as products for the human nutraceuticals and pet feed markets can be framed as a series of 'go/no go' stage gates, each representing disctinct decision points for the progression (or otherwise) of the CS production venture.

1.1.1 Stage Gate 1: Demonstrate the product; assess industry uptake

- *Demonstrate the Product*: A key first step is to confirm the interest of both the nutraceutical and pet food industry in buying the product. Production of a high quality, high concentration, pure product is of commercial interest, particularly within the nutraceutical market (as determined by industry interviews undertaken during this report), and so early batches of CS need to be assessed by industry to confirm their commercial interest. As players within the nutraceutical and pet foods industry are potentially valuable partners, this step needs to be conducted with thoroughness and commercial sensitivity.

- *Scalable technology*: Demonstrate that the technology to extract CS from meat processing by-products can be scaled up. Pilot and larger scale production runs will also generate, firstly, product that can be analysed for quality, secondly, product that can be released to end-users for assessment, and thirdly, production data to refine capital and operating cost estimates. The demonstration of the process at scale may be undertaken by a manufacturing contractor (CMO - see insert). A manufacturing contractor is also a potential partner for this venture.

- *Production targets*: Interaction with the human nutraceutical and pet food industries to define the rate and volumetric uptake of CS. Understanding production targets will define the scale of feedstock supply needed to support a reliable and sustainable supply of product to market on commercial terms. In addition, an understanding of production targets will also refine the meat industry's assessment of the commercial viability of the value-adding venture overall.

What value does a CMO bring?

Toll or contract manufacturing organisations (CMOs) are able to generate proprietary products made exclusively for and on behalf of the contracting firm.

The manufacturing contract may be for small, short-term prototype runs, to full-scale high-volume production that span years. In the context of building a value-added venture, the critical advantage to the meat processing industry of outsourcing manufacturing lies in the CMO's experience and capability to translate the research-derived manufacturing technology (CSEP) into a robust, reliable industrial process. Additional benefits to the contracting firm of using a CMO may also include:

- Compensation for lack of capacity or technical capability within the contracting firms operations, based on the CMO's manufacturing knowledge and experience;
- Streamlined time-to-market of a new product;
- Quality control, reliability and reproducibility within all phases of product manufacture;
- Control of processing and refining intellectual property;
- Efficient manufacturing costs based on the CMO's efficient operations;
- Lowered or circumvented capital investment in equipment, personnel and training required to create an effective in-house production operation, at least at the outset of manufacturing; and
- Lowered material costs, depending on the purchasing power of the CMO compared to that of the customer.

1.1.2 Stage Gate 2: Establish a collaborative partnership or joint venture

- *Strategic relationship(s):* Identification of potential partners and negotiation of the relationship based on new ingredient (CS) manufacture and product development. Those strategic relationships may be developed with partners who participate anywhere along the supply chain from feedstock processing to manufacturing of the final CS-containing product, and may include collaborative relationships or joint ventures.

1.1.3 Stage Gate 3: Define the supply chain

- To minimise the distance the feedstock is transported, the cartilage value-adding industry is anticipated to be based within meat producing areas and concentrated around a small number of regional processing facilities. Based on the need for timely processing of the cartilage feedstock and the geographic spread of feedstock producers, a *hub and spoke precinct model* for feedstock processing is recommended within the meat producing regions, with the refining hub at the centre of the spokes of meat processors.

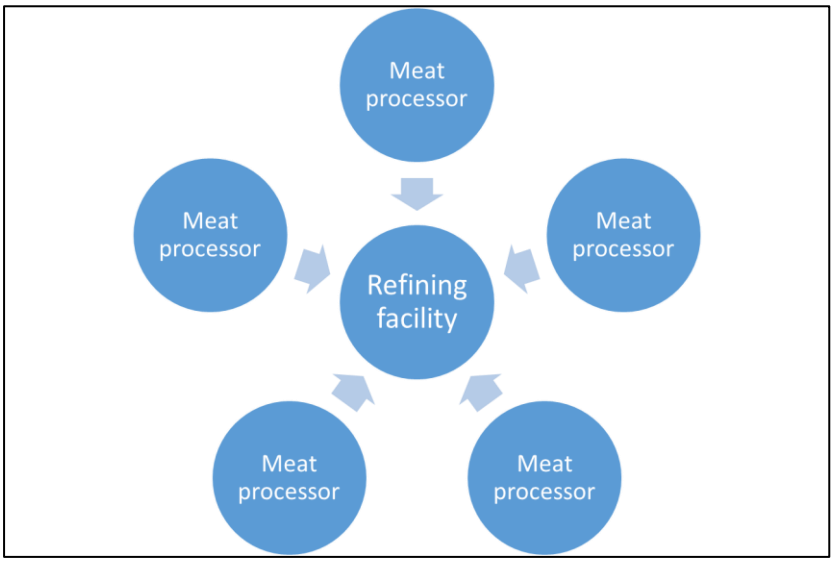

Figure 5: Hub and spoke model for the chondroitin sulphate value-adding industry: the refining hub at the centre of the spokes of meat processors

The critical factor determining the co-location of the refining facility hub within its coterie of feedstock producers is the radial distance of the refining facility from those producers, dictated by the time required to transport the feedstock. The number of processors within the precinct structure is determined by the quantity of feedstock required to meet volumes of production of the value-added product.

- Aggregation of feedstock needs to be achieved within suitable timeframes based on feedstock instability. The Australian meat industry and its partners may consider using *strategic logistics modelling* to manage feedstock aggregation over the wider meat processing footprint. The model is needed to predict the location of each centralised regional refining plant co-located with the meat processors, based on the hub and spoke model to meet the time constraints posed by the feedstock. Each refining plant will be located within the precinct at an optimal logistical distance from the coterie of feedstock suppliers based on the optimal time needed to aggregate feedstock. Therefore, the geography of the hub and spoke model is based on aggregation of adequate volumes of

feedstock of appropriate quality: such that volumes of feedstock meet production targets at each refining centre.

- How will each refining plant be equipped? Each centralised regional refining facility may share the same set of technologies, capacity, and know-how to produce the entire value-added blood-derived product portfolio. Alternatively, as the dairy industry has done, individual refining centres may specialise in a subset of that entire portfolio, based on the volumetric demand for each product line and the availability of feedstock.

- The definition of those production volume targets needs to be modelled with input from the feed industry, for each stage of product rollout, for each product type, and for each precinct by means of *production scenario modelling*.

- A small number of distribution and warehousing centres may be needed to meet the logistical demands of export of the value-added chondroitin sulphate. These may be located at ports and/or road and rail transport interchanges.

1.1.4 Stage Gate 4: Define the Business structure

There are a number of options for structuring the business venture to refine cartilage within the meat industry, predicated on optimising various significant business considerations such as feedstock aggregation and supply, technology deployed, partnership structures, and relationships with end-users.

- Feedstock aggregation: A number of recommended business structures for the value-adding refining venture is suggested, based on different models of feedstock aggregation: in-house feedstock production from a single meat processor (independent model) or on feedstock production from a number of stakeholder meat processors (joint venture (JV) or cooperative models), with supplementary volumes provided by contract suppliers as required to meet production volume targets.

- Transparent and auditable supply chain: is anticipated to be a key attribute of the commercial arrangement with end-users [31].

- Technology: The business structure of the value-adding venture may also consider the issue of the refining and extracting technology. At the outset, the business model may therefore consider a joint venture with an appropriate manufacturer, and/or transfer of the scaled up extraction technology from a contract manufacturing organisation (CMO or CSIRO) into the refining business.

- Partnering: In addition, the value-adding business may consider a JV based on a partnership between the meat processor(s), refining or manufacturing business and an end-user, for example, a feed ingredients producer or feed compounder. The advantage of such relationships for the feed industry partner might be to secure meals and/or bioactive additives to meet quantity, quality, delivery, and/or sustainability targets. The advantages for the meat industry partner may include access to technical capability, highly valuable off-take agreements as well as financial and risk mitigation benefits. There are a number of financial and operational arrangements within this scenario that the meat industry may find worthwhile considering.

1.1.5 Stage Gate 5: Staged technology rollout

- Technology rollout: The prospective chondroitin sulphate refining business may be established using a *staged approach*, which takes advantage of different manufacturing options. These options allow the meat industry to develop, in a step-wise approach: scale-up of the technology (currently at lab scale) to a commercial-ready process,

assessment of the market readiness of the product and its performance and chemical documentation, and to secure and/or develop the skillsets needed to operate the refining operation, before achieving full scale commercial manufacturing. The recommended staged technology rollout includes such options as:

1. Outsource cartilage processing to a contract manufacturer (CMO or tolling) to establish the scalability of the technology, and the market-readiness of the products.

2. Establish the refining facility by means of a JV with, or acquisition of, an established value-adder/refiner with the appropriate manufacturing capability.

OR

3. Establishment of a greenfield, independent refining facility co-located with the feedstock producer(s) and building in-house extraction capability based on transfer of the technology from the CMO.

7.2 Implementation Team

The Implementation Team will support the staged Implementation Strategy and be responsible for

- Strategic partnerships: Identification of strategic partners, and the development and management of relationships, on behalf of the meat processors and the refining venture. Strategic relationships are as essential as supply chain optimisation to overcoming the barriers and uncertainties that the meat industry may face in developing a sustainable and competitive value-adding CS venture. In one aspect, outsourcing in the agri-industry to build a value-adding venture (i.e. by means of a CMO) may evolve towards partnership and strategic alliance, bringing both tangible financial and strategic benefits to the venture. On the other hand, strategic relationships with end-users of the value-added products may reduce the risk of the venture by securing off-take agreements;

- Product assessment: evaluation of the CS product refined from Australian meat processing by-products by potential end-users within the human nutraceutical and pet foods and supplements industries; and

- Strategic modelling: Project management of the modelling needed to assist the Australian meat processing industry to define and initiate a successful CS refining venture, with input from all partners and end-users. In particular, the financial modelling would be valuable in supporting commercial decision making by the meat processing industry and understanding the time to pay-back on capital expenditure.

CHONDROITIN SULPHATE: STAGED IMPLEMENTATION STRATEGY

Target market: human nutraceutical market, driven by the current issues of poor quality and inconsistent concentration CS supply; and the pet food and supplement markets, driven by the demand for "natural" bioactives or cereal-free ingredients to improve pet health and wellbeing.

Stage Gate 1: Define & demonstrate the product; estimate industry uptake

Stage Gate 2: Establish a collaborative partnership or joint venture

Stage Gate 3: Define the supply chain: consider a *hub and spoke precinct model* for feedstock processing within the meat producing regions, with the refining hub at the centre of the spokes of meat processors.

Stage Gate 4: Define the business structures to achieve: feedstock aggregation, technology deployment and end-user alliances

Stage Gate 5: Staged technology rollout, and secure or outsource the skill sets needed to operate the refining operation, for full scale commercial manufacturing.

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