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Potential commercial and economic value of bovine amniotic fluid and placental material for the Australian meat processing industry

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Executive summary

While the original remit of the project was to investigate bovine amniotic fluid and placenta, cultural preferences of relevant markets brought ovine amniotic fluid and placenta into consideration also.

Currently both amniotic fluid and placenta are collected from the Australian red meat processing industries in small volumes to be incorporated in limited products for niche markets. Placental material has some commercial value in the Asian medicine industry and the cosmetic industry. There is real opportunity to supply these 2 markets at far larger scale. There are already many cosmetic products on the market containing extracts from this tissue, in both cream and capsule form. Chinese medicine has utilized placenta for hundreds of years and there are opportunities to generate Australian products for Chinese medicine practitioners and for the Chinese hospital system. The main obstacles are achieving TGA registration of products to realize access to these large markets, and an underdeveloped supply chain to deal with larger volumes of raw materials.

Amniotic fluid contains many biologically active peptides that could be extracted and purified for therapeutic purposes. Preliminary research has shown that these components could be useful in the promoting maturation of preterm neonates, wound and bone healing, burns treatment (including scarring) and stem cell culture. Access to these opportunities will require substantial but staged R&D. However, this approach needs to be underpinned by 2 fundamentals – the composition of amniotic fluid and its safety.

There are players in the meat processing industry who are interested in developing opportunities but lack infrastructure and sometimes the knowledge necessary to do so. We have identified potential industry personnel who are keen to expand their operations to add value but all indicated that there would need to be a commercially sound case to do so. At the simplest level export opportunities for frozen unprocessed placenta could be developed.

Recommendations

- Develop opportunities to supply placental material to a Chinese medicine industry exporting globally (but to China in particular). This opportunity could be effectively progressed through collaboration with individuals that are knowledgeable, well respected and connected in the Chinese community and interested in the promotion of Chinese medicine products from Australia. Regulatory accreditation and safety also are very important for these products as it would allow distribution within Australia and so would raise global consumer confidence in the products.
- Address critical knowledge gaps that currently limited the development of therapeutic products from amniotic fluid, and that will hamper some of the following recommendations. The major issues are the lack of knowledge of the composition amniotic fluid at any stage of gestation from any species and guaranteeing its safety to collaborators and customers. We recommend 2 linked R&D projects to resolve these issues
    1. development of protocols and tests to ensure freedom of amniotic fluid or its extracts from infectious agents and reduction in the levels of natural hormones, with minimal loss of bioactivity; and
    2. a detailed analysis of the composition of bovine amniotic fluid through 3 stages of gestation. The reasons to support such an analysis are a) some of the obvious protocols for the first project may reduce the bioactivity of the treated amniotic fluid, b) some applications require thorough definition of compositions for regulatory approval, and c) knowledge of composition of 3 different stages will allow for selective harvesting of amniotic fluid for specific high value applications.

Australia does have strong capacity to conduct these analyses.

- Facilitate development of opportunities to supply both amniotic fluid and placenta to cosmeceuticals markets servicing Western and Asian customers by establishing a strong

supply chain and promoting regulatory accreditation of high quality products to raise consumer confidence. The global cosmeceutical industry is growing at 8-12% per annum and amniotic fluid and placenta derived products can be developed within Australia to supply the Asian market. Customer/cultural preferences particularly around species could be addressed by developing an ovine (rather than bovine) supply chain for markets such as China where ovine derived products are preferred. We have identified parties that are interested in participating and improving the value chain.

- Facilitate R&D investigation of the use of amniotic fluid (or extracts) for wound healing applications. Two very different markets have been discovered – treatment of wounds from chronic disease in the developed world and acute wound care in the developing world. The opportunities for animal derived wound healing products supplying the more sophisticated health systems industry have a limited time window (approximately 20 years) as more recombinant molecules are developed and reach the market. The R&D required and path to market for these products is well understood by research institutions.
- The second opportunity is developing and supplying amniotic fluid or placenta derived wound dressings to developing countries with high incidences of burns and injuries. These countries also have less stringent regulatory requirements than Australia, which would mean a quicker path to market, and fewer costs. However, our current knowledge about developing the path to market for these countries in this sector is sparse and further investigation is needed for this strategy.
- Australia has excellent capacity in R&D to the clinic and beyond in wound healing.
- Pursue opportunities in supplying amniotic fluid (or extracts) to assist in the maturation of very low birth weight premature neonates. A leading clinician and researcher is interested testing the feasibility of such an application.
- Pursue development of amniotic fluid as an additive for stem cell culture media. Australia has a strong network of researchers in this field. Feasibility could be tested very quickly.

A final recommendation is to address the lack of awareness among some of the supply chain members of the possibility of contracting notifiable diseases such as Q fever through handling animal derived materials. There is a need for a higher level of information dissemination (maybe through WorkSafe) around health risks to target all industry operators so that as they are all aware of the dangers, particularly when procedures are alerted, and can take evasive action such as immunisation.

Contents

Abbreviations

AF	Amniotic Fluid
AFS	Amniotic fluid stem cells
AICS	Australian Inventory of Chemical Substances
AMH	Australia Meat Holdings – now JBS Swift Australia Pty Ltd
ARTG	Australian Register of Therapeutic Goods
AQIS	Australian Quarantine and Inspection Service
BSA	Bovine Serum Albumin
BSE	Bovine Spongiform Encephalopathy
CCS	Cold carcase
CHC	Complementary Healthcare Council
CMEC	Complementary Medicines Evaluation Committee
COGS	Cost of goods
CSIRO	Commonwealth Scientific and Industrial Research Organization
Deprec	Depreciation
cGMP	Current Good Manufacturing Practice
FCS	Foetal calf serum
FDA	Food and Drug Administration
FSANZ	Food Safety Standards of Australia and New Zealand
GDP	Gross Domestic Product
GMP	Good Manufacturing Practice
HACCP	Hazard Analysis and Critical Control Point
HIV	Human immunodeficiency virus
MHRA	Medicines and Healthcare products Regulatory Agency
MLA	Meat and Livestock Australia
MSDS	Material Safety Data Sheets
NBUVB	Narrow band ultra-violet light of type B
NEC	Necrotizing enterocolitis
NICNAS	National Industrial Chemicals Notification and Assessment Scheme

NHMRC	National Health and Medical Research Council
PBS	Prescription Benefits Scheme
QUT	Queensland University of Technology
RBWH	Royal Brisbane Woman's Hospital
SG&A	Selling, general and administration
SUSDP	Standard for the Uniform Scheduling of Drugs and Poisons
TGA	Australian Therapeutic Goods Administration
QA	Quality Assurance
UWA	University of Western Australia
VLBW	Very Low Birth Weight
VLU	Venous leg ulceration
WIRF	Women and Infants Research Foundation
WHO	World Health Organization

1 Introduction

Currently amniotic fluid from livestock has little commercial value and much of it goes to render or is discarded in meat processing plants and dairies. It is known that amniotic fluid contains numerous biologically active peptides and other bioactive molecules that are involved in the protection and development of the foetus and the amniotic membrane (Berger and Bergemann, 1958). The individual concentrations of active molecules are very low (100 -1000 pg/ml) but combinations and ratios of bioactives vary through the stages of gestation. (See Appendix 12 for a list of bioactives reported in the literature to date).

Similarly, placenta currently does not have a high commercial value in Australia and most goes to render. In the past bovine placenta has been exported to Japan in container load quantities but the operation ceased due to perceived animal welfare concerns, the BSE concerns of 2001 and due to attitudes within the work force. A discussion with Dennis Wyatt of the Northern CO-OP. Meat Co Ltd. revealed that it would be possible to recommence collecting bovine placenta on a fairly large scale again if it were demonstrated to be commercially viable. There would also be a possibility that a portion of the extra value could be passed to the producer. If growers knew they could obtain better prices for pregnant animals they would almost certainly supply them. This occurred on a small scale when the foetal blood prices were at their highest and some growers were offered 10% premiums for “pregtested” cull cows in 2004 (<www.mla.com.au/TopicHierarchy/InformationCentre/Coproducts/Bioactives/default.htm.

Ovine placenta is collected intermittently on a small scale in some southern Australian abattoirs and exported to Japan, Asia and New Zealand (pers. comm. John Langbridge AQIS, June 2007). Ovine amniotic fluid is collected on a small scale and most is exported to Asia for cosmetic purposes (Thimba Li) with a small amount (approx. 60 litres in 2006) being used by Australian cosmetic manufacturers in products, which are exported to Asia. A large bovine processor indicated that there is some interest in Australian bovine placenta from China but collection is not currently economically viable.

The 2006 Australian bovine herd included approximately 13 million female (30-40% of total herd) and approximately 2.3 million are slaughtered annually. It is believed that 10-15% of these would be pregnant (pers. comm. MLA April 2007) which indicates that the total number of pregnant animals that go to slaughter annually is approximately 290,000. There is approximately 8 litres of bovine amniotic fluid (including allantoic fluid) at term (Miles *et al.*, 2004). Assuming an average of 4 litres of amniotic fluid per animal and a 30% collection rate, a potential annual collection of 348,000 litres is possible. The weight of a bovine placental material at full term is 2 - 4.5 kg (Zhang *et al.*, 1999). The placenta collected through abattoirs would not be full term so collection volumes could be calculated on a 2 kg average weight to give an annual total of 580,000 kg (5,800 tonnes) and assuming a 30% collection to a give final possible collection of 1,740 tonnes in Australia annually.

Placental material is currently collected from other species including ovine, deer and goat and these materials could be considered as well as bovine material.

There is between 250 ml and 1,800 ml of amniotic fluid in a late gestation ewe (Miller *et al.*, 1997). Approximately 1.67M (2003 figures and excluding lambs) sheep are slaughtered annually and approximately 30% (501,000) of these are female with 10-15% pregnant (pers. comm. MLA July 2007). These figures indicate that approximately 50,000 pregnant ewes are slaughtered annually to produce a potential 50,000 litres of amniotic fluid. Assuming that 30% is collected a final possible annual collection estimate of 15,000 litres can be calculated. Sheep placental material weighs 209-600 g at term (Wallace *et al.*, 2002) and using the above figures and an average placental weight of 200 g and 30% collection rate a possible annual yield of 450,900 kg (451 tonnes) of placenta is possible.

Goat amniotic fluid could also be of use and there can be up to 500 ml at full-term (Bongso *et al.,* 1979). Australia is the largest goat meat exporter in the world with Queensland producing 36% of

the national total. The Australian 2004-5 slaughter was 1,257,000 head (MLA fast facts goat meat 2005). Assuming 30% female (377,100) and 10% pregnant (37,710) and 200 ml of amniotic fluid per pregnant doe gives an absolute yield of 7,500 litres. Assuming a 30% collection rate this gives an approximate a potential final volume of 2,300 litres of caprine amniotic fluid per annum in Australia.

Deer placental material is collected within Australia and New Zealand for complementary medicine purposes and is in demand in Asia. The number collected is unclear but approximately 56,000 deer were slaughtered in Australia in 2000, which would include 2,520 pregnant animals to produce a possible 1,510 kg (1.5 tonnes) of placenta (assuming 30% collection and a 200 g average placental weight) (<www.rirdc.gov.au/reports/DEE/01-085.pdf>).

Figure 1 shows a typical nutraceuticals value chain (based on chondroitin sulphate) with a break down of costs at each stage of production. In reality processors often receive much less than AUD$12/kg for materials collected at the abattoir; for example an ovine abattoir in Victoria received AUD$5/kg for placental material in July 2007. Meat processors could become active in and gain more value from the bioactives industry by establishing well defined collection activities. A further option could be the establishment of extraction plants close to their abattoirs to boost their revenues and expand their activities.

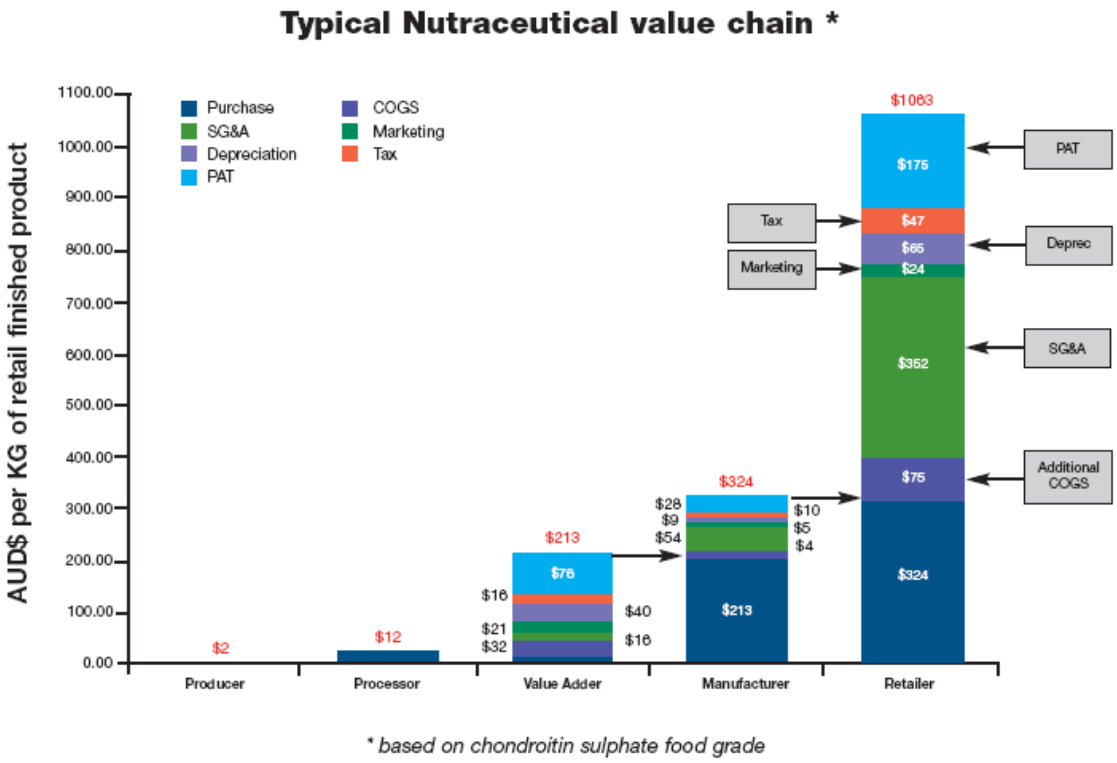

Figure 1 Adapted from MLA Bioactive Bulletin (<www.mla.com.au/TopicHierarchy/InformationCentre/Coproducts/Bioactives/default.htm>)

The gaps (accreditation and capacity) that have been identified in the value chain for placental and amniotic fluid derived products in Australia. These gaps are common to the bioactives industry and lead the possible value adding opportunities being lost to the Australian meat processors. The lower volumes of placenta and amniotic fluid available in Australia compared to countries such as China and the USA mean that there is little established infrastructure (capacity) for their collection and processing. Accreditation is expensive and difficult to obtain and so processors and other members of the supply chain are discouraged. These issues add costs and would indicate that Australia products will be more expensive but may do well with marketing on quality and safety.

Placentation in Ruminants

The term placenta is used loosely in some literature and by many industry personnel, so it is important to note that some processors collect the complete uterus containing the membranes and slink while others collect the membranes only. Both are further processed under the term “placenta”. The yield would be vastly different in that the placental membranes weight approximately 200-600 g at term (Wallace *et al.*, 2002) while a gravid uterus including the slink would be approximately 2,650g at midterm gestation (Grazu-Bilska *et al.,* 2006). The bioactive components will differ. The placental bioactive molecules identified in Appendix 14 are present in the placental membranes rather than the whole uterus. Furthermore, the term “amniotic fluid" is sometimes used to describe combined allantoic and amniotic fluids. In Appendix 13, the bioactives are reported separately for these 2 fluids.

In the interest of clarifying the terminology the following section describes the differences between the placentation methods in humans and ruminations. The means by which the foetus is attached to the uterus and the compartmentalisation of fluids surrounding the foetus are different in ruminants compared to humans.

In humans, the membranes of the foetus attaches to the mother at single site in the uterine wall, creating a structure known as the placenta. This organ is comprised of both maternal and foetal tissues, which become enlarged, and highly vascularised through the course of the pregnancy. The maternal and foetal tissues interdigitate with each other and so the entire structure appears as one, which overall resembles a fleshy dinner plate. At birth, the entire placenta, comprising both maternal and foetal tissues, is expelled from the mother. This expulsion has led to the name ‘decidua’ given to this structure.

Ruminants do not have a true placenta as is observed in humans. They differ in that the foetal membranes instead attach at numerous sites to the uterus as compared to humans where attachment is singular. For each of these attachment sites, there is a swelling on the maternal side known as a caruncle, which contacts a similarly vascularised node on the foetal side known as a cotyledon. Each of these combined structures is known as a placentome (<www.vivo.colostate.edu/hbooks/pathphys/reprod/placenta/ruminants.html>).

The placentomes of cattle differ from the placenta in humans, in that in cattle the maternal portion is not shed post-parturition, but instead are retained in the uterus. Ruminants are thus said to be non-deciduous.

Ruminants further differ from humans in the way that the fluids surrounding the foetus are distributed. In all pregnancies there are three membranes that surround the foetus. The inner most membrane surrounding the foetus is known as the amnion. External to this are two more membranes, the chorion and the allantois, which are fused in mammals to form a single layer known as the chorioallantois. The fluid immediately surrounding the foetus is amniotic fluid. This in turn is surrounded by the allantoic fluid, which is confined between the amnion and the chorioallantois.

In human pregnancies, the volume of amniotic fluid is large and takes up the majority of the inter-uterine space. Only a small amount of allantoic fluid is present.

In contrast, in ruminant pregnancies, the volumes of the allantoic and amniotic fluid are similar to each other. In these animals, the allantoic membrane immediately surrounds the foetus and with the allantois creating an outer layer which also extends into each of the horns of the uterus. This is significant because it means that any fluid collected from the intra-uterine cavity is likely to contain both allantoic and amniotic fluids, whereas in humans only amniotic fluid is significant.

The compositions of amniotic and allantoic fluid are similar but have some important differences. Both fluids are derived from foetal urine but differ due to active transport across their respective membranes. The two fluids play slightly different roles, as the amniotic fluid is in direct contact with the foetus, whereas the allantoic fluid forms a protective outer layer, which is postulated to have a greater role in deterring infection.

2 Project aims

The project was designed to identify opportunities to realize the commercial and economic potential of harvesting bovine amniotic fluid and placental material generated within the Australian meat processing industry. Aspects that require investigation are the market potential for applications of bovine amniotic fluid and placental material (or extracts), the supply chain and the product(s) for each potential application. This information will ensure that an informed strategy to develop applications and products from bovine amniotic fluid and placental material is formulated through an understanding of the feasibility, timeline to market and associated costs where possible. However as the project proceeded, potential markets for ovine amniotic fluid and placenta (in particular) were revealed. These are findings are also presented in the report.

3 Methods

Information was collected through database searches, scientific literature searches and interviews with appropriate industry, regulatory and R&D personnel. Contacts were chosen to cover the clinical areas that were identified through the literature as being relevant to placenta and amniotic fluid including wound healing, burns and scarring, neonatal maturation, stem cell culture, complementary medicine and ophthalmology. Industry contacts relevant to areas such as animal components collection, biologic processing and bulk manufacturing, regulatory organizations and cosmetics were developed through CSIRO networks and referrals as the interview process proceeded.

Interviews were initiated through email contact and phone conversations first to ascertain the suitability of the contact and their level of interest and then to set up face to face interviews. The interviews were unstructured to allow for maximum information exchange and respect for the interviewee's integrity.

The interview techniques used were development of discussion points before the interview and then with 2 personnel, from CSIRO, being present for maximum interaction and written recording. The interviews were not tape recorded. The resulting notes were reviewed by interviewers and correlated immediately after each interview to ensure complete and accurate records. These notes were then edited and incorporated into the appropriate sections of the report after review by the interviewee.

The aspects investigated were the feasibility of the application, status of current uses of placenta and amniotic fluid, regulatory requirements, potential market, the supply chain including collection *points, the processing stages and quality control*, *distribution* and *users* and the *products* for each potential application including product characteristics and regulatory regimes.

4 Potential uses of amniotic fluid

Amniotic fluid is a colourless liquid that surrounds and protects the foetus inside the amniotic sac within the uterus. It consists mostly of water, mesenchymal stem cells and many biologically active substances including cytokines, proteins and growth factors. During pregnancy the amniotic fluid increases in volume as the foetus grows and there is approximately 8 litres of bovine amniotic fluid at term.

Historically, amniotic fluid has not been greatly utilized, but in recent years there has been some research around possible applications. These centre mainly on the use of human amniotic fluid. A small volume of ovine amniotic fluid is currently collected in Australia and most is exported to Asia for use in the cosmetic industry. A small amount is also utilized by the Australian cosmetics industry in lotions and creams for export products.

A large volume of bovine amniotic fluid is currently discarded in Australian meat processing plants. This volume is estimated to be approximately 350,000 litres per year. Facilities in abattoirs, which collect foetal blood, would be suitable as collection points with a small amount of alteration to current operations. Upon collection this material could be fractionated for specific molecules such as growth factors or the fluid could be formulated for applications such as cosmetics and Chinese medicine.

We have identified maturation of neonates, wound healing, bone healing, burn and scar treatment, ophthalmology, neurology, amniotic stem cell culture, stem cell culture, Chinese medicine and cosmetics as potential applications for amniotic fluid or components thereof.

4.1 Wound healing and burns and scarring

Wound healing is an important natural response to preserve the integrity of any complex organism. Over history man has experimented with many natural materials such as spider webs, animal dung, extracts from various species of animal and insects, leaves, tree bark, honey, vinegar, beer and wine to promote it. However wound care has been based on simple bandaging for many centuries. However as our knowledge and understanding of the mechanisms of tissue repair increases more sophisticated approaches are under development. The application of growth factors, hormones and cytokines, use of tissue matrix products, chemical manipulation (protease inhibitors) and mechanical devices such as vacuum assisted wound closure, new methods of debridement (biosurgery), hyperbaric oxygen and healing enhancement products are all currently in use (Sussman 2007). Commercial products that contain animal derived actives are Apligraf (bi-layered cell therapy) and Integra (dermal regeneration template) both of which contain bovine products (collagen type I and growth factors) while Oasis is a wound matrix prepared from porcine submucosa. These indicate that if an animal product is effective then the clinician and consumer will accept it. The major companies working in the wound healing area are J&J (Ethicon), Bayer, Smith and Nephew, 3M, and Kinetic Concepts Inc. None of these organizations currently conduct developmental work in Australia.

Prof. Sussman suggested that there could be an application for amniotic fluid components in the treatment of internal surgery wounds particularly with tissues such as lung.

4.1.1 Slow healing wounds

In the developed world, one of the major wound problems is the slow healing venous ulcer of diabetics. They occur when vein valves, which normally prevent the backflow of blood, become incompetent and venous congestion (ulcer) is created by the backflow (<www.medicaledu.com/venous.htm>). The 2006 global figure for diabetes was 171M affected individuals. Currently venous leg ulceration (VLU) affects approximately 0.6% of the western population and the annual cost of managing VLU in Australia ranges between AUD$554 and $655 million. Four months of conventional outpatient leg ulcer treatment costs an estimated AUD$3,245

per individual. Additional financial and economic implications of leg and other ulceration treatments include personal costs, such as transportation and time lost from work (Leach, 2006). The scenario below gives an economic picture of the potential benefits of using AF or fractions thereof to expedite the healing of chronic wounds.

Prof. Michael Stacey of Fremantle Hospital pointed out that wound healing products are expensive for patients and because they are not covered by Pharmaceutical Benefits Scheme and these are out of reach of many people. He pointed out that there is trade off between the cost (~$1,500) and the longer healing time (extra 3 weeks) of a wound not treated with a product such as Dermagraph, a neonatal fibroblast culture product for wound treatment developed by Smith and Nephew. Prof. Stacey also suggests that accreditation by FDA and TGA is expensive and prohibits some new (and innovative) products from coming to the market place. He went on to say that FDA and TGA are more comfortable with single action products and this would pose problems for “mixtures” such as several growth factors, which may well be effective as concurrent or sequential wound treatments. He saw an opportunity for amniotic fluid derived growth factors in wound healing but emphasised the importance of profiling the constituents of fluid first and stringent experimental design. He has seen first hand an example of a potentially effective product not progressing through the clinical trials because the support medium was changed from saline in the animal trial to an untested gel in the clinical trial without appropriate experimentation.

Scenario for the use of amniotic fluid in wound healing products

Currently the cost of treating a venous ulcer is AUD$4,530-5,450 for four months of conventional treatment (averaging $300/week). Treatment with a more developed product such as Dermagraph (pers. comm. Stacey, 2007) reduces the healing time by 3 weeks but costs a further AUD$1,500 (Total AUD$5,100).

Annual cost of managing VLU in Australia ranges between AUD $554M and $655M p.a.

If an AF product was developed at cost half of Dermgraph (AUD$750) and still reduced the healing time by 3 weeks the cost of healing the saving per person would be =	AUD$150
Annually 120,000 (Leach, 2006) suffer venous ulcer sufferers so total saving =	AUD$18M.
Assume 10% uptake of new product and the saving =	AUD$2 M

While saving for the health system are low the economic benefits for the patient or their carer and the economy is high. For example the reduction in lost work days (average wage = $1000/week) would be AUD$36M p.a. (1,200x1000x3).

Disclaimer:
It should be noted that the authors have relied upon data from referenced sources and anecdotal information from the meat processing industry. This information and data constitutes a snapshot of the situation between June and October 2007 and the situation in this area is subject to constant variation. The reader should make their own enquiries and exercise their own judgement before relying on the conclusions set out herein.

4.1.2 Burns and scarring

Injuries and burns are highly prevalent in developing nations such as China and India and because of their economic structure are in need of fast, cheap and effective wound healing solutions. 80% of

health expenditure in the developing world is devoted to wound treatment (pers. comm. Prof. Zee Upton of QUT June 2007).

Amniotic fluid has been experimented with as a treatment for burns and scarring by the Royal Children's Hospital Burns Research Group in Brisbane. Fraser *et al*., (2005) used an ovine model of thermal injury and subsequent analysis of foetal and lamb response to burn injury. This novel model of foetal and lamb response to deep dermal injury indicates that the foetus heals a deep burn injury in a scarless fashion. Further elucidation of this specific foetal process of burn injury repair may lead to improved outcome for patients with burn injury. They suggest that something intrinsic to the foetal skin itself enables healing without scarring and that the elucidation of the factors could prove to be invaluable in the treatment burns and the research team has identified fetuin A, which is unregulated in foetal skin, as a potential wound healing enhancer.

Scarring caused by burn wounds can be significantly reduced by faster healing. For example if a wound heals within 10 days there is 4% risk of developing scar hypertrophy while a wound that takes 21 days to heal has a 70% risk of scar hypertrophy (Wood, 2003). Wood has developed commercially available wound treatments ReCell® and CellSpray® which are single use single-use medical devices for harvesting autologous keratinocytes, melanocytes, fibroblasts and Langerhans cells from the epidermal-dermal junction of the patient for immediate application onto a wound surface in order to promote effective wound healing. They are used to treat burns and scalds, donor sites, glabrous injuries, congenital nevi, hypopigmented scars and vitiligo, chronic wounds and prophylactically in cosmetic rejuvenation procedures. Advantages of this system include improved wound healing time and scar quality, repopulation of melanocytes to reduce hypopigmentation, on-site processing for immediate application, increased viability through immediate harvest and application and finally the ability of the process to be conducted by a clinician without the need for specialised laboratory staff (<www.recell.info/hc_about.asp>).

Two of the major hurdles around the development of new wound healing treatments are the accreditation of the products by TGA and that PBS does not cover wound healing products because it defines them as devices rather than medicine. Due to the fact that PBS does not subsidise the more sophisticated products they are unaffordable for many patients.

Prof. Upton pointed out that animal derived products would be accepted in developing nations if they were highly effective and cheap and there could be an opportunity for amniotic fluid derived products in these regions. Hindu consumers would not accept bovine products but ovine products would be acceptable. Ovine derived products rather than bovine would be considered to be therapeutic in China (pers. comm. Prof. Lin Sept 2007 and Prof. Upton July 2007).

An opportunity does exist in the developing world for the development of a cheap, effective and accessible wound healing product for injuries. Three wound healing experts expressed their interest in trialling amniotic fluid derived products by offering to test them in various models. Prof. Upton has *in vitro* capabilities using pig and cell culture models. Prof. Stacey has access to *in vivo* capabilities for human trials. Prof. Wood has ready access to mouse models and experience in working with the regulatory organizations. Prof. Upton also has access to biotech companies and experience in commercialization (pers. comm. Prof. Lin Sept 2007, Prof. Upton July 2007 and Prof. Wood August 2007).

4.2 Maturation of preterm neonates

One of the most lucrative potential applications for bovine amniotic fluid is assisting in the development of pre-term infants. In utero, the developing foetus swallows amniotic fluid which in humans occurs at a rate of >250 ml/kg foetal weight/day. In sheep it has been shown that amniotic fluid and colostrum whey proteins markedly stimulate the development of the small intestine and the immune system of the foetus (Trahair and Sangild 2000). This work also showed that oesophageal ligation results in a gut-specific growth retardation which can be restored by reversing the ligation (which reinstates swallowing). Analysis of hospital data of preterm infants shows that feeding with

human milk soon after delivery markedly decreases time to full feeding and the length of stay in hospital. However, mothers of premature babies often cannot produce their own milk, and colostrum is not easily procured from another source thus creating a possible application for amniotic fluid or extracts of the same.

The costs for preterm infant care are enormous; for example the direct costs for low birth weight infants in their first year of life accounts for 35% of the total health care costs for all infants in the USA (Richardson et al., 2001). In Australia each high-level neo-natal intensive care cot costs in excess of $500,000 per year to operate (<www.health.nsw.gov.au/news/2005/20050331_00.html>).

Prof. Paul Colditz (Director of Perinatal Centre, RBWH) said that there are approximately 2,500 very low birth weight (VLBW) (1.5 kg and under) babies/year, in Australia that would need specialized nutrition. Currently Nestle and other infant formula companies provide bovine whey derived products which go some way to meeting these nutrition needs. Nestle and some other formula companies have recently conducted experiments with probiotics in these formulas to increase immune support and some of these products are currently in the market place (<www.nutraingredients-usa.com/news/ng.asp?n=79475&m=2NIU906&c=zgzcrgarwbsqfwc>).

Since 2002 a group of researchers at the Florida Collaborative Neonatal Clinic have been performing trials with the enteral administration of an amniotic fluid-like solution to neonates (25 to 31 weeks). This solution contains human albumin, two enterocyte growth factors, recombinant human erthropoietin and recombinant granulocyte colony-stimulating factor with the electrolyte composition of human amniotic fluid. The solution is well tolerated at doses of up to 20 ml/kg/day administered while the volumes of milk feedings were being gradually increased. When milk feedings reached 80 ml/kg/day the test solution was discontinued. All very VLBW infants tolerated the test solution for periods up to 14 days with no significant adverse effects. This group has concluded that the solution is an effective preparation to bridge the neonate between their intra-uterine environment and that of the neonatal intensive care unit and suggest that a phase III efficacy trial should be conducted, using the recent data for sample size calculations (Sullivan et al., 2002; Calhoun et al., 2004; Christensen et al., 2005; Barney et al., 2007).

Hirai et al., (2002) conducted in vitro assays and confirmed the growth promoting effect of amniotic fluid on human foetal small intestine cells. Schubring et al., (1999) suggest that maternal leptin in amniotic fluid seems to be derived from different sources and hypothesizes that leptin plays gestation-specific roles for the mother and the foetus indicating that fluid from different gestation time points would have different bioactivities. This work suggests that fluid from each trimester could be assayed for confirmation of the optimal collection point for specific applications (authors comment).

The Women and Infants Research Foundation (WIRF) is Western Australia's leading community-based research organisation dedicated to the fields of obstetrics, gynaecology and newborn medicine and runs a breast milk bank for babies (including preterm) who are not able to be fed by their mothers. The bank is currently developing pasteurization methods of human breast milk. One difficulty faced with this method is that the pasteurization damages some of the bioactive components in the milk. These components are important in that they are beneficial to preterm infants who have very immature immune systems. WIRF are currently working to develop other methods with the hope of further reducing damage to milk proteins (<www.wirf.com.au/>). Human breast milk and banked human breast milk do not fall within the definition of a therapeutic good (section 3 of the Therapeutic Goods Act 1989) and, therefore, fall outside the scope of the TGA's jurisdiction (<www.wirf.com.au/>) but do fall under the supervision of FSANZ.

The WIRF is closely associated with the Australian Breastfeeding Association who are very much opposed to artificial formula feeding (primarily derived from bovine milk) and so are not interested in pursuing any discussions that allude to bovine products (pers. comm. Dr. Ben Hartmann, July 2007).

A difficulty with feeding preterm neonates with formula milk or human milk is that neonates more than 2 weeks premature may develop necrotizing enterocolitis (NEC). NEC is a very serious disease often requiring surgery and with a significant mortality rate and very high morbidity. Its

aetiology is multifactorial but fundamental is the fact that the gut is not mature enough to process milk feeds. The symptoms of NEC include vomiting, gastric residuals, abdominal distension and bloody stools. In the USA 2% of neonatal deaths were attributed to NEC in 2001. The Australian prenatal death rate was 0.8% in 2002 (<www.wrongdiagnosis.com/c/childbirth/deaths.htm>) and assuming that the incidence of NEC is similar in Australia the death rate from NEC would be approximately 10 deaths per year (0.004% of 259,800 births (ABS 2005 figure)). WIRF has been operating for one year and do not have data on NEC frequency and outcomes (per. comm. Dr. Ben Hartmann 2007).

Prof. Colditz said that a surfactant, which has been widely used for over a decade in neonatal medicine to treat immature lungs, is derived from pigs or cows. Whilst synthetic sources are possible and have been marketed, these have not achieved the widespread acceptance of the more 'complete' animal derived product. Prof. Colditz is of the opinion that if a bovine or ovine amniotic fluid derived product was developed and successfully trialled parents of neonatal infants and practitioners would accept it. He explained that the amniotic fluid could act as maintenance and maturation medium for the gut and other internal organs of the neonate while a continuous drip would be the source of nutrition until enteral nutrition could be commenced and graded up.

Any reduction in the length of hospital care for these infants would have a positive impact on the health care system as well as the family of the infant. The scenario below gives an economic picture of the potential benefits of utilizing AF for maturation of VLBW neonates.

Scenario – Maturation of neonates with amniotic fluid
Australia has 2,500 VLBW infants per year. If an infant could be moved from a high-level neo-natal intensive care cot one week earlier due to gut maturation with amniotic fluid and consequentially released from hospital earlier the saving to the health care system would be $9,600. There would be further savings generated for the family through fewer hospital visits, less child care for siblings, and a more rapid return to work for the parents. NEC affected infants can require hospitalization for up to 49 days (Holman *et al.*, 2006) at costs of up to AUD$1,370 per day (<www.health.nsw.gov.au/news/2005/20050331_00.html>)

Australia

High-level neo-natal intensive care costs/neonate/week	AUD$9,600
Total cost for one week of care for 2500 VLBW neonates	AUD$24M
Price of potential AF product (assume 20 x the cost of cosmetic grade AF (AUD$60/L))	AUD$1,200/litre
One course of AF product requires 600 ml (~30 ml x 21 days) per baby	AUD$720
Savings to health care system per baby on released from hospital 1 week early (92% savings)	AUD$8,800
If achieve a 20% market penetration, the medical system saves	AUD$4.44M

Due to savings achieved per infant for the health system there is much scope for pricing to achieve excellent margins.

US

High-level neo-natal intensive care costs/neonate/week (google.com/answers/threadview?id=559733)	USD$14,000
Total cost for one week of care for 50,000 VLBW neonates	USD$700M
Price of potential AF product	USD$1,200/litre
One course of AF product requires 600 ml (~30 ml x 21 days) per baby	USD$720
Savings to health care system per baby on released from hospital 1 week early (95% savings)	USD$13,280
If achieve a 20% market penetration, the medical system saves	USD$132.8M

Due to savings achieved per infant for the health system there is much scope for pricing to achieve excellent margins.

Declaimer:
It should be noted that the authors have relied upon data from referenced sources and anecdotal information from the meat processing industry. This information and data constitutes a snapshot of the situation between June and October 2007 and the situation in this area is subject to constant variation. The reader should make their own enquiries and exercise their own judgement before relying on the conclusions set out herein.

4.3 Stem cell culture

There has been recent research on the culture media used to support embryonic stem cells in the laboratory setting with the aim of replacing animal derived supplements in mediums. Companies such as Invitrogen and Chemicon (Millipore) have developed serum free media for these applications. This work is still reliant on murine feeder cells (3T3) but human feeder lines are being investigated (pers. comm. Zee Upton July 2007). Animal derived products could be a cost effective alternative for cell maintenance and amniotic fluid (or components of) could be useful in this application particularly if the fluid from various stages of gestation was investigated. A conversation with Sean Meehan of Millipore (at the time of interview he was the Australasian manager of their stem cell product line) indicated that the stem cell market in general is interested in recombinant

products but he did consider that some of the growth factors from amniotic fluid could be of interest. He also saw some merit in amniotic fluid being used in mouse stem cell culture media. Australia has a strong interest in stem cell research with many groups such as Monash University and CSIRO's Livestock Industries working in the area. Chemicon developed many of their stem cell products in Australia in collaboration with Australian researchers from institutes such as Monash University and Royal Melbourne Hospital (pers. comm. Sean Meehan July 2007).

Barria *et al*., (2004) conducted studies on hematopoietic stem cells substituting foetal calf serum with human amniotic fluid in culture medium and found that 25% amniotic fluid will maintain multipotent cells while differentiation and apoptosis are down regulated. This research group was contacted for an update on their work and Haas replied *"We have tried - though not extensively so - to grow ADULT stem cells, from human amniotic fluid and from human prostate, in human amniotic fluid. As I said, we did not do a thorough job, just tried a few times, without significant results. It would be a good idea to try this out, bovine or human, as it certainly was the ONLY thing we have tried that allowed us to keep murine HSC alive and to proliferate a bit and maintain full biological activity.*

We still work extensively on both systems and seem to have grown almost pure cultures of prostate stem cells; amniotic fluid stem cells are to be tested next. One would like to do some fractionation, but since the experiments are so simple, one could have significant results in a few months. Amniotic fluid surely beat recombinant growth factors!! as far as price is concerned. However, since we now can grow almost pure cultures of apparent stem cells in both systems, we are not interested in pursuing this direction" (Email, July 2007).

Opportunities in the stem cell industry could be developed around the growth factors contained in amniotic fluid which could be utilized in grow medium. It could also be used as a serum replacement in the culture media for animal cell lines. Chemicon has shown an interest in developing a project around the growth factors. However due to the departure of Sean Meehan, this opportunity has not been followed up for the time being.

4.4 Other Clinical Applications

4.4.1 Adhesions

Animal studies have demonstrated that amniotic fluid may be useful in the prevention of adhesions. Ozgenel *et al*., (2001) found that human amniotic fluid to be effective in preventing peritendinous adhesion formation without impairment of tendon healing in a rabbit model. Durmus and Han (2006) performed experiments using a Wistar rat model to show that bovine amniotic fluid is effective in the prevention of intra - abdominal adhesions. This result is thought to be the result of a relationship between the high concentrations of hyaluronic acid and its stimulating activators in bovine amniotic fluid.

4.4.2 Neurology and repair

Experiments are indicating that amniotic fluid may have a role in neurological medicine and some research has shown encouraging results. Ozgenel and Filiz (2003) investigated the effects of human amniotic fluid on peripheral nerve scarring and regeneration in rats and found that nerves treated with amniotic fluid had greater fibre maturation possibly due to the rich content of neurotrophic and neurite-promoting factors.

Another study by Lee and Kim (1996) demonstrated that topical application of amniotic fluid led to faster nerve regeneration and recovery of sensitivity in rabbits' eyes following excimer laser photokeratectomy. These results suggest that the factors in AF helped the recovery of corneal sensitivity, nerve regeneration, and reduced scar formation.

A conversation with Prof. Alan Harvey of UWA (School of Anatomy and Human biology) who specializes in the use of cell/tissue transplantation, gene therapy and pharmacotherapy in the repair of the central nervous system suggested that some experimentation with amniotic fluid sampled before the blood brain barrier closes (14 weeks in humans) may reveal some neural repair factors. He would begin this work by investigating neural expression factors and the effect of amniotic fluid in cell culture systems and is keen to develop such a project.

4.4.3 Bone healing

There is evidence that amniotic fluid has an effect on bone healing. Karacal *et al.,* (2005) performed experiments on rabbits with calvarial (cranial) defects and found that human amniotic fluid increases ossification in bone healing. Histological examination at 6 weeks postoperative revealed that the defects treated with human amniotic fluid group had superior ossification compared with the control group defects. With its positive effects on bone healing and ability to withstand freezing if made cell-free, human amniotic fluid would appear to be a useful adjunct in the treatment of bone healing. Karacal *et al*., (2005) attributes these effects to the high concentrations of hyaluronic acid in amniotic fluid. Dahl *et al*., (1983) found that there is 1 – 20 *u*g/ml hyaluronic acid in human amniotic fluid depending on the stage of gestation.

4.4.4 Ophthalmology

There has been experimentation with human amniotic fluid as a topical treatment in the field of ophthalmology. Herretes *et al*., (2006) performed mouse trials and found that topical application of preterm and term human amniotic fluid was an effective therapy for limiting the damage after acute alkali burns of the eye. Similarly Brito *et al*., (2004) ran trials with rabbits using 15 week gestation and full term human amniotic fluid and determined that the topical application of term amniotic fluid reduces corneal neovascularization and so seems to aid the recovery of the ocular surface after ocular alkali burns. He suggested that these results may indicate a possible alternate therapy to amniotic membrane placement for ocular alkali burns.

4.5 Cosmetics

Amniotic liquid does not have a long history of uses within the cosmetics industry but there appears to be a growing interest in ovine fluid. The FDA says that it is “promoted for beauty benefits and has limited use in moisturizers, hair lotions, scalp treatments and shampoos” (<www.fda.gov/fdac/reprints/puffery.html>).

There have been reports that amniotic fluid is processed and put into capsules and marketed as a beauty product in Asia (pers. comm. Craig Pearson July 2007). Bruce Galloway of Galpac Pty Ltd (Geelong) told us that they have collected and processed ovine amniotic fluid for the cosmetics industry and in particular for the Sydney based Pharma Cosmetics Pty Ltd, which is a formulator and contract manufacturer of cosmetics. A conversation with Pharma-Cosmetics confirmed that they do manufacture amniotic fluid containing lotions and creams for the Asian market. They indicated that there is little interest for these products within Australia. Galpac also manufactures a product called placental oil for use in facial lotions and creams, which is a by-product of the placental powdering process and has high hyaluronan content. There are some cosmetic products on the market, which contain amniotic fluid, which target the anti-ageing market (they are not Australian made).

Prof Charlie Xue (RMIT University) suggested that health foods and cosmetics would be easier to bring to market because therapeutics accreditation is costly and requires efficacy data which expensive to generate (pers. comm. Aug 2007, Prof. Xue)

4.6 Amniotic cells and stem cells

Amniotic stem cells are increasingly been used in cosmetic tissue repair procedures in humans over recent years. One current cosmetic procedure utilizes bovine amniotic fluid cells for anti-ageing treatment and is approved by FDA.

Fauza (2005) reported using tissue engineering to reconstruct defective tracheas (windpipes) in foetal lambs, first using cells from the amniotic fluid to grow sections of cartilage tube, and then implanting these living grafts into the lambs while still in the womb. This research group specializes in making connective tissues, including muscle, bone, cartilage, fat and tendon. The FDA is now reviewing Fauza's application to conduct a clinical trial in human babies with a prenatal ultrasound diagnosis of congenital diaphragmatic hernia; the amniotic fluid would be collected several months before birth and a tissue-engineered patch made ready for use soon after delivery (<www.childrenshospital.org/newsroom/Site1339/mainpageS1339P1sublevel175.html>). His team is also working on stem-cell-based, tissue-engineered grafts to repair spina bifida (in which the spinal column doesn't close fully during foetal development) and structural cardiac defects, using similar principles.

Stem cells could be routinely obtained from human amniotic fluid, using surplus cells from amniocentesis specimens that would otherwise be discarded (De Coppi et al., 2007). The amniotic fluid stem cells grow easily in culture and appear to be phenotypically and genetically stable. They are capable of extensive self-renewal, a defining property of stem cells. The absence of senescence and the maintenance of long telomeres for over 250 population doublings far exceed the typical 'Hayflick limit' of about 50 population doublings for many post-embryonic cells, which generally is attributed to the progressive shortening of telomeres.

DNA CryoStem™ Therapy (Invertageing) uses stem cells obtained from bovine amniotic fluid for the treatment of acne and aging. The cells are massaged into the skin, which is then treated daily with a ‘special’ solution for several days. These cells are obtained from a free-range herd of bovines, which are raised under pristine and controlled conditions in France (<www.invertageing.com/treatment_cryostem.htm>). DNA CryoStem technology is approved and registered by the FDA (<www.invertageing.com/treatment_cryostem.htm).

Opportunities involving amniotic stem cells from animals would be around tissue repair, which could be applied to high value animals with deformities or injuries. The Australian race horse and stud cattle industries breed highly valuable progeny and preserve stock with desirable traits and so the high costs of tissue repair procedures may be accepted.

4.7 Composition and Bioactives in Amniotic Fluid

Amniotic fluid contains many biologically active peptides such as collagens and proteoglycans, growth factors and other bioactive molecules that are involved in the protection and development of the foetus and the amniotic membrane (Berger and Bergemann, 1958). The individual concentrations of active molecules are very low (100 -1000 pg/ml). Appendix 12 lists the components in amniotic fluid that have been identified thus far. Most studies have focused on a single molecule or activity at a single gestation period and are associated with pathologies of human pregnancy. Amniotic fluid also contains six major proteins (total concentration of 3 g/100ml – Michel *et al.*, 2006). The major proteins are important in a range of biological activities.

4.8 Risk Assessment

4.8.1 Health Risks

There are risks associated with the handling, collection and storage of placenta and amniotic fluid. For example viruses such as bovine papillomavirus type 1 can be detected in placenta and amniotic fluid samples and are transferred from the maternal source (Freitas et al., 2003).

A further risk is the possible contraction of Q fever by personnel while handling animal tissue. Q fever is a nationally notifiable disease within Australia (<www.health.gov.au/>). Animals such as cattle, sheep, and goats can carry the Q fever bacteria (Coxiella burnetii) in tissues involved in birth - the uterus, placenta, and birth fluids. Infected animals also shed the microbe in milk and manure. People acquire the infection by inhaling infectious aerosols and contaminated dusts generated by animals or animal products (<www.ccohs.ca/oshanswers/diseases/qfever.html>). A biologic processor in Victoria reported that 4 workers had contracted the disease after draining amniotic fluid from ovine placenta (pers. comm. August 2007). This incident occurred at a time when there had been a Q-fever outbreak (27 cases) in South Australia where the placenta had been collected (Turra et al., 2006). Details of this incident can be seen at (<www1.worksafe.vic.gov.au/vwa/vwa097-002.nsf/content/LSID158120>). The Q fever microbe can be eliminated by heating to 71.7 ◦C for 15 seconds or 30 min at 63 ◦C (Cerf and Condron, 2006). Any personnel handling placenta and amniotic fluid need to be educated about and immunized against Q fever as is the requirement for abattoir workers.

4.8.2 Accreditation

Accreditation procedures are of great importance and should be taken into account when considering a successful supply chain for amniotic fluid derived products.

There are no products containing amniotic fluid listed with the TGA. There is some evidence that bovine amniotic fluid is collected in other parts of the world as the FDA alludes to bans placed on the importation of it in 1998 (<www.fda.gov/ora/fiars/ora_import_ia1703.html.>). John Langbridge of AQIS has indicated that there is no restriction on the export of amniotic fluid and it is known that a small amount of ovine amniotic fluid is exported to Asia. The import restrictions would be the same as for other bovine derived products and dependant on the country of import.

A conversation with Jason Tong of TGA (Acting Parliamentary Liaison and Communication Officer) indicated that there is no reason against amniotic fluid being approved as a therapeutic good. He said that applications around amniotic fluid have not been presented recently. He also recommended that an independent operator would be well advised to use a Therapeutic Goods Consultant (fee for service) (<www.tga.gov.au/docs/html/regafair.htm>) to assist with the lodgement of an application and that it normally takes 6-12 months to gain accreditation for a product. The application forms and procedures can be viewed on the TGA website in the Australian Regulatory Guidelines for Complementary Medicines section (<www.tga.gov.au/docs/html/argcm.htm>). The Complementary Healthcare Council (<www.chc.org.au>) gives advice and assistance with applications and is a membership based organization, which collaborates closely with TGA. Their activities include policy development, information gathering, assessment and dissemination; regulatory affairs and government liaison; issuing relevant publications; organizing trade and consumer promotions and trade shows; providing education and training seminars, and facilitating industry self-regulation. Large pharmaceutical companies such as Sigma Herron, Symbion and Blackmores employ regulatory specialists who handle TGA affairs.

The first step in the registration of an amniotic fluid derived product as a “listed” or complementary medicine with TGA would be the lodgement of ‘pre-clearance application for animal-derived ingredients’, which requires AQIS approval. After the appropriate fees are paid, applications for the registration of complementary medicines pass through four or five phases: pre-assessment, evaluation and peer review, consideration by the Complementary Medicines Evaluation Committee (CMEC), decision and, if acceptable, implementation (<www.tga.gov.au>). Costs are estimated at AUD$15,000 – 20,000 per product formulation to conduct stability testing and AUD$75,000 – 125,000 to conduct small-scale clinical trials (to obtain evidence of efficacy) (CDI Report, 2006).

The evaluation fee for a listed medicine for distribution within Australia is currently set at $5,720 while an export only product only attracts application and processing fees (total $810) and efficacy does not need to be shown (<www.tga.gov.au/fees/fees07.htm#listmed>).

A representative from Pharma-Cosmetics Pty Ltd said that if an Australian based company obtained TGA approval for amniotic fluid derived products it would “open the whole industry up” and there would be a number of companies offering products within Australia. He went on to say that obtaining accreditation is prohibitively expensive because of the clinical trial costs as well as the registration fees.

Topical preparations and medical devises have the advantage of easier accreditation access. As an example the Tissue Therapies product VitroGro that is used for wound treatment is listed with the TGA as a Level 3 medical device rather than as a therapeutic product.

4.8.3 Raw Material Availability

The availability of raw materials is a further risk to the development of a viable industry utilizing amniotic fluid. The seasonal nature of reproduction means that supplies can be sporadic. This is further compounded by the current lack of capacity within the processing industry to harvest amniotic fluid. Bruce Galloway of Galpac reported that ovine amniotic fluid is collected, frozen and exported to Asia for use in the cosmetic industry. He said that it (30% of the weight) is collected by draining placenta that has been collected from abattoirs in Southern Australia and Victoria. Some ovine amniotic fluid is used within the Australian cosmetics industry with the finished products exported to Asia (pers. comm. Eugene Ng of Pharma-Cosmetics, August 2007). A conversation with a large bovine processor confirmed that there is no commercial scale collection of amniotic fluid within the Australian industry due to a lack of demand, the difficulty of collection and labour shortages.

Meat processor management teams also identified a risk that an animal parts collection venture could be short term or intermittent as a barrier to entering the industry. Most managers indicated that they would need to be assured that the project would be a reasonably long-term income source. The Australian Cartilage Company (now b.a.p.a) confirmed this view when Nigel Fairclough (company Director) said that they had found that they needed to set up contracts of at least a year in length to satisfy the abattoir managers when they were securing supplies of low value streams for their bioactive extraction operation at Cootamundra, NSW.

Another risk factor is fluctuation of supply due to seasonal conditions and their effect on the types and condition of animals being presented to the abattoirs. This is particularly important for collection of placenta and amniotic fluid because growers tend to keep pregnant animals in good seasonal conditions but are often forced to sell under drought conditions. If growers knew they could obtain better prices for pregnant animals they would almost certainly supply them. This has occurred on a small scale when the foetal blood prices were at their highest and some growers were offered 10% premiums for “pregtested” cull cows in 2004 (<www.mla.com.au/TopicHierarchy/InformationCentre/Coproducts/Bioactives/default.htm

Collection of amniotic fluid

A visit to the Kilcoy Pastoral Co abattoir confirmed that collection of bovine amniotic fluid (possibly including allantoic fluid) would be relatively simple in a plant that is set up to collect foetal blood. The collection would need to be done soon after slaughter to avoid contamination by meconium and possibly from younger foetuses for the same reason. A large Queensland processor processes 207 head of cattle per hour is well equipped and staffed for foetal blood collection. Utilizing this same facility it is proposed that the collection of amniotic fluid could be carried out within 18 minutes of animal slaughter using larger suction equipment and extra storage facilities. Collection of amniotic fluid for stem cell purposes could possibly be carried out under these conditions but there would be a need to transport them immediately to a tissue culture laboratory for culturing.

Bovine amniotic fluid can not easily be collected during gestation, as there is a very high incidence of foetal death associated with this procedure. Some harvesting using ultra sound for guidance has been done with good success rates at day 79-90 gestation (Garcia and Salaheddine, 1997) but Dr. Jon Hill (CSIRO) cautioned that in reality there is in general a high risk of foetal death associated with this procedure.

4.8.4 Biologics Processing

Biologics processors work between the collection agents and the pharmaceutical contract manufactures. They are exposed to seasonal variation and health risks. Seasonal variation can be accounted for, but at extra cost, in part for by forward planning and bulk freezing of raw material. Health risks such as the contraction of Q-Fever are more difficult as these diseases are not evident in the raw material and remain unidentified until personnel become ill. There is more information around these issues in section 4.12.1.

Currently in Australia amniotic fluid is collected in small volumes by draining it from collected and frozen ovine placenta (30% of total wt). See sections 6.5.5 and 6.5.6 for more details. It is filtered or fractionated to exclude cells, denatured proteins and other contaminants and then processed by an Australian cosmetics manufacturer or exported to Asia for use in the cosmetics industry. (This information was collected during discussions with Rick Clements of Bovogen and a subsequent conversation with Bruce Galloway of Galpac).

4.9 Commercial Potential

There are few commercial products containing amniotic fluid currently in the market place but some USA and European beauty salons use bovine amniotic fluid stem cells for skin rejuvenation procedures. These treatments cost UK£150 to UK£20,000. The procedures are not permitted in the UK but British clinics arrange for them to be carried out in Moscow, New York, Rotterdam, Dominican Republic and Barbados (Thompson, 2006). In the USA bovine stem cells for cosmeceutical purposes cost USD$175 to $350 per treatment. These cells are frozen on collection and thawed at time of application and this could represent an opportunity for Australia meat processors that collect foetal blood (<www.variety.com/index.asp?layout=weekend&content=jump&jump=article&articleID=VR1117933203&category=2039>).

Ovine amniotic fluid appears to be growing in popularity but not bovine. In India, the predominantly Hindu culture does not accept bovine products. There is also a question around whether the amniotic fluid would be acceptable to Muslim consumers even though the animals have been slaughtered in accordance with halal practice (pers. comm. Rick Clements, Bovogen). Prof. Lin indicated that in the Chinese culture, bovine materials are historically used as food rather than therapeutics while ovine products are considered to be “warming”. These are possibly factors that influence the choice between ovine and bovine material (pers. comm. August 2007). Craig Pearson of Australasian Casing pointed out that Asian manufacturers strongly prefer ovine and deer material over bovine material.

There are some cosmetic products available which contain amniotic fluid such as Serum Revital Eyes (Reviva Labs) for beautifying eyes (<www.evitamins.com/product.asp?pid=2813>) and Hydroderm which is designed for anti-wrinkle applications. More details of these products can be seen in Appendix 4.

Australian ovine amniotic fluid is added to a small number of Australian made skin care products but most are exported, according to Eugene Ng of Pharma Cosmetics Pty Ltd. He is of the opinion that generally Australians don’t consider amniotic fluid to be a beneficial skin care product but that the Asian population does (pers. comm. Eugene Ng Aug 2007).

Bruce Galloway of Galpac said that they cost single strength ovine amniotic fluid at AUD$60/ litre when they sell it on to contract manufactures such as Pharma Cosmetics Pty Ltd. Currently there is not a high demand in Australia and we only found one manufacturer using it.

There is potential to expand the applications in the cosmeceutical industry by streamlining the collection and processing and of bovine fluid. Ovine and bovine amniotic fluid could well be incorporated and promoted in cosmeceutical products within Australia using the clean, green concept and then using this acceptance move into the global market. This route would be faster than the development of a therapeutic product and could be a forerunner to further products with higher claims. Companies such as Pharma-Cosmetics currently use ovine amniotic fluid because of its availability and the BSE outbreaks in recent years.

Wallace Bridge of Entrepreneurs in Science (University of New South Wales) suggests that low concentration products need to be of high value for example AUD$500- $10,000 per kg when he spoke at the 2007 MLA Bioactives workshop. This is an important observation because there are currently few commercial products containing amniotic fluid in market place and the components are in low concentrations. Products derived from amniotic fluid could target a niche market in the developed world market place. Asian consumers (particularly Japanese and Korean) will pay premium prices for high quality, safe cosmetic products and could potentially represent a further niche market.

4.10 Economic Potential

Bovine amniotic fluid is not currently collected so there are no established values for the raw material. Ovine fluid is collected in small volumes (we believe approximately 60 litres/year). One industry source suggested that an abattoir would need to ask at least AUD$3/kg (or litre) to justify a collection activity. Because there is so little material utilized it is difficult to estimate yields or expected returns.

Wound healing devices is an area where amniotic fluid factors have potential applications and this market could be developed in the developing world where the burn and injury incidence is high and there is a need for cheap, simple treatments. In the developed world there is an opportunity to use AF factors in the treatment of venous ulcers, which are associated with diabetes. This would be a longer termed project and require accreditation from TGA.

4.11 Relevant patents

In all sixteen patents were found that are current and relevant to amniotic fluid applications - seven of which are focused on cosmetic applications and the rest are around medical and stem cell applications. Appendices 7 and 8 summarize these patents. All except one patent are focused on human material. There is one patent of interest around bovine amniotic fluid (at 5 weeks gestation) being used in a hair restorer. There are currently few patents on the use of amniotic fluid. This provides an open environment for innovation within this field.

4.12 Summary

We investigated a number of clinical and “self medicating” applications of amniotic fluid. The major opportunities are in gut maturation of preterm infants, wound healing and cosmetics. The search of the patent literature and databases has shown that there a few if any freedom-to-operate issues for

these applications of potential amniotic fluid products. However each requires quite different development pathways and memberships in the supply chain.

Any products with functional claims will require TGA regulation. The TGA has no experience with amniotic fluid so the first application will be a test case. It will need to be done well to facilitate registration of further products. The composition of matter and understanding of the active agent is a significant TGA requirement. Any products with a medical purpose will also require AQIS approval.

Collection can be intermittent due to seasonality, drought, workforce availability and interest on part of the processor. Amniotic fluid is most efficiently collected at abattoirs that are already collecting foetal calf blood. Harvesting during pregnancy is not feasible.

Amniotic fluid contains infectious agents and needs to be handled accordingly. Awareness needs improvement and furthermore there is the need to develop sterilization methods for the amniotic fluid without compromising the bioactives of interest.

5 Potential uses of amniotic membrane

Amniotic membrane is the translucent innermost layer of the placenta and consists of a thin epithelial layer, supported by a basement membrane that is in turn connected to a thin connective tissue membrane by filamentous strands. In early history it was considered lucky for a child to be born with these membranes intact. The first recorded clinical application of human amniotic membrane was in 1910 when it was used in skin transplantation. Thereafter it has been used in surgical procedures related to the genito-urinary tract, skin, brain, and head and neck, and others (Dua et al., 2004). In 1980s the Russians developed “Allotransplantat” (preserved human foetal membrane) which was used by Russian and other European doctors in conjunctival, tarsal, orbital and tendon surgery. In more recent times amniotic membrane has been experimented with for grafting applications for the treatment of wounds and burns but the work was discontinued due to concerns around HIV (pers. comm. Prof. Fiona Wood, Royal Perth Hospital). There are two cell types of different embryological origin precent in amniotic membrane: amnion epithelial cells derived from the embryonic ectoderm and amnion mesenchymal cells from the embryonic mesoderm making it an interesting matrix for some stem cell culture applications. The applications that have been identified all utilize human amniotic membrane except one, which uses bovine material.

We have identified clinical applications including burns treatment, wound healing, bone and cartilage repair, ophthalmologic treatments and as a stem cell matrix as potential applications for amniotic membrane.

5.1 Clinical Applications

5.1.1 Burns

It is estimated that 90% of burn injuries occur in developing countries and 70% of these are in children (Potokar *et al*., 2007) so creating a need for simple, cheap and highly effective burns treatments. Human amniotic membrane has been experimented with as a treatment for burns and in recent years with some success.

The Burn Centre of the Army Hospital (Research and Referral) New Delhi, India has been using human amniotic membranes preserved long term in 85% glycerol for treating superficial and superficial partial thickness burns. The results have been excellent as measured by pain relief, protect the wound from infection, promote healing, prevent heat and fluid loss, elasticity and non-antigenic properties. The hospital has now developed a protocol for the long-term glycerol preservation of these membranes and is advocating the establishment of "Amnion Banks" in all hospitals especially in developing countries (Ravishanker *et al*., 2003).

Work by Quinby *et al*., (1982) was encouraging in the use of amniotic membrane for the healing of burns. More recently Singh *et al*., (2006) discovered that the application of radiation sterilized human amniotic membranes to a burn wound favoured epithelialization. In all the patients in the clinical trial, membranes desiccated and separated in 10 -14 days time leaving behind an epithelialized surface. This work suggests that amniotic membrane would be a powerful tool in the prevention of scarring associated with burns.

5.1.2 Wound Healing

Fresh and preserved human amniotic membrane has been used as a biological bandage for the treatment of ulcers, surgical wounds and injuries in the past with some success (Dua *et al.*, 2004). It was found that amniotic membrane stimulated healing and reduced the levels of pain and these effects are attributed to the high concentrations of anti-inflammatory and angiogenic factors.

Human amniotic membrane is commercially available in a dried state for use in wound healing. AmbioDry Amniotic Membrane Tissue Grafts (dehydrated, decellularized human amniotic

membrane) are marketed for use for wound repair and wound healing. However the FDA only allows the wound covering application because dehydration and decellularization of the membrane could alter the characteristics of the original amniotic tissue in a way that could have a meaningful bearing on how the product performs when used for wound repair or wound healing (<www.fda.gov/cber/compl/ambio062305.htm>).

5.1.3 Bone and Cartilage Repair

Cells from the amniotic membrane have angiogenic potential and could possibly be harnessed to develop vascular grafts for bone and cartilage repair. Alviano *et al*., (2007) conducted studies and suggest that AM-hMSCs (Amniotic Membrane-human Mesenchymal Stromal Cells) may emerge as a remarkable tool for cell therapy of multiple diseased tissues.

Jin *et al*., (2007) found that that denuded human amniotic membrane could be one of the ideal cell carrier matrices for cartilage regeneration. Jin *et al*., (2007) cultured cell-substrates for up to 4 weeks and examined their proliferation rate and phenotypic stability. Chondrocytes seeded in stromal side of the denuded human amniotic membrane penetrated and spread into the whole thickness of the stromal layer. The proliferating activity of these chondrocytes was continuous and remained stable for up to 4 weeks and the expression of type II collagen gradually increased with time. The technique has been successfully used to regenerate hyaline in rabbits.

5.1.4 Ophthalmology

The first documented ophthalmological application of human amniotic membrane was in the 1940s when it was used in the treatment of ocular burns. Following the initial reports, its use in ocular surgery abated until recently when it was re-discovered in the Soviet Union and South America. Its introduction to North America in the early 1990s heralded a massive surge in the ophthalmic applications of this membrane (Dua *et al*., 2004).

During the early 2000s there was some research around the use of human amniotic membrane for the healing of ocular burns and varying success rates have been reported. For example Joseph *et al*., (2001) reported failures but attributed these in part to the inaccurate reporting of the severity of the burns while Prabhasawat *et al*., (2007) performed trials and concluded that treatment of ocular burns with amniotic membrane patching promoted rapid epithelial healing and reduced corneal complication and reported a 70% success rate.

Dua *et al*., (2004) postulated ‘the reintroduction of amniotic membrane in ophthalmic surgery holds great promise; however, although it has been shown to be a useful and viable alternative for some conditions, it is currently being used far in excess of its true useful potential. In many clinical situations it offers an alternative to existing management options without any distinct advantage over the others. Further studies will undoubtedly reveal the true potential of the membrane, its mechanism(s) of action, and the effective use of this tissue in ophthalmology’. Dua *et al*., (2004) go on to suggest that many of the features of amniotic membrane make it an attractive tissue for use in glaucoma surgery. Ainsworth *et al*., (2006) reported a novel technique using a double layer of bovine amniotic membrane the inner one acting as a graft and the outer as a patch to cover exposed glaucoma tube shunts.

Ishino *et al*., (2004) discovered that human amniotic membrane maintains cultivated human corneal endothelial cells morphology, density and function and can serve as a carrier for human corneal endothelial cell transplantation. Morphologically, the cultivated human corneal endothelial cell sheets consisted of a fairly continuous layer of flat squamous polygonal endothelial cells that appeared uniform in size with tightly opposed cell junctions *in vitro* and *in vivo* after transplantation. The corneas that received transplanted for human corneal endothelial cell sheets had little edema and retained their thinness and transparency.

Tseng *et al*., (2004) found that the transplantation of human amniotic membrane as a temporary or permanent graft promotes epithelial wound healing and exerts potent anti-inflammatory and anti-scarring effects on the ocular surface. The success of the treatment is dependant on the killing of allogeneic amniotic cells and preservation of the cytokine-containing matrix during the preparation of the amniotic membrane.

Bredehorn *et al*., (2002) reported that amniotic membrane could be used as a natural matrix for the reconstruction of the ocular surface following a corneal ulcer, recurrent erosions, chemical burns, or excision of large conjunctival lesions and in patients with limbal stem-cell insufficiency. He suggested that amniotic membrane could be prepared from fresh human placenta and stored at -70 °C. The transplanted amniotic membrane promotes the growth of corneal epithelium and restrains inflammatory processes. Amniotic membrane transplantation and transplantation of the limbus can be combined to treat severe insufficiency of corneal stem cells. Bredehorn *et al*., (2002) suggested that multilayer amniotic membrane transplantation is a possible option for the treatment of deep corneal ulceration and descemetoceles and could provide stability for 12 months.

Tejwani *et al*., (2007) reviewed the research around the use of human amniotic membrane for the treatment of ocular burns and concluded that it helps in ocular surface reconstruction, promotes rapid epithelial healing and partially restores limbal stem cell function and can be considered as an effective modality for the ocular surface restoration in chemical and thermal injuries in selected cases.

In spite of these references a conversation with Traian Chirila of the Queensland Eye Institute pointed out that although human amniotic membrane grafts are big business in the USA, there are an increasing number of concerns about its use, apart from its rather enormous cost (~$1000/$cm^2$)(pers. comm. Traian Chirila, Aug 2007). These concerns are: (1) As with any human-derived tissue, the amniotic membrane is a potential vector for infectious disease (Schwab, 1999) (2) Variation in donors and processing methods make impossible a qualitative standardization, and significant variability in the mechanical properties of the commercially available preparations has been reported (Chuck *et al*., 2004) (3) Amniotic membrane transplantation is not effective in most surgeries for ocular surface disorders without being combined with transplantation of limbal epithelial stem cells or/and the use of mitomycin (which causes serious side effects), or if not performed within days in case of acute trauma (e.g. burns) (Tseng *et al*., 2007) A recent study showed that in reality the amniotic membrane transplantation is associated with significant lack of clinical success, especially when stem cell loss is involved (Maharajan *et al*., 2007).

In December 2004 the NHMRC placed a five year moratorium on clinical research into animal-to-human whole organ transplants, animal cellular therapies and animal external therapies in Australia (<www.nhmrc.gov.au/news/media/rel05/asm.htm>). This would currently preclude the use of viable bovine or ovine amniotic membrane within Australia. If the NHMRC moratorium is lifted in 2009 there maybe opportunities to utilize amniotic membrane for ophthalmologic purposes and TGA indicated that the registration costs for a product such as a bovine amniotic membrane graft as a Class III medical devise would cost up to AUD$80,000.

5.2 Stem Cell Culture Matrix

Amniotic membrane is increasingly being used as a matrix on which to grow stem cells. For example Tsai *et al*., (2007) used a porcine amniotic membrane to develop functional endothelium in the construction of blood vessel equivalents. Using amniotic membrane enhanced expression of intercellular molecules, platelet-endothelial cell adhesion molecule-1, and adhesion molecule VE-cadherin at the intercellular junctions. In addition, the expression level of integrin was markedly higher in endothelial cells cultured on amniotic membrane than on plastic dishes. Using amniotic membrane also led to the down-regulation of the expression of E-selectin and P-selectin in both LPS-activated and non-activated embryonic stem cells. Consistently, adhesion of leukocytes to both activated and non-activated cells was decreased in endothelial cells cultured on amniotic membrane (Tsai *et al*., 2007).

5.3 Risk Assessment

5.3.1 Health Risks

The health risks associated with handling amniotic membrane are considered the same as for handling amniotic fluid. See section 4.12.1 for detailed information.

5.3.2 Accreditation

There are no specific regulations for amniotic membrane and for this report the regulations are assumed to be the same as those for placenta. The differences may become apparent when end uses are determined such as medical uses. Amniotic membrane grafts would be evaluated under medical device standards for medical devices incorporating materials of animal origin by TGA. This regulation would require traceability of the donor animal, GMP facilities and a licence. Currently there is a five year moratorium(to end in 2009) on clinical research into animal-to-human whole organ transplants, animal cellular therapies and animal external therapies in Australia (<www.nhmrc.gov.au/news/media/rel05/asm.htm>) which precludes the use of viable bovine or ovine amniotic membrane within Australia.

5.3.3 Raw Material Availability

Bovine amniotic membrane is currently not collected separately in Australia. Currently ovine placentas are frozen after collection, which compromises the integrity of the amniotic membrane. The collection process would need to be adjusted to ensure high quality material. Fresh bovine amniotic membrane is readily available in abattoirs where foetal blood is collected where the placenta is available within 20 minutes after slaughter but major upgrades to meet TGA requirements may be required.

5.3.4 Collection of amniotic membrane

Collection of amniotic membrane would entail the collection of the placenta and then stripping the membrane from the inside of the placenta. This would entail separating the two sides of the placentomes, the cotyledons of the foetus and the caruncles of the uterus thus enabling the foetus and its membranes to be removed from the uterus. The foetus can then be removed and the membranes used for downstream processing. This would be a procedure that would require specialized training of personnel. Packing and transportation techniques, which are set down by the TGA regulations, would be necessary for medical applications (devices) and must adhere to GMP.

When biologics collector was asked about the feasibility of collecting ovine amniotic membrane he said “Anything is possible and entirely dependent upon the consistency of the market and also profitability of the collection exercise which would be quite tedious depending upon the specification of the end users”. He went on to say, “The bovine (membrane) is certainly easier to work with as it is a larger membrane which gives a better yield” (pers. comm. Craig Pearson, Sept 2007)

5.3.5 Biologics Processing

If amniotic membrane is to be used for grafts or other medical applications it needs to be processed within a 24 hr time frame under GMP conditions as set down by TGA. If it were to be preserved as suggested in some of the scientific literature the time frame would be longer but GMP requirements would still apply.

5.4 Bioactives in Amniotic Membrane

Dua *et al*., (2004) suggested that the distribution of collagens, proteoglycans (such as biglycan and decorin) and hyaluronon account for the bioactive properties of amniotic membrane. There

are also high concentrations of anti-inflammatory factors (including IL6 and 8) and these have possibly attributed to the success of biological bandages of amniotic membrane (Dua *et al.*, 2004).

5.5 Commercial Potential

Human amniotic membrane is currently used in some medical applications and is commercially available for ophthalmologic applications while the uses of animal amniotic membrane have not been extensively explored. Stem cell culture matrix is a promising application and could possibly be expanded. Dr. Zee Upton (QUT) sees these applications as important research tools for drug discovery and testing. Human amniotic membrane (Amnion) is currently approved in Australia for use in cornea treatments by the TGA.

5.6 Relevant patents

A total of four patents were found that are current and relevant to the application of amniotic membrane. Three are specifically around human material and the fourth doesn't specify the species. Two of the patents that don't specify species are application patents for the treatment of venous ulcers and eye disease. The assignee is Anthrogenesis a US biotherapeutics company owned by Celgene. Appendix 9 summarizes these four patents. The lack of existing patents indicates that there is reasonable evidence that an organization pursuing work with bovine or ovine amniotic membrane would have freedom to operate.

5.7 Summary

Amniotic membrane has potential applications in the clinical arena including wound and repair treatments in a number of tissues as well as a research laboratory application as a stem cell matrix. Human amniotic membrane is currently used in some medical applications and is commercially available for ophthalmologic applications. The use of animal amniotic membrane has not been extensively explored in part due to concerns of infectious agents and the anticipated immune response that is likely to develop to the implanted membrane components. Stem cell culture matrix is the most promising application and could possibly be expanded. There is interest in developing this application in the research sector.

Bovine amniotic membrane is readily available within the Australian meat processing industry and could be collected by skilled operators; however, the collection facility may need to be upgraded to meet GMP requirements.

6 Potential uses of placental material

Placenta material has a long history of health related applications particularly in the Chinese culture, which has attributed its therapeutic benefits to it especially when combined with certain herbs, for at least 1400 years. This long history means that the placental market is far more mature than those of amniotic fluid and membrane. Western scientists have conducted research around the clinical advantages of sheep placenta since the 1930s. Through repeated experiments, Filatov, a well-known Russian scientist, concluded that sheep placenta had a mitigating effect against tissue degeneration (anti-aging effect) and helped in healing of traumatized tissues and ulcers. Japanese and Western scientists have also conducted research around the therapeutic benefits of sheep placenta. Current uses in western society include the

extraction of placenta and immune globulin from sheep placenta for use in health supplements (<www.careline.com.au/products/product.php?id=11>). There are many organizations working with placenta (particularly ovine and deer) both in Australia and globally producing therapeutic products as well as soaps, shampoos and a large array of cosmetics.

We have identified Chinese medicine, cosmetics and clinical applications such as vitiligo treatment, wound and fracture healing and burns treatment as well as industrial applications, as potential uses for placenta. This section of the report is structured towards investigating these applications. Appendix 13 lists some components of placenta and their assigned bioactive properties.

6.1 Asian Medicinal Applications

In traditional Chinese medicine the human placenta is considered to be an invaluable part of the postpartum healing process for both mother and child. For thousands of years, the Chinese people have revered placenta in their Materia Medica as regenerative. It is considered to be “full of Qi (life force)”, which aids in recovery from childbirth, restores lost hormones, augments lactation, shortens bleeding time, prevents mood swings, and ultimately helps the child in this vital time of bonding and nurturing. In Chinese medicine placenta (combined with herbs) is used to treat asthma, kidney conditions and male and female fertility conditions. Cai Gan, Chief Director of the Chinese Medicine Department of Shuguang Hospital, China reiterated this when he said, "Placentas (human) are dried and powdered and used as an effective medicine to enhance the functions of the kidney and to treat asthma," (<app1.chinadaily.com.cn/star/2005/0602/fo4-1.html>).

Most Chinese medicines are derived from ‘active’ animal parts such as chicken feet and placenta and there does not appear to be a history of products derived from amniotic fluid. The amniotic fluid products that are marketed in China appear to be cosmetic rather than therapeutic preparations and there is little information easily accessible around these products.

When interviewed, Prof. Lin Tzi Chiang (Vice Chairman of the World Federation of Chinese Medicine Societies and National President of the Federation of Chinese Medicine and Acupuncture Societies of Australia Ltd.) told us that Chinese medicine is a particular art and that placenta alone is “heavy on the stomach” and needs to be combined with various herbs for particular beneficial outcomes. The placenta is prepared fresh (freezing is not recommended) with rice wine, specific herbs and fresh ginger to disperse the medicine deeply into the body. It is cleaned, steamed, and cut into very thin slices, then placed in a dehydrator until thoroughly dry. Then it is finely ground and encapsulated. The dosage is two capsules thrice daily for the first two to three weeks or until strength has been restored (<pregnancy.about.com/cs/placentas/a/placenta.htm.>).

Dried sheep placenta is also sometimes used in traditional medicine to facilitate labour (<cat.inist.fr/?aModele=afficheN&cpsidt=3259929>). In another example, sheep placenta powder combined with *Lysium barbarum* (red berry) enhances the immune system, retards ageing, lowers cholesterol, combats lung tumours, protects the liver, increases red blood count, reduces blood sugar, reduces blood pressure and cures common viruses (this information was extracted from the Chinese Pharmacopeia for Bruce Galway (Galpak)). There are further examples of the different combinations and their therapeutic effects in Appendix 6.

Human placenta is rarely used in Chinese medicine practice now due to difficulties in obtaining them and concerns of specific diseases such as AIDS (pers. comm. Prof. Charlie Xue (Head, Division of Chinese Medicine, RMIT University)). The risk of disease transmission has let to the withdrawal of some products from Western markets. For example the traditional Chinese medicine Nu Bao (menstruation-regulating) capsule has been withdrawn from the UK market as it contains human placenta, deer antler and donkey skin as ingredients all of which are considered potential sources of infection (<www.nutraingredients.com/news/ng.asp?id=51983>). Human placenta is still used in more traditional markets. For example the Shanghai Institute of Biological

Products (SIBP) has been certified as a designated unit for collecting human placentas from hospitals. SIBP pays hospitals 5 yuan (60 US cents) for each placenta, processes them into medical preparations, involving more than 20 different procedures, and sells the placental powder for about 400 to 600 yuan (USD$48 to 72) per 1 kg (<app1.chinadaily.com.cn/star/2005/0602/fo4-1.html>).

Prof. Lin pointed out that bovine placenta is rarely used in Chinese medicine because cattle products are looked on as sources of food rather than having therapeutic properties. He also said that sheep and deer products are also food sources but are considered to be more gentle and pure than cattle products and have more 'warm energy'.

Prof. Xue stated that for the complementary medicine industry attention should be primarily given to quality and safety instead of efficacy. Traditionally, the determination of the therapeutic effects was not based on the chemical components of the medicinal substances. Prof. Xue said in the modern research, validated markers and outcome measures are commonly used to determine quality and efficacy. Chinese culture is much more open to using various animal parts in their diet and traditional medicine practice.

Prof. Xue pointed out that many Australian patients use a combination of herbal and western medicine and that Asian people sometimes turn to Chinese medicine and self medicate when they think that western methods are not benefiting them.

Chinese medicine practitioners can manufacture and supply Chinese medicines to their own patients but are not permitted by TGA to sell them in Australia. For example Prof. Lin manufactures sheep placental capsules, prescribes them to his patients and also exports 10-20,000 capsules per year to Hong Kong.

Prof. Lin suggested that Australia is in a position to develop an industry around placental derived products by setting up a research program to validate and further develop products so that they could be approved by the TGA and be marketed here. The collection of material and research program would need to have substantial input from Chinese medicine professionals with a comprehensive understanding of the medicines so that both Chinese medicine and TGA requirements would be met. This validation would also enhance export opportunities, as overseas buyers would have more confidence in products that have total TGA accreditation rather than the current export only accreditation. The Complementary Healthcare Council (<www.chc.org.au>) which assists with TGA applications (fee for service consultants) could be approached for support in gaining accreditation (pers. comm. Jason Tong, TGA, August 2007). Development of collection procedures for the raw material would need to be overseen by a Chinese medicine professional so that the collection is in accordance with their needs. This would require a high level of collaboration between meat processors, collectors and biologic processors and interested Chinese medicine practitioners.

6.2 Cosmetic applications

Human placenta has been used for a variety of cosmetic applications for many years. When placental materials were first used as cosmetic ingredients in the 1940s, manufacturers promoted the products as providing beneficial hormonal effects such as stimulating tissue growth and removing wrinkles. Later, the hormone content and the tissue-growth and wrinkle-removing claims led to the classification of placenta-containing products as drugs. Placenta containing cosmetics marketed in the US carry the statement "This statement has not been evaluated by the Food and Drug Administration. This product is not intended to diagnose, treat, cure or prevent any disease" (<www.fda.gov/fdac/reprints/puffery.html>). Some examples of cosmetic products containing placenta can be seen in Appendix 1.

Currently placenta is used widely in the cosmetics industry for topical applications and also for oral preparations. Most of the claims around placenta are based around anti-ageing and anti-oxidant advantages. These advantages would benefit the ageing population (over 65s expected are to be 12.5% of the population by 2030) and this demographic will be aligned with the current

and predicted trend of consumers being influenced by scientific evidence when purchasing cosmeceuticals (Datamonitor DMCM2376).

In the cosmetic industry in recent years there has been an increase in demand for natural products as a result of concerns around synthetic substances including the possible dangers of parabens, petrochemicals, silicones and petrochemicals in personal care products (<www.neem-products.com/cosmetic-industry-trend.html>). Such growth is illustrated in the Italian personal care products market where the natural and organic sector is the fastest growing with annual growth of over 20% per annum (Business Wire, Jan 2007).

The Russian company Plazan promotes placental material for anti-aging treatments claiming – "The placental components (elastin, collagen, glycosaminoglycans, hyaluronic acid) have an indisputable advantage compared with analogues of microbe origin. They are completely or mainly (from pig placenta) analogous to substances of human skin". They allude to collecting human placenta from maternity wards of Russian hospitals (<www.ost-cosmetics.com/ostcosmetics-faq-page.html#properties>).

Korean company Hwamiae Cosmetics Co. produces a range of human placental based products including soap, toner, revitalizing cream, serum extracts and essence lotion. They have been in operation since 2001 and face production constraints due to limited supplies of raw material (<hwamiae.en.ec21.com/company_info.jsp>).

The antioxidant activity of human placental material was investigated and it was discovered that it is due to glycine (G)-XY amino acid repeats in peptides derived from the collagen (Togashi et al., 2002). This could have application in the cosmetics industry because these peptides help maintain moisture within the skin. Bruce Galloway of Galpac believes that the high iron content (18.0 – 30.0 mg/100 g) of placenta is also responsible for the health promoting characteristics.

There are a number of Australian companies that manufacture ovine placental based products for the skin care market. The manager of one such company (Aqi Care) indicated that the placental extracts are not Australia sourced but he was reluctant to reveal their sources (pers. comm. Brian Baldwin, June 2007). Another such company is Lanocorp Australia Pty Ltd also declined to reveal their source of placenta and Russell Hogg (Director) said "We keep information like that tightly secure. Quite frankly, I'd rather see a report on the abuses of the "Australia Made" logo and labeling regulations that are prevalent from all the Chinese made imports that are killing our industry…..?" Companies including Careline Group Pty. Ltd, Johnson and Barana, Lanocorp Australia Pty Ltd and Nature's Hive Pty Ltd all manufacture placental derived facial creams and in some cases capsules with claims about immunity and anti-aging. John Bridgewater of Nature's Care, which is based in Australian but Thai owned revealed that they source placenta from New Zealand for the capsules, which they manufacture for export.

A conversation with Craig Pearson (Australasian Casing) revealed that ovine placenta is collected in Australia and exported for processing (in Asia or New Zealand) and then returned to Australia as a powder or paste, which is used for capsule and cosmetic production (pers. comm. Craig Pearson). Pearson also pointed out that Asian consumers (Japan in particular) are very strongly against bovine products (from any country) in their formulations presumably due to concerns around BSE. Pearson said that and he switched to collecting deer and sheep placenta after the initial BSE outbreaks in 2001. He also said that the US market would probably accept bovine material because they have had BSE outbreaks.

Aurora Pharmaceuticals Australia imports ovine placental powder from New Zealand and encapsulates it for the Chinese market. They also sell bulk powder into China (pers. com. Gina Luck, August 2007). Luck showed a strong interest in working with bovine placenta and knows of no reason for it not to be accepted in China, which is contrary to other information that we collected.

New Zealand based company Alpha Laboratories is a contract manufacturer which produces a number of placental derived formulations including ovine and deer powders, creams and capsules, supplementary products for skin health, immune support and men's and women's

health (<www.alphalabs.co.nz>). A phone conversation with the manager revealed that they also use bovine placenta in some products (pers. comm. John Rawcliffe, June 2007).

There are a number of organizations in Asia such as Superbee Network Singapore, Nanjing Health Light Business (China) and Trade Suzhou Longlifu (Hong Kong) that market sheep placenta products. Companies such as Sofface Cosmetics (China) and Guangzhou Sisder Health & Beauty (China) manufacture sheep placenta derived cosmetics. Hangzhou Huajin Pharmaceutical Co., Ltd (China) markets placental powder, which is extracted from fresh and healthy human or animal placenta (<products.ec21.com/manufacturers/placenta_AND_sheep.html>).

Daily Vita markets sheep placenta capsules, which are made in the US, and claim “can improve the look of the skin, alleviate menstrual pain, improves resistance to infection and increase sperm production and potence” (<www.dailyvita.com>). NuHealth and Mila Products are other US companies that market placental products (such as EMK placental cream) and target the beauty industry with skin rejuvenation and moisturizing claims.

The Japanese consumer pays premium prices for supplements made from domestically sourced placenta due to perceived higher levels of the safety and quality (<digimint.com/>). The Japanese have started to use "SPF Placenta" which comes from "Specific Pathogen Free" (SPF) pigs, which avoids the need for sterilization which has the effect of destroying many bioactive components. (<digimint.com/placenta_details.htm>). BikenMura and Yuki Cosmetics are major Japanese suppliers of placental derived cosmetics.

Suppliers of Australian bovine placenta have a distinct industry advantage in that their product is ‘clean and traceable’. This gives it a competitive edge in the global supply chain for high quality cosmetics. There are traditional (China) and preference (India) constraints on bovine products but bovine stem cells are currently used in Europe and US for beauty applications indicating that these markets would accept bovine placental products that are guaranteed clean of BSE. TGA accreditation is not necessary for cosmetics as long as the hormone levels of the finished product are below those set out in section 6.5.2 and unless specific claims are made so this opportunity could be developed by companies with the necessary infrastructure such Sphere and Pharma-Cosmetics.

6.3 Clinical applications

6.3.1 Vitiligo

Vitiligo results in a patchy loss of pigmentation due to the demelanization of melanocytes. Whilst it is not considered physically harmful, its emotional and psychological effects can be devastating. A social consequence is that, in India, women with the disease are sometimes discriminated against in marriage and developing vitiligo after marriage can be grounds for divorce. A famous victim of vitiligo is Michael Jackson.

Globally as many as 65 million people have vitiligo and in the USA 1 to 2 million people suffer from the disorder. Half of the affected individuals will have developed vitiligo by 20 years of age and most develop it before their 40th birthday. The disorder affects both sexes and all races equally but is more noticeable in people with dark skin and seems to be more common in people with certain autoimmune diseases (<www.niams.nih.gov/hi/topics/vitiligo/vitiligo.htm>).

The current treatments for vitiligo include strong corticosteroid creams, immunomodulators, placental extract, phototherapy (including photochemotherapy) and surgical methods. These have been tried with different individual response. Currently narrow band ultra-violet light of type B is the treatment of choice worldwide for vitiligo.

Extracts from placenta may play a role in treating vitilgo have been trialled both *in vitro* and *in vivo*. These extracts proved to be a strong stimulant for melatonin production (Pal *et al*., 2002).

6.3.2 Wound healing

Wound healing is a dynamic and complex process that can be divided into three main and partially overlapping phases: the early inflammatory, the intermediate proliferative, and the late tissue remodelling phases. In diabetics, wound healing becomes defective, often resulting in ulcer formation. Cianfarani *et al*., (2006) conducted research to show that growth factors in placenta, including placenta growth factor, are effective in the treatment of these wounds. Fibronectin Type III like peptide, an important compound in wound healing, can also be isolated from human placental extract (Chakraborty *et al*., 2005). Berger and Bergerman (1958) conducted early trials around the use of placenta in wound healing.

6.3.3 Burns

A small amount of work has been done around the treatment of burns with placental material. Smirnov *et al*., (1994) treated third degree burns by applying a suspension prepared from human placenta and foetal skin and it proved to be as effective as plastic surgery. This approach could be particularly helpful when supplies of donor skin are limited, in the therapy of patients with polyvalent allergy, elderly patients with severe somatic pathology hampering autodermaplasty (purification of infection), in the therapy of children, and in cases of untreatable infected burns

6.4 Risk Assessment

6.4.1 Health risks

The health risks associated with handling placenta are the same as those for collecting amniotic fluid. These are discussed in section 4.12.1.

In the cosmetics industry placenta is washed and processed many times to destroy bacteria or viruses. In addition and the cosmetic matrices (components that bind the ingredients in products) are typically made using a wide variety of substances, such as alcohol and preservatives, which present a hostile environment to any surviving pathogens (<www.fda.gov/fdac/reprints/puffery.html>).

The incorporation of placental material in cosmetic solutions has been clouded by a report of premature sexual development in very young children treated with shampoos containing a placental extract (Tiwary *et al*., 1997). However this has been refuted as placental extracts form a very minor constituent of cosmetic preparations and that the actual bioactivity of the extracts is often questionable (Nair and Elmore 2002). The FDA has noted the unregulated use of the term “placental extract” and in 1994 declared them to be ineffective and therefore misbranded which resulted in them being offered without medical claims - only as a source of protein for applications such as “to nourish, tone & create healthy looking skin” (<www.fda.gov/fdac/reprints/puffery.html>).

6.4.2 Accreditation

In Australia products derived from placenta are subject to both AQIS and TGA approval for both import and exportation activities. AQIS allows the import and export of placenta both as a cosmetic and as a complementary medicine of animal origin (<www.aqis.gov.au/icon32/asp/ex_QueryResults.asp?Commodity=placenta&Area=All+Countries&EndUse=All+End+Uses&QueryType=Search>). Under their guidelines, if the product is edible at source it must be treated as an edible meat product under the current domestic and export legislation. A further conversation with Langbridge revealed that the export of placenta and amniotic fluid (bovine, porcine and ovine) are currently classified as inedible (J. Langbridge pers. comm. Mar 2007).

If a product (including cosmetics and complementary medicines) is considered therapeutic it must be placed on the Australian Register of Therapeutic Goods (ARTG), which is administered by the

TGA. These products are evaluated for quality, safety and efficacy and evidence of good manufacturing practice including compliance with standards and the code of good manufacturing practice (<www.nicnas.gov.au/Cosmetics/Considered_Therapeutic.asp.>). For the registration of export only goods the TGA does not require any evidence of efficacy, which reduces costs for producers (see section 4.12.2). Placenta as an ingredient is listed as a *Category* II (medium infectivity) with TGA, which requires that the TGA Laboratories Branch issue a clearance certificate before export can occur. Certification requires an AQIS inspection and assays for viruses and prions. (<http://www.tga.gov.au/pmeds/argpmap10.pdf>). There are 20 products containing placenta (all except one are capsules) listed on the ARTG and they are predominantly sheep derived products and all are export only products. A list of these products can be seen in Appendix 17.There are no placental products available in Australia for oral consumption. There are many cosmetic creams containing placenta available in Australia and because they do not claim therapeutic effects they do not require TGA accreditation entry for on the ARTG.

Prof. Charlie Xue of the School of Chinese Medicine (RMIT) reiterated this when he pointed out that medicines would be closely monitored by the TGA while placental creams containing low concentrations of placental material would be free from TGA constraints as they are not considered therapeutic.

The Korean Food and Drug Administration launched a safety inspection of some European cosmetics and medicines that use bovine placenta as a preventative measure against a possible entry of BSE into Korea (Kim Hyung-jin, 2001). The Korean government continues to be very cautious of imports and has rejected several shipments of meat from the US in recent months (<www.upi.com/NewsTrack/Top_News/2007/09/06/banned_us_meat_found_in_south_korea/3804/>)

A placental derived product would need to be characterized and a genuine use be identified before an application to TGA for product for use within Australia could be developed (pers. comm. Bren Milsom, Technical and Regulatory Affairs Consultant with Advantage Medical Products Consulting Pty Ltd Nov 2007). Milsom expressed concern around the possible high levels of hormones in placenta. Any preparation containing sex and/or growth hormones are considered high risk and must be registered as a “prescription only” medicine. The Standard for the Uniform Scheduling of Drugs and Poisons (SUSDP) (22nd.edition Appendices I and J) sets down that the hormone levels for listed substances must be below 1 mg/kg for progesterone, testosterone and growth hormones and 10 ug/kg for oestrogen. There are some placental derived products in the market place, which claim to contain “Hormone Free” placenta such as Placenta and Honey Cream (<www.manuka-nz.co.nz/index.php/cPath/42>). Milsom indicated that the application fee for a new ingredient is AUD$8,000. There would be further costs for the scientific report of AUD$10-20,000 and clinical trial costs. He said that an application developed around a topical preparation may be successful but again pointed out the importance of characterization. Sex hormones are easily absorbed through the skin (<www.nytimes.com/2006/10/17/science/17puberty.html?_r=1&oref=slogin>). When we asked Bruce Galloway of Galpac if they prepare hormone free placental powder he said, “*We have never tried to remove hormones but advise customers that the level is natural and that we do not offer a hormone free product. We issue a manufacturers statement that the products are free from added or artificial hormones*” (pers. comm. Bruce Galloway, Nov 2007).

Placenta is listed on the Australian Inventory of Chemical Substances (AICS), which indicates that it could be used in cosmetics within Australia as long as it does not contain hormones at levels above the concentrations indicated above. National Industrial Chemicals Notification and Assessment Scheme (NICNAS) have not assessed placenta and there does not appear to be an MSDS sheet available.

Some operators find TGA difficult to communicate with and feel that information/advice is not easy to obtain. Jason Tong of TGA told us that TGA personnel are not able to give advice, as this is not their role and that the CHC and regulatory consultants are able to help in this role (pers. comm. Jason Tong Aug 2007). Prof. Fiona Wood sees the TGA approval as an important safety

net for new products as they enter the market place. She values the long and sometimes complicated process as an indicator that the product is safe and that the developer is protected from any issues that may arise. Wood said that TGA approvals provide her with confidence in the products that she uses in burns and wound treatments (pers. comm. Prof. Wood, Aug 2007).

6.4.3 Raw Material Availability

Placenta is not readily available in the Australian market. Supply is limited by seasonal availability and a lack of capacity within the abattoirs. Despite this, export of ovine placenta is occurring to Japan and other parts of Asia (pers. comm. J. Langbridge, June, 2007)

An e-mail discussion with Bernard Gooch of Fletchers International Exports an ovine processor at Dubbo brought the following response "*We do not keep these items (placenta and amniotic fluid) as to do so is not really financially viable for us. Labour shortages and distribution are the biggest problems for us. Obviously the ewes have to be pregnant and production is spasmodic*". A discussion with Norvic (Wodonga) revealed that ovine placenta is collected upon demand. They said that they could collect 800 kg within a few days if there was a request (and the price was right). They collected 750 kg of placenta within 4 weeks in this winter at $5/kg (pers. comm. Antoine Valterio of MLA, Sept 2007).

Dennis Wyatt of the Northern CO-OP. Meat Co (a bovine processing plant at Casino) revealed that in the past bovine placenta had been collected and exported to Japan in container quantities but the operation ceased due to the BSE outbreak and some resistance within the work force. A further discussion with Wyatt revealed that it would be possible to begin collecting placenta on a fairly large scale again if it were commercially viable. Another large bovine processor indicated that they had considered the collection of placenta and were aware of opportunities in China but had found that it is not economically viable due to small returns and labour shortages.

A major Queensland processor showed an interest in collecting placenta and amniotic fluid in their blood room and said that if a case to support commercial viability were presented they would certainly engage in such a venture .

Raw material availability is influenced by seasonality. Figure 2 shows that the Australian beef supply is characterised by low summer production with January and December being the lowest production months and late autumn and spring peaks. There is a relatively stable winter supply. These variations need to be accounted for in the design of a supply chain for any meat-derived bioactive industry.

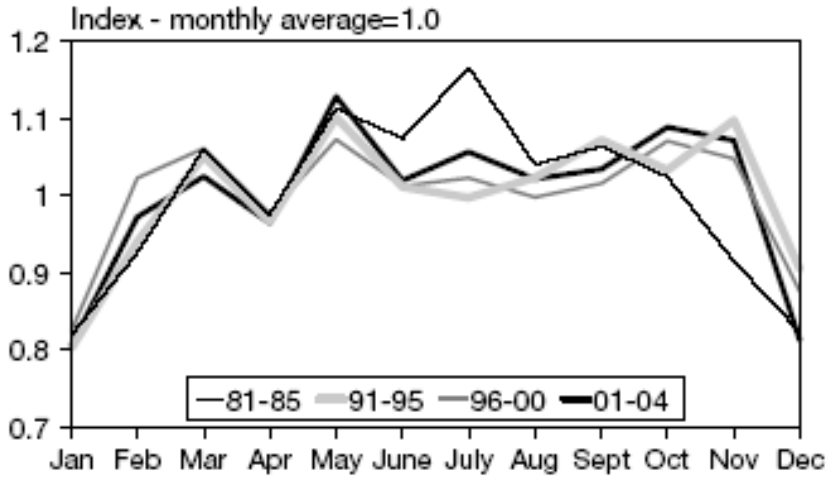

Figure 2 Australian beef production. Each monthly data point was divided by the corresponding annual average, creating a monthly index, where a value of 1.0 represents an average for the year concerned. Source: MLA, 2005.

The effect of seasonality on the most productive cattle regions can be seen in Figure 3. The peak season for Queensland is between June and September, whilst production decreases sharply during December and January, coinciding with the wet season and the Christmas/New Year holidays, which provides the opportunity for abattoirs to close for annual maintenance (<www.npicenter.com/ >). The behaviour is less predictable in NSW and VIC, although the low season in both states is also in the months of December and January. Therefore, it would make sense to plan storage space for raw materials to allow for 3 months supply of placenta for the leaner months of summer.

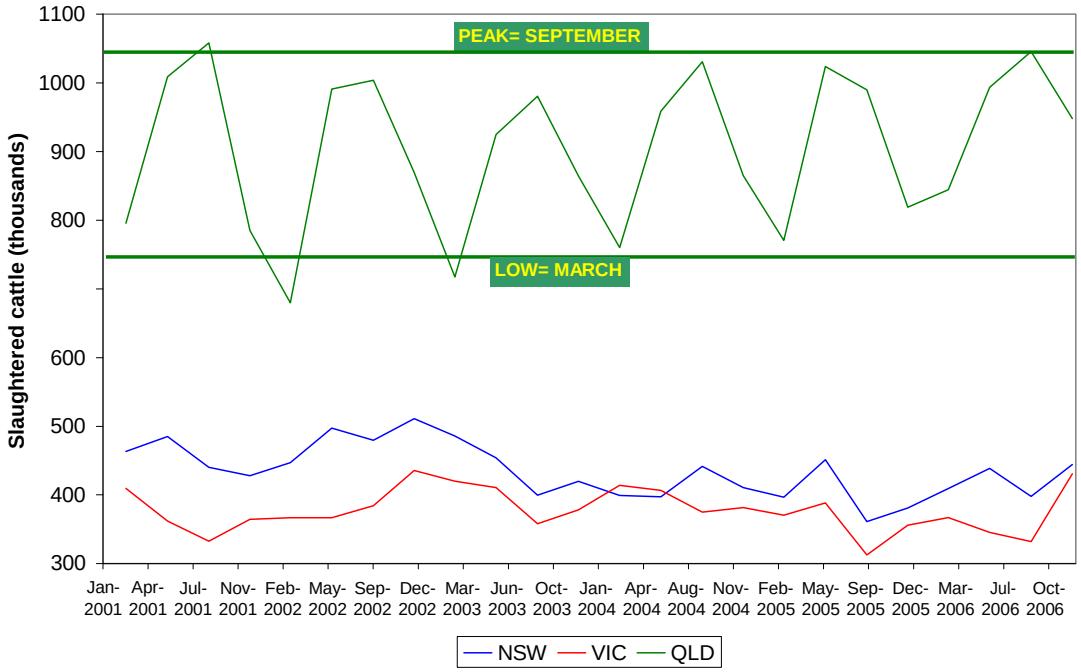

Figure 3 Cattle slaughtered (thousands) in the three main producing states. Source: ABS. Livestock Products, Australia, Mar 2007.

6.4.4 Logistics

The majority of the supply chain companies are located in Queensland, New South Wales and Melbourne. Further to this Sydney and Brisbane are the major ports for meat export and 40% of the total livestock production in Australia is located in the Murray-Darling Basin. Therefore, it would make sense to consider these areas as the major regions of interest for collection and location of possible manufacturing facilities.

A discussion with Cameron Crowley (Maverick) revealed that there are currently operational logistical issues to be considered, a major one being the small volumes of raw material available within Australia which means that a collection of material is made over weeks and then is shipped internationally (usually to New Zealand, Asia or China). Companies such as Australasian Casing collect the animal components such as placenta from abattoirs when it is frozen (for 22 - 48 hours after kill) and hold it until they have enough for a shipment. Crowley said that cost of collection, storage and shipment is usually less than the price paid to the abattoir for the material.

6.4.5 Collection of placenta

Bovine placenta could be collected in any abattoir that currently collects foetal blood as the placenta could be stripped from the uterus and packed and frozen rather than being discarded after the slink has been removed for blood collection. A discussion around collection methods with Craig Pearson of Australasian Casing brought the following response "*When the beef placenta was being collected many years ago I had trained people to remove the placenta from the inside of the uterus and only pack this portion. It is not practical to do the same thing with the sheep as the yield is very low*". The current practice in some plants that collect ovine material is to collect and freeze the whole uterus with the slink inside. Other plants such as Norvic collect just the placental membranes (pers. comm. Antoine Valerio, Dec 2007). This material is currently collected on demand in abattoirs that are set up for pharmaceutical collection of various animal components and are AQIS accredited for export such

as Norvic at Wodonga (Vic), T&R at Murray's Bridge (SA) and Cedar Meats at Brooklyn (Vic)(pers. comm. Craig Pearson of Australasian Casing Co.). The yield would be vastly different in that the placental membranes weight approximately 200-600 g at term (Wallace et al., 2002) while a gravid uterus including the slink is approximately 2,650 g at midterm gestation (Grazu-Bilska et al, 2006).

6.4.6 Biologics Processing

The first stage of processing for biologics simply involves chipping, mincing and cooking (heating to 65° C). When the whole uterus is processed the liquid is collected and marketed as amniotic fluid. The cooked material is then dried and homogenized to a powder. The powder is distributed to bulk (contract) manufacturers such as Sphere and Pharm-Cosmetics in Australia and Alpha Laboratories in New Zealand who manufacture products such as creams, lotions, shampoos and capsules for export or Australian companies such as Careline Group who bring the product to market either locally or globally. Bruce Galloway of Galpac said that the final yield from placenta is approximately 10% dry weight where "placenta" refers to the whole uterus containing the membranes and slink (pers. comm. Bruce Galloway, Nov 2007).

A conversation with Sphere revealed that they purchase powder from one of two Australian organizations and process it into capsules for export. They are not currently producing placental based produces. They also indicated that they make creams for the Australian market on demand if the claims are within the regulatory requirements.

Eugene Ng from Pharma-Cosmetics said that Australians do not consume many placental based products and that most of their exports are to Asia.

6.5 Commercial Potential

The primary commercial opportunities for placental derived produces are the cosmetics (including cosmeceuticals) and nutraceutical markets. Cosmeceuticals are cosmetic products that are claimed to have specific benefits such as anti-ageing. The world's cosmeceuticals market is estimated at USD $ 60B in 2007, with growth of 8 to 12%. In terms of the geographical market for cosmeceuticals, Japan is by far the biggest, valued at USD$6B to USD$8B (<www.nutraingredients-usa.com/news/ng.asp?id=76516>). The US cosmeceuticals demand is expected to grow 8.5% annually, propelled by a stream of new products offering age defying and other appearance-enhancing benefits. Skin care products will remain dominant while professional products (skin clinic distribution) will grow the fastest (<www.freedoniagroup.com/Cosmeceuticals.html>). The US has the highest spend per capita for both cosmeceutical personal care products and nutraceuticals. In the US, according to the Euro report, sales of cosmeceuticals are expected to reach USD$5B to $6B in 2007, accounting for a quarter of the total skincare market. The EU market is estimated to be between $3B and $5B (<www.marketresearch.com/product/display.asp? productid=1526550&g=1).

Drug developments in the USA and EU are becoming increasingly expensive and time consuming, with new products typically requiring investment of over 4 years (absolute minimum) and USD$1B from concept to commercialization. As a result, China has emerged as an increasingly attractive option for companies aiming to reduce such prohibitive investments in time and finance (Sahoo, 2007).

In Australia the offer of "natural" beauty products, along with continual segmentation of the consumer market, are having the strongest impact on the Australian cosmetic market. On a global level, cosmeceuticals are driving industry growth, particularly products aimed at reversing signs of ageing, minimising wrinkles or reducing the ageing effects on hair. Consumers are also turning to cosmeceuticals for relief from stress and for increased energy, as opposed to pharmaceutical solutions. The strongest growth is occurring in products, which combine both cosmetic and "natural" elements such as vitamins and herbs (<www.bandt.com.au/news/33/0c006a33.asp>). This indicates possible opportunities for placental derived products, which target the ant-ageing market.

The development of nutriceuticals, which are foods and drinks incorporating bioactive elements, presents another opportunity for formulating placental derived products. A 2007 study by Kline & Company valued the global market for what it terms 'nutricosmetics' at USD$1billion. The company forecasts that the market will double over five years (<www.nutraingredients-usa.com/news/ng.asp?n=76432&m=2NIU516&c=kflraxafxcxabzo). In Europe there has been a sharp rise in new cosmeceutical food and drink product launches between 2005 and 2007. In 2005, 14% of global cosmeceutical new product development originated in Europe and this rose to 23% in 2007 (<www.globalbusinessinsights.com/content/rbcg0165m.pdf>). The US cosmeceuticals market is experiencing 6.3% growth per annum the European cosmeceuticals market is growing by 4.8% a year(<www.nutraingredients-usa.com/news/ng.asp?n=76432&m=2NIU516&c=kflraxafxcxabzo). Bruce Galloway of Galpac developed and attempted the marketing of a cosmeceutical drink containing placental powder on the Hong Kong market. This product had limited release because the returns to Galpac were small (pers. comm. B. Galloway Aug 2007). However, the expansion of the nutricosmetics market indicates that this situation may change for new products.

Frozen raw ingredients from New Zealand (Central Hawkes Bay, New Zealand), eligible for export to Japan and many other countries for nutraceuticals include placenta (from many species including pig and sheep), adrenal cortex, adrenal medulla, deer cartilage, bovine salivary glands, bovine prostate, testes, frozen ovaries, placenta, pituitary glands, pineal glands, frozen eye extracts, blood, serum etc. Agri-lab Co-Products is a major supplier of animal components from New Zealand. Bovine and cervine (deer) foetal tissues are supplied to order. These are brokered through the Trade Tie-up Promotion Program, which is part of the Japanese External Trade Organization.

The current national expenditure in Australia (on health) is 10% of GDP with the average individual expenditure being AUD$4,256 per annum. Half of all adults in Australia use some form of complementary medicine. Many countries such as Japan (72%) have even higher uptake. In China, nearly all hospitals have a traditional medicine unit. See Appendix 17 for more details. The size of the complementary medicine industry is difficult to ascertain. The industry has no representative body and is highly fragmented with some 60% of manufacturing being conducted by private companies. Despite this the industry is estimated to be worth between AUD$800 million and AUD$1 billion.

Many complementary medicines are cheaper than conventional medicines. However certification is required to ensure their efficacy and safety. Certification is seen as a way of allowing consumers to make informed decisions and hence would lead to an uptake in complementary medicines.

6.6 Economic Potential

We will assume that a 2 kg bovine placenta yields approximately 200 g of dried powder (10%) per animal. Current pricing structures have been identified for placenta derived products. Australian abattoirs such as Norvic in Victoria will collect and pack ovine placenta for AUD$5 per kg on demand. Each kilogram of placenta yields 100 g of powder which indicates a real cost of AUD$50/kg. Nutrimart market bovine placenta powder sourced in the USA at AUD$85/ kg for a 50 kg plus quantities showing a 1.5 fold value add (See Appendix 3 for specification sheet).

Alpha Laboratories (NZ) sells ovine placenta tablets at wholesale rates of NZD$52/1000 x 2000 mg capsules ($26/kg). These capsules are advertised as containing 2000 mg of placenta “equivalent to fresh” which would mean 10% (200 mg) dried material because the dried yield is 10% (pers. comm. Bruce Galloway, Aug 2007) so the value of placenta powder is $2.6/kg per kilo of capsules. This indicates a 3-fold value add from the powder at $85/kg. Green Health (NZ) retail 60 x 2000 mg placenta capsules at $14.95 ($80/kg) indicating a 5-fold value add. These figures indicate that currently the meat processors are the smallest value adders in the value chain. These details are tabulated below. There are also more details in Appendix 2.

Item	Refinement	Price	Price/original kg	Value add factor

Collection	-	AUD$5	5/kg	-
Homogenization	1:10	AUD$85*	8.5/kg	1.5
Encapsulation	N/A	AUD$26	26/kg	3.2
Retail	N/A	AUD$125	125/kg	5

This price is converted from a spot US price Dec 2007.

Table 1 Value add factors for placental value chain

The scenario below gives a picture of the possibilities for a meat processor. An Australian processor may be able to ask for more than the US price because of the BSE free status and "clean green" image but we have not attempted to put a value on this competitive advantage in the scenario.

1.2 Scenario for adding value for the meat processor

A processor processing ~ 600 pregnant animals per week and would be in a good position to produce placental powder as value adding activity. If the processor already has AQIS approval they would be able to export the powder without further approval. Alternatively they could sell raw placenta and /or amniotic fluid. It should be noted that there are no firm figures available around building a production plant so an ROI has not been calculated and the amniotic fluid market has not been developed.

Assume unprocessed placenta price at	AUD$5/kg
10% of animals that are processed are pregnant (10% of 18,000) =	1,800/week
Assuming an average bovine placental weight of 2 kg =	4,000kg/week
Assume price of AUS$5/kg and 48 week production year (48x4000x5)=	**AUS$1M/yr**
Assuming an average bovine placental weight of 2 kg and yield 10% powder.	
Dry wt =	200g/animal
Processor processes ~ 1800 pregnant animals per week, which would yield =	360kg/week
The annual yield =	18,000kg
Assuming a price of AUD$75/ kg the annual return =	**AUD$1.2M**
Each animal produces ~ 4l of amniotic fluid. Total (1800X4X48) =	350,000l/yr
Current price =	AUD$60/litre
Total return to processor =	**AUD$21M**

Disclaimer:

It should be noted that the authors have relied upon data from referenced sources and anecdotal information from the meat processing industry. This information and data constitutes a snapshot of the situation between June and October 2007 and the situation in this area is subject to constant variation. The reader should make their own enquiries and exercise their own judgement before relying on the conclusions set out herein.

6.7 Relevant patents

A total of 16 patents were found that are current and relevant to placental applications – two of which are focused on cosmetic applications and the rest are around medical and stem cell applications. Of the sixteen, 2 patents concern the use of ovine placenta for cardiovascular, immunity and skin applications but they describe production (preparation) methods rather than the activity (use) of the end product. The remainder of these patents are specific for human placenta. This would indicate that there is reasonable evidence that, an organization pursuing work with bovine or ovine placenta would have freedom to operate. Appendices 10 and 11 summarize these patents.

6.8 Summary

Chinese medicinal products and cosmetic products also mostly for the Asian market are real opportunities for Australia. However, there is strong preference for use of ovine placenta in these markets. There is a strong interest within the Chinese medicine industry in the development of Australian placental derived products.

TGA accreditation is important for the realization of these opportunities although processing of placenta for these products is quite physically and chemically robust and the need for 'bioactivity' preservation is not high. But TGA will still require evidence if functions are ascribed to the products.

Ovine and bovine placenta can readily be collected within the Australian meat processing industry, nevertheless members of the supply chain need to aware of and assured that the risk of infection by pathogenic agents is low and well managed.

7 The value chain

The value chain for placenta and amniotic fluid derived products begins at the abattoir and passes through collection agents, biologic processors, formulation companies, bulk processors, wholesalers and retailers (shopfront and internet). Several of the biologics processors act as their own collection agent. Figure 4 shows a flow chart of the value chain for animal derived bioactive (including ovine placenta based products) products in Australia and is populated with industry players identified in preparing this report. The value chain for placenta is not well developed in Australia and has only been in place for a few years. The number of players is small particularly at the biologics processor stage and are no organizations handling bovine placenta (only ovine and deer placenta).

Ovine placenta has been collected in Australia and New Zealand for some years and initially was collected from the paddocks after lambing (mainly in New Zealand). This practice was altered in Australia to abattoir collection in 2003 to obtain a cleaner and AQIS approved produce after there were problems with stones (from the paddock) damaging the processing equipment. Currently ovine placenta is collected on demand at ovine processing plants in South Eastern Australia. This material is either exported to Asia or New Zealand or processed by biologics processors. There appears to be 2 Australian biologic processors that handle placenta. Figure 5 shows the current network identified for ovine placenta and most of the activity occurs in the southern states.

Bovine placenta has been collected by at least one meat processor in the past and exported to Japan. There is no evidence of current collection or export activity for bovine placenta (pers. comm. J. Langbridge, AQIS, June 2007). There is no information to suggest that it has ever been processed within Australia. Although bulk bovine placenta powder is available through Nutri-Mart in the US there are few finished products that promote bovine placental content. Most commercially available products are labelled with claims that they contain ovine or deer (or occasionally porcine) material. Some products such as “J&B Australian Sheep Placenta Capsules” specify the origin of the placental material.

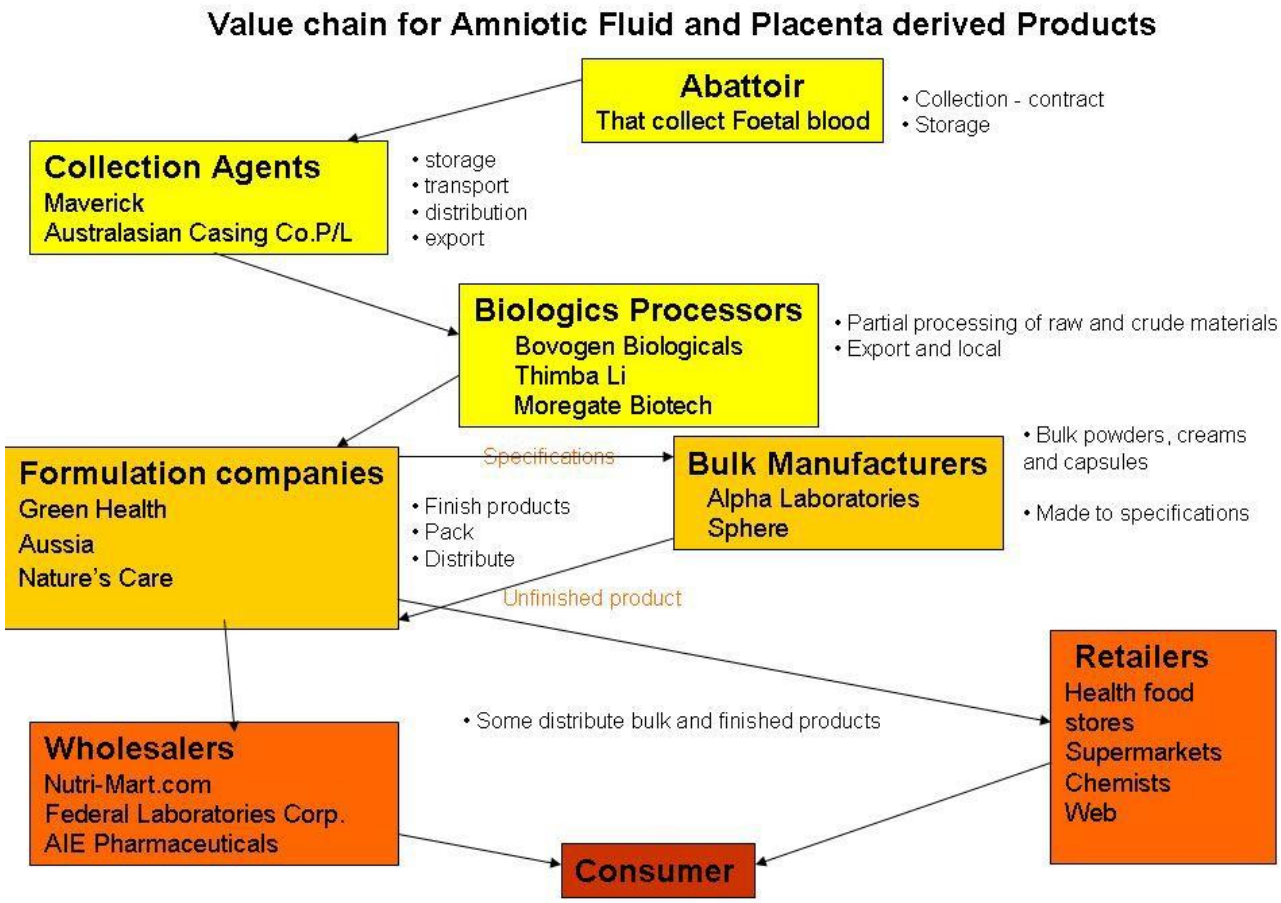

Figure 4 Value chain for amniotic fluid and placenta derived products

Albert Fusella (biologics processor) said that some animal components are collected and exported to China where they are processed, the processed product is exported to the US and then back to Australia. He says that these products are often “reworked” in Australia before they are incorporated into final products. He also pointed out that in China animal components such as trachea or placenta are sometimes collected by individuals, dried on their roof and then sold to an agent who then sells it on to a processor who extracts the product of interest such as chondroitin sulphate or placental powder for export. This collection process is prone to contamination and inconsistency of product quality and is likely to contribute to the questionable quality of some Chinese products.

A well-defined value chain for amniotic fluid has not yet developed. It is currently collected as a by-product by draining frozen, gravid placenta. We have identified that at least 2 biologics processors who collect AF and process it by filtration for use within the cosmetics industry. There is a cosmetics manufacturer in Sydney that incorporates it into cosmetics and exports them to Asia.

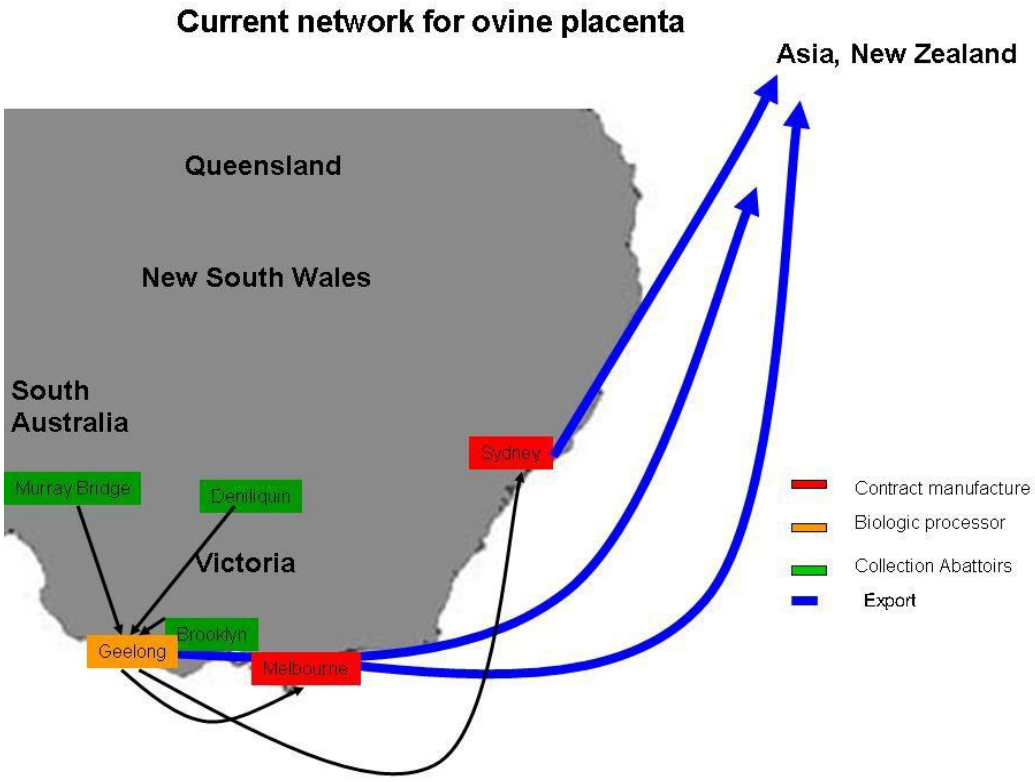

Figure 5 Current networks for ovine placenta

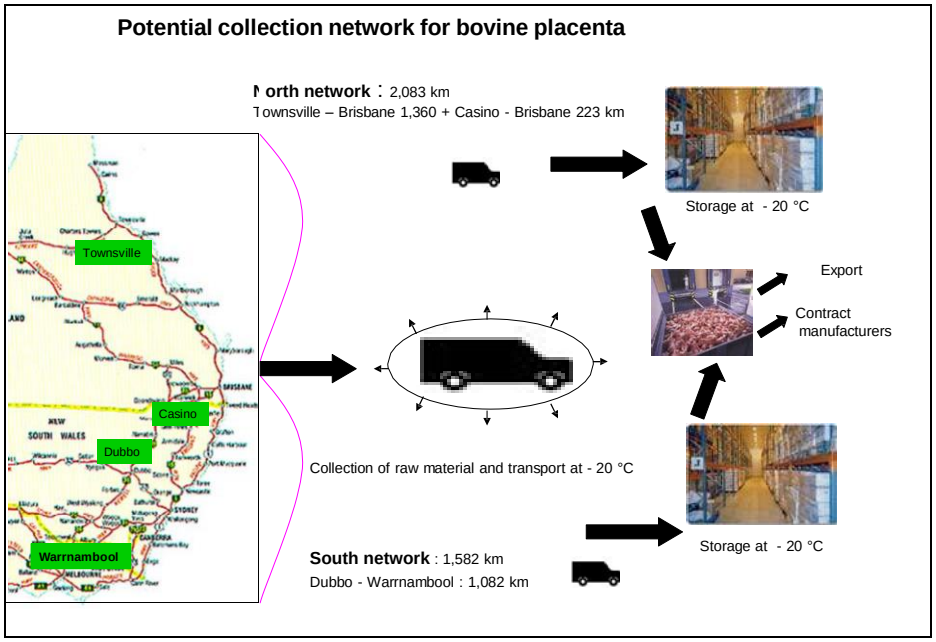

Figure 6 Potential networks for the collection and processing of bovine placenta

Most of the meat processing activity occurs in eastern Australia because a large percentage of the West Australian stock goes export. Eastern Australia can be divided into two distinct regions for collection and transport purposes - North and South. The Northern network would consist of Townsville to Brisbane (1,360 km) and Brisbane - Casino (223 km) while the Southern network would stretch from Dubbo to Warrnambool and covering 1,082 km. The northern network would feed into a central -20˚C storage unit in Brisbane while the Southern network would feed into a -20˚C storage unit in Dubbo. A collection network, drawing placenta from these areas could be developed to supply a placenta processing plant in Dubbo. This potential network is shown in Figure 6.

Due to the distances between Dubbo and North Queensland, it is unlikely that the collection of bovine placenta can be achieved by means on a single transport network and it is proposed that the collection is carried out using two networks. The North network (Townsville - Casino, with a central reception centre in Brisbane) is expected to be the largest both in terms of logistics movement (2,083 km) and in terms of volumes transported, providing about 65% of the total raw materials. The South network (Warrnambool – Dubbo, with a central reception centre in Dubbo) is estimated to encompass 1,582 km, just slightly shorter that the North network. In the future the Northern network may be serviced by rail rather than road transport as this the currently preferred transport for processed meat (for export) from remote plants. The southern network could also collect ovine material from the large sheep producing areas of Victoria and South Australia as well as NSW.

Volumes of placenta would fluctuate over breeding seasons and the network outlined may be used to transport other material such as trachea at some times. This would indicate that a manufacturing plant at Dubbo could be equipped to handle a number of raw materials. There is also a down turn in meat processing during the months of December to February each year which would need to be taken into account when storage capacity is being considered as well as pick-up schedules. The effects of climate change could also have an impact on the value chain in that as variability of seasons increase, stocking levels would decrease particularly in feed deficient areas of the country.

There are two recent developments that will have impact on the value chain. The first is the world grain shortages, which will drive the prices of meat derived products up and in some cases cause a drop in supply. The other factor is that the proposed Australia and New Zealand Therapeutic

Products Authority will not be formed in the near future as had been expected (this decision was taken in July 2007). This means that companies such as Alpha Labs (NZ) will need to obtain TGA accreditation for their products such as placental powder in order to export them into Australia because their current New Zealand accreditation (Medicines Act, 1981) will not be recognized by the TGA, as has previously been the case. The practical implications will be higher GMP compliance levels, more rigorous enforcement of regulations and all steps of manufacture being scrutinized for New Zealand products being exported into Australia.

7.1 Abattoirs

Some animal components such as trachea, pancreas and intestines are collected and packed for various markets while items such as the placenta and amniotic fluid are waste products which are either discarded or go to render. Rendering plants pay about 7c per kg for the waste (pers. comm. May 2007 a renderer). Table 1 tabulates porcine components and the prices received for them in 2006. The prices vary to reflect the difficulty of collection and demand. A table of bovine offals supplied by Swickers reveals that they account for 28% of the total carcase weight indicating the importance of increasing the value of these produces rather than allowing them to go to render (Appendix 14).

A discussion with a large meat processor revealed that they would need to charge at least $3 per kg to meet the costs of collecting animal parts. They do not collect placenta currently and to do so would need to investigate the logistics because they would be collected in the blood room (which is small and wouldn't accommodate packing procedures) of the abattoir and need to be moved a considerable distance to the freezer rooms. The collection of amniotic fluid would be done in the same area and would require the installation of some infrastructure such as additional suction equipment. Plate freezers, would allow a fast (22 hrs versus the 48 hrs required for blow freezers) freeze down and distribution of the frozen product.

Product Group	STD Yield %/CC	Collection %	Sale Price
Ears	0.240	96.0	$ 5.00
Heart Whole	0.400	80.0	$ 1.09
Heart Cut/Broken	0.400	16.0	$ 1.29
Kidney	0.235	80.0	$ 0.88
Liver	2.000	96.0	$ 1.17
Omentum Fat			$ -
Snout	0.060	90.0	$ 1.83
Spleen			$ -
Testicles			$ -
Diaphragm	0.330	95.0	$ 1.86
Tongue Roots	0.133	90.0	$ 1.73
Tongues (swiss cut)	0.266	90.0	$ 1.80
Pork Head Meat	0.138	34.0	$ 1.80
Pork Short Front Feet	0.350	23.0	$ 0.81
Product Group	**STD Yield %**	**Collection %**	
Maw	0.490	92.0	$ 2.00
Uterus	0.190	50.0	$ 1.32
Sweet Runner	0.600	0.0	$ 2.85
Rectum	0.160	92.0	$ 4.55
Pancreas	0.029		$ -
Runners (each)	100.000	92.6	$ 1.21

Table 2 Porcine offal yields and prices (2006) supplied by Hans/Swickers

Column 2 indicates percentage of the cold carcase weight that the organ represents, for example the ears weigh 0.240% of the total cold carcase. Column 3 indicates the percentage of the total number of organs that are collected at Swickers abattoir, for example 92% of the possible maw is collected while 8% is discarded.

7.2 Collection Agents

Collection agents are organizations that work with abattoirs to collect animal parts such as placenta and amniotic fluid. They often (but not always) set up contracts with abattoirs to ensure a constant supply of products at an agreed price. Some small operators have arrangements with abattoirs where they just order material as they require it and so there are variables in these agreements around prices, volumes, collection requirements, storage and transport. Larger companies such as Maverick Biosciences and Moregate Biotech work in this area to supply organizations such as pharmaceutical and nutraceutical manufacturers, vaccine manufacturers, medical device manufacturers and research companies, media and diagnostic manufacturers and biotechnology companies. Products include bovine plasma, livers, lung lobes, brains, pituitaries, hypothalamus, spleens, hearts, cartilage materials, bone and meat extracts, connective tissues, membranes, adult serum, new born calf serum, donor serums, defibrinated calf blood, calf serum, horse serum, foetal blood and amniotic fluid.

One coproduct processing company has set up equipment in abattoirs for collection and then works with the abattoir to the advantage of both parties to collect various animal components. They collect mainly from the ovine industry and supply casings, placenta, adrenal glands and any other animal parts that the market demands. They indicated that they need to get a return of at least AUD$3 per kg for most products to provide a slim margin. Collection agents often freeze produce to overcome fluctuations in supply and demand and also price fluctuations. For current applications, there is no shelf life for these products so they can be stored for very long periods before being processed.

The coproducts company observed that collection of amniotic fluid would be very simple in an abattoir that is already collecting foetal blood in that they would be able to use a wire mesh table with a funnel and collection vessel under it where the placenta could be slit open, the foetus taken to one side for bleeding while the amniotic fluid drained through the table into the collection vessel. He estimated that such a table would cost around AUD$1200 to install. However this method would possibly lead to the inclusion of contaminants such as meconium has solid components in the fluid, which would be removed later by filtration.

7.3 Biologics Processors

Biologic processors are organizations that source products (some raw and some processed) from organizations such as Maverick, Moregate and Bovogen and process and/ or sell them on to global and local markets. For example Bovogen collects and fractionates blood serums and produces BSA, FCS, purified proteins, dried blood products and blood clotting proteins. They also market other animal derived products such as ovine placental extract (Certificate of analysis can be seen in Appendix 5). Some of these companies work in both collection and processor roles.

Thimba Li obtains animal components from collection agents such as Australasian Casing Co. and manufactures and markets products such as sheep placenta powder, sheep placenta paste, ovine amniotic fluid, deer placenta powder, deer spatula powder, kangaroo flesh powder, kangaroo bone powder, shark cartilage powder, bovine trachea powder and liquids and whey protein powders.

Moregate Biotech collects and distributes animal components such as bovine red cells, hearts, intestines, kidneys, livers, lungs, trachea mucosa pancreas glands, thymus glands, pituitary glands and spleens. They also distribute processed bovine serum albumin and sera products.

Galpac has worked on several products containing placental powder including a drink for skin health and satiety. Galloway sees that the strengths, apart from the traditional uses, are in the iron levels, amino acids, peptide and protein (with some vitamins) levels in the placental powders and the hyaluronan levels and amino acids in amniotic fluid.

7.4 Formulation Companies

Formulation companies are those who design the final product according to identified consumer needs and accreditation requirements such as Blackmores and Sigma Herron. They sometimes manufacture the product but most find it more economical to have a contract manufacturer such as Sphere (Australian), Probiotec (Australian) or Alpha Laboratories (New Zealand) produce unfinished bulk products which they then pack, label and distribute (market). Some of the formulation companies such as Sigma Herron have plants in China do the contract manufacturing step to reduce costs. In some cases TGA may physically inspect a Chinese plant that produces bovine derived products for an Australian Formulator. The use of Chinese manufactured components may decrease over in the immediate future with increasing public concern around the safety and integrity of Chinese manufactured produces. For example in July 2007 Food for Health International (US company) announced that it will begin labelling boxes for its dietary supplements with a sticker that reads "safe" and "China-free" following highly publicized discoveries of contaminated food imports from China. (<www.nutraingredients-usa.com/news/ng.asp?id=78111-fda-food-for-health-contamination>). For the full editorial see Appendix 15.This trend emphasises the importance of Australia's clean and green reputation and also highlights a competitive advantage that could be further developed.

7.5 Bulk Processors

Bulk processors are also known as contract manufactures because formulation companies contract them to produce products of specific specifications in bulk quantities. Alpha Laboratories of New Zealand and Probiotec, Lipa Pharmaceuticals Limited and Sphere of Australia are such companies and all manufacture placental derived products including capsules, powders and creams on a contract basis on demand. These processors are required to work under GMP standards and have TGA accreditation for products, which will be marketed with therapeutic claims.

7.6 Wholesalers

Wholesalers buy large quantities of finished goods for resale purposes and work between manufacturers and retailers to utilize the most effective distribution channels for the products. Sometimes they pack and label products for particular retailers.

7.7 Retailers

Complementary Medicines are available to consumers through a number of different channels, the total Australian market having a value in the range of AUD $800M to $1B (<www.asmi.com.au/Complementary%20Medicine.htm >). In Australia health food stores distribute approximately 20% of complementary medicines; pharmacies distribute approximately 40% while approximately 10% are distributed through complementary healthcare professionals (<www.asmi.com.au/Complementary%20Medicine.htm >). Other outlets include supermarkets, duty free shops and speciality shops. The other growing retail area is the Internet which is an arena that can facilitate the undercutting of the traditional outlets' pricing structure and is easy for "dodgy' operators to work in. Prof Charlie Xue (Head, Division of Chinese Medicine at RMIT) suggests that Duty Free shops would be effective retail outlets for placental and amniotic derived creams and low dose capsules. TGA export only products can be marketed through Duty Free shops and some products are currently marketed in this way. Xue also pointed out that the retailers in the "Chinatowns" of the large cities of the US would be effective outlets for such products.

The health care systems of many countries cater for complementary medicine particularly the Asian countries and these systems could prove to be major market opportunities for safe, efficacious products. Most hospitals in China (92%) have a traditional medicine unit. In India 2,869 hospitals provide traditional medicine treatments and in Thailand and Vietnam traditional medicine is integrated into the health care systems (Debas *et al.*, 2006). A more complete list, which was developed by WHO, of the major countries that use complementary medicine in their health care systems, can be seen in Appendix 16.

Cosmeceuticals are marketed through pharmacies; health food stores, department stores, hairdressers and skin care clinics. Affluent, ageing females are the core target and are far more likely to buy a product that is backed up by verifiable scientific research and make clear, realistic and measurable claims (DMCM2376) indicating the importance of developing products that have proven efficacy and TGA accreditation. There is a notable difference between the preferences of genders. For women, the prime target is those who are 50-years plus while in men it is the 25 to 34 age group that is showing the most interest in products for outward appearance **(**<***www.nutraingredients.com/news/ng.asp?id=7746>)*.

In Australia the cosmetics and toiletries market was valued at USD$1B in 2006 (6% growth), with the market for skin care alone at USD$342M (<www.buyusa.gov/asianow/acosmetics.html>). The key growth areas in Australia are in products such as men's grooming products, baby products, and dermatological products, 'doctor brands', cosmeceuticals, aromatherapy products and suncare (<www.austrade.gov.au/Cosmetics-and-Toiletries-overview/default.aspx>) The top 10 markets in 2005 for Australian cosmetics were New Zealand, USA, UK, Hong Kong, Singapore, Japan,

Taiwan, Korea, Malaysia and Fiji. But there are new emerging markets such as China, Vietnam, Thailand and Russia that are demonstrating strong opportunities for the Australian cosmetics industry. However, it is important to note that in Asia, the bigger customers are looking for well known 'established' brands or brands with clear unique value propositions (<www.austrade.gov.au/Cosmetics-and-Toiletries-overview/default.aspx>).

7.8 Summary

A sparsely populated value chain does exist in Australia for ovine placenta and amniotic fluid. There is no evidence of a value chain for bovine placenta or amniotic fluid. Bovine placenta and amniotic fluid could be collected at abattoirs which currently collect foetal blood. However, since the larger opportunities are with ovine placenta, some consideration of collection protocols for sheep abattoirs is needed.

There is a value chain for other animal derived materials in place and placenta and amniotic fluid could follow this route to market if there were reasonable commercial returns. A number of current supply chain members are indicated in figure 4. An important aspect of the value chain would be the development of a strong market both in Australia and globally for placental and amniotic fluid products. There is a growing cosmetic and complementary (and Chinese) medicine industry to be supplied but success would be dependant on developing therapeutic products that are TGA accredited and the promotion of safe "clean, green" products at all stages of the value chain.

8 Conclusions

Placental tissues and their associated fluids represent new commercial opportunities for the Australian meat industry. Markets lie in Chinese medicine, wound healing, neonatal maturation, stem-cell culture and cosmeceutical areas.

The Chinese medicine industry is well established in China but is hampered by lack of product quality and certification. In China, there is a preference for imported products particularly in the hospital sector. Professors Lin and Xue are both interested in assisting with the development and marketing of Australian derived Chinese medicine products. However, the Chinese medicine industry prefers ovine material.

Opportunities exist for the use of amniotic fluid as a therapeutic in healing wounds. Two major markets have been identified. The first of these revolves around the populous nations of the developing world, such as India and China. These countries have a high per capita incidence of injuries and burns to which they require cheap and effective treatments. These nations require less stringent accreditation, which offers a faster route to markets if efficacy and safety can be demonstrated and supply chains established.

In developed countries, it is envisioned that applications for amniotic fluid would target chronic wounds such as venous ulcers. Such applications will require highly efficacious, well defined and highly refined products to meet consumer, clinician and regulatory expectations and requirements. Besides being effective, these products need to be sterile and described at the molecular level. These and similar opportunities in human medicine may only have a 20-30 year window as the sector aspires use recombinant molecules for most therapeutic applications.

Other opportunities are uses of amniotic fluid as a supplement in culturing stem cells, and in gut maturation of premature infants. These applications will be marketed in low volumes but will command high prices.

The cosmeceutical applications include opportunities for placenta and amniotic fluid and targets hair, skin and oral products. In Asia there is wide and long standing acceptance of these products and there is a demand for reliable, efficacious, safe products. However, for Australia and most countries with western traditions, such products would only service niche markets. The cosmeceutical products from amniotic fluid and placenta could be developed relatively quickly as the regulatory barriers are not high although safety requirements are still paramount.

This investigation has shown that the current placenta and amniotic fluid derived products on the market are predominantly ovine. Prior to the international BSE outbreak of 2001, Australian bovine placenta was collected and exported. Currently it is not. Ovine placenta and amniotic fluid are successfully collected and processed on a small scale and interest is increasing both nationally and globally. There are some cultural barriers to the use of bovine products in some countries and this problem could be overcome by using ovine material in these markets. India and China are examples of countries where the consumer preference is for ovine derived products. There are no barriers to using bovine material in the US and Australian markets, with Australian based exports of raw material or partially processed material permissible from AQIS accredited plants.

We have identified 2 majors hurdles if Australian industry aspires to value add from amniotic fluid and placenta, and scale up the development and production of products derived from these materials. Firstly, there are no placental or amniotic fluid derived products with TGA approval for use within Australia and there have been no recent applications. TGA approval for use in Australia allows sale of products in this country, however, more importantly, potential customers in other countries with weaker regulatory regimes see TGA approval as a very strong stamp of quality and safety.

TGA approval requires substantial financial outlay (up to AUD$400,000 in fees including clinical trials) and long processing times both of which are prohibitive for many organizations. Furthermore, many small organizations are unaware that the application process requires expertise and

familiarity with the process. This hurdle has led to organizations such as Pharma-Cosmetics exporting all of their ovine placental and amniotic fluid derived products rather than developing the Australian market. The burden of TGA application fees could be reduced by companies submitting joint applications if they are working on the same product. Assistance with TGA fees and consultancy would almost certainly encourage the development and distribution of more innovative products.

The second major gap in the Australian industry is a perceived limited local capacity for processing placenta and amniotic fluid into end products. The current limited capacity most probably stems from the lack of incentive for meat processors. A recent survey of a number of South East Queensland meat processors revealed that they would be keen to add value to their operations as long as their outlay was minimal or a commercial opportunity had been identified.

An Australia based industry will face competition from external sources, with countries such as China and India having lower production costs. Some pharmaceutical companies such as Sigma Herron have products manufactured under TGA approval there and then pack, label and distribute products in Australia. It is known that this is the case with chondroitin sulphate but it is unclear where the raw material collected. It is known that some animal components are collected in Australia and processed in these countries but the volumes are far less than would be necessary to supply the Australian market. There is an opportunity for Australian processors to increase their collection levels and supply animal components such as placenta to manufacturers in these countries.

Besides having a strong regulatory regime, Australia has a clear advantage through its 'clean and green' image of its products. This is aided by the livestock industry having in place a well-documented traceability scheme of animal derived products. Export abattoirs maintain records of all animals slaughtered which includes the entire history of each animal. These facts can be used to promote the high quality of our produces and possibly generate higher prices for products on the global market.

In conclusion, opportunities do exist to increase the commercial and economic value of bovine (and ovine) amniotic fluid and placental material for the Australian meat processing industry particularly in the Chinese medicine industry. A range of opportunities (possible projects) has been identified and could be realised in time and in collaboration with interested industry players and R&D providers.

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11 Appendices

11.1 Appendix 1 Commercially available products containing placenta

Product	Company	Species	Health Claim	Price
	Green Health (NZ)	Sheep	Super Ovine Placenta is 100% pure and natural used for rejuvenating your body cells and good health.	60x6000mg/USD $24.95 Dose 3 caps /day
	NZ Pure Health	Sheep	Anti-aging - Revitalizing to the skin - Boosting the immune system - Improving physical vitality - Promoting general health	60 x 12000 mg/ USD$35.85. Dose 3 caps/day(50c/gm)
	Dragonshow Australia Pty Ltd (Careline Group)	Sheep	5-in-One placenta nourishing cream formulated with placenta, Lanolin, vitamin E, collagen and elastin. It is designed to have multi-functions. This special formula can enlighten your skin.	
	Jean Charles Cosmetics	Not specified	The combination of Lanolin and Placenta Protein makes this cream the ideal product to nourish, tone & create healthy looking skin. Blended with Vitamin C to help penetrate & rejuvenate the skin while you sleep	65gm/ USD$9.00
	Placenta Acne Scar Anti Aging Day/Night Face Creams	Not Specified	Helps to Heal Black Head and Acne Scars by up to 98%.	USD$25

	Set			
	Johnson and Barana. (Australian company)	Australian Sheep	Placenta is a rich source of nutrients, growth factors and bio-active cytokines. Promoting general health, and maintaining youthful skin.	100x3000mg caps/AUS $25.15
	Lanocreme	Australian sheep	An exquisite moisturising complex with Placental Extract, a source of 56 natural bio-stimulants that revitalises and renews, bringing beautiful skin to life	AUS$13.75/ 150g
	Re-birth skin care products **(**Lanopearl)	Sheep	A revolutionary skin serum containing concentrated natural & pure placenta extract derived from sheep. Placenta extract is a rich source of bioactive nutrients like essential amino acids, placental protein, SOD, nucleic acids and growth factors. Provides intense hydration, firming of skin, while diminishing age spots and pigmentation.	USD$39/15ml

	**HASK PLACENTA Super Strength No Rinse Hair Repair Treatment for Extremely Damaged Hair**	Sheep	Quickly repairs and strengthens dry, brittle, lifeless hair. Will not change hair color. Placenta extract, derived from animal placenta*, is combined with amino proteins to revitalize and protect every hair type.	USD$4.73/2oz

11.2 Appendix 2 Suppliers of placenta derived products at different value chain points

Supplier	Type of product	Species of origin	Country of manufacture	Notes	Approx. price per kg
Norvic Food Processing Pty Ltd	Raw placenta	Sheep	Australia	Meat Processor	AUD$5
Nutri-Mart.com	Bulk powder	Bovine	USA (Buffalo, NY)	Large wholesale supplier	*AUD$91
Alpha laboratories (N.Z.) Ltd	Capsules (unfinished)	Sheep and deer	NZ	Contract Manufacturer	AUD$25,000
Nature's Care Australia	Finished products	Sheep	Australia	Export only	AUD$120,000

*Using US spot price July

11.3 Appendix 3 Certificate of analysis for bovine placenta powder

Nutri-Mart
Http://www.nutrimart.com/Bulkraw.htm
3604 Hawkwood Rd
Diamond Bar, CA. 91765 U.S.A.
Tel: (909) 396-6530, Fax (909)861-0588 , Email:bulk@nutrimart.com

Certificate of Analysis

Raw Material Data

Sample Of:	BOVINE PLACENTA POWDER
Sample ID:	PL-072804
Lot Size:	420 KILOS
Date of Manufactured:	SAMPLE
Date C.O.A.:	SAMPLE
Shelf Life:	TWO YEARS, TO BE KEPT IN TWO CLEAR, TIGHTLY WRAP PLASTIC BAGS, IN A COOL DRY ENVIRONMENT
Country of Origin:	USA
Site of Manufacture:	BUFFALO, NY

Bovine Placenta Powder	Specification	Result
Appearance:	Fine powder	Conforms
Particle Size:	60 - 80 mesh	Conforms
Taste:	Characteristic	Characteristic
Odor:	Characteristic	Characteristic
Moisture:	< 7%	4.3 %
Ash:	< 8%	5.7%
Crude Fat/Oil	< 6%	5.4%
Arsenic:	< 1 ppm	Conforms
Mercury:	< 1 ppm	Conforms
Lead:	< 1 ppm	Conforms
Bulk Density:	.30-.40 g/cc	0.336 g/cc
Tap Density:	.50-.60 g/cc	0.623 g/cc

Microbiological		
Standard Plate Count:	< 2000 CFU/G	< 2000 CFU/G
Pseudomonas	Negative	Negative
E Coli:	Negative	Negative
Salmonella:	Negative	Negative
Yeast & Mold:	< 100 CFU/G	< 100 CFU/G

The information is a direct translation provided to Nutri-Mart from the manufacturer of this product. This COA should be used for information purposes, and is not intended as a substitution for strict quality control analysis by the purchaser of this product.

11.4 Appendix 4 Commercially available Products Containing Amniotic Fluid

Product	Manufacturer	Claim	Ingredients	Price
 Serum Revital Eyes	Reviva Labs	To help firm and vitalize eyelid tissue-to avoid eyelid sag or drooping. Our serum is ideal for eyelid problems-and now offers brightening ingredients to help lighten under-eye dark circles	Purified Water, Compound of Extracts (hops, rosemary, horsetail, pine and lemon), DNA (nucleic acid), Glycerin, Amniotic Fluid, Lady's Mantle Extract, Magnesium Sulfate, Methyl and Propyl Paraben.	USD$17.60/5ml
	Hydroderm	Hydroderm claims to remove wrinkles and other aging signs	Collagen (Marine), Distilled Water, Igepal Cephene, Methyl Paraben, Ethyl Paraben, Propyl Paraben, Butyl Paraben, Isobutyl Paraben, Synasol, Serum Protein, Purified Water, Amniotic Fluid, Placental Protein, Calfskin Extract, Hydrolyzed Collagen, Sodium Methylparaben, Imidazolidinyl Urea, Ethoxylated Glycerides, Trisodium EDTA, Potassium Sorbate, Citric Acid, Ascorbic Acid.	USD$79/30ml

11.5 Appendix 5 Bovogen Biologicals Certificate of Analysis for Ovine placental powder

Specification:

Chemical

Moisture	<7.0%
Glycosaminoglycans/Glycoproteins	>4.0%
Carbohydrate :	3.0 – 4.0%
Ash	35 – 45%
Crude Protein :	45 – 55%
Crude Fat :	7.0-8.0%
Preservatives	None
Hyaluronic acid	0.33 – 0.41 nmol/mg
Iron	18.0 – 30.0 mg/100g
Energy kJ/100g	1100 - 1200
Energy kcal/100g	263 - 287
Particle Size	3% (max.) retention on 150 micron screen

Microbiological

Total Aerobic Count	<1,000 cfu/g
E.Coli	Absent
Coliforms	Absent
Salmonella	Absent

Documentation:

A Certificate of Analysis is supplied with all ovine placenta extract orders. A Certificate of Origin is supplied for all export orders.

11.6 Appendix 6 Thimba-Li Sheep Placenta Powder

Sheep placenta powder is manufactured for Thimba-Li Pty Ltd at the premises of Galpac (Australia) Pty Ltd under GMP conditions with AQIS registration and is offered in 10 kg Cartons.

Thimba-Li Sheep Placenta Powder Alone

1) Kidney nourishment
2) Enhance qi
3) Enhance potency
4) Kidney repair
5) Muscle build up
6) Combats Fevers
7) Counters Anemia

With *Lysium barbarum* (Red Berry)

Enhances immune system
Retards ageing
Lowers cholesterol
Combats lung tumours
Protects the liver
Increase red blood count
Reduces blood sugar
Reduces blood pressure
Cures common viruses

With *Paeonia lactiflora. pall.*

Reduces aches and pains
Prevents lack of oxygen in the blood
Detoxifies the liver
Prevents tumours
Cures gastroenteritis
Addresses women's illnesses and discomfort
Beautifies women

With Angelica Dahurica

Purifies the skin
Repairs pigmentation
Reduces aches and pains

Prevents tumours
Aids liver process
Helps rheumatism
Reduces headache pain
Beautifies the body of women
Slows ageing process down.

Thimba-Li Deer Placenta Powder

Deer placenta powder is manufactured for Thimba-Li Pty Ltd at the premises of Galpac (Australia) Pty Ltd under GMP conditions with AQIS registration and is offered in 10 kg Cartons.

Deer Placenta Powder Alone

Nourishes the kidneys
Improves libido
Improves body weaknesses
Enhances qi
Cures backaches
Helps leg weakness
Assists stopping palpitations
Strengthens the body
Assists in negative weight loss

With Asian Ginseng (*Radix et rhizome ginseng*) Renshen – Use stem and leaf

Improves failing energy
Improves qi
Improves alertness
Stops sweating hands and feet
Stops heart muscle degeneration
Stops Fits
Cures insomnia
Stops heart seizure

With *Angelica sinensis*

Improves blood count
Regulates the heart beat
Cures dizziness
Lowers cholesterol

Softens arteries

Enhances the immune system

Aids the spleen

Aids the liver

Is an antioxidant

In general **Thimba-Li Deer Placenta Powder** is recommended to enhance sexual impotence, improve the immune system, detoxify the body and improve the blood count.

This information is provided from notes taken in consultation with Professor Li at SHXK Biotechnologies headquarters in Beijing. Professor Li is a professor of Traditional Chinese Medicine and a Doctor of Western Medicine. The references to the various recommendations were quoted from the Chinese Pharmacopeia or in colloquial terms “The red book” that is spoken off as the “bible” of TCM. On many occasions the Professor advised that particular aspects of these details were “proven” with inference that they must be proven to be entered into the red book.

11.7 Appendix 7 Patents for amniotic fluid – cosmetic applications

Patent Number	Application	Species	Title	Assignee
WO2005016297-A1; AU2003258739-A1; BR200316862-A; EP1655015-A1; US2006159646-A1	Hair restoration	Bovine	Hair restorer, useful for treating alopecia in both sexes, comprises a bovine extract containing epidermal growth factor, dexpanthenol and sodium hyaluronate	FRANCO VELASCO A (VELA-Individual); VELASCO A F (VELA-Individual)
KR2002024213-A	Extraction method	Human	Use amniotic fluid and placental extracts in the manufacture of infant articles e.g. baby clothes, milk bottle sacks, cosmetics, pharmaceuticals, and health foods	CHANG H S (CHAN-Individual)
WO200123532-A; WO200123532-A1; AU200074379-A	Storage of cellsTherapeutic and cosmetic	Human	Cryopreserved amniotic cells, useful for growing tissue or in gene therapy, can be stored in viable condition for a long time	TSAKAS S (TSAK-Individual); LINARDOS N (LINA-Individual)
JP6345636-A	Inhibitory factor Cosmetic	Unknown	Cosmetic material - contains collagenase inhibitor and controls reduction. of dermal collagen and loss of skin elasticity	NONOGAWA SHOJI YG (NONO-Non-standard)
FR2627385-A1; FR2627385-A	Component fractions for cosmetics	Unknown	Dermatological and cosmetic compsns. - contain lipid phase and nitrogenous compounds especially amino acid, oligo or polypeptide	LAB SEROBIOLOGIQUES SA (SERO-Non-standard)
EP333328-A2; WO8907425-A; EP333328-A; AU8932183-A; AU640609-B; EP333328-B1; DE68911178-E; CA1330418-C; ES2060750-T3; US5612028-A	Cells for therapeutic purposes	Human and animal	Medical use of amniotic cells or tissue - for tissue regeneration, implant treatment, production of useful substances, detoxification of body fluids and skin or scalp treatment	GENETHICS LTD (GENE-Non-standard)
JP6345636-A	Loss of skin elasticity	Unknown	Cosmetic material - contains collagenase inhibitor and controls reduction of dermal collagen and loss of skin elasticity	NONOGAWA SHOJI YG (NONO-Non-standard)

11.8 Appendix 8 Patents for amniotic fluid- medical applications

Patent Number	Application	Species	Title	Assignee
CN1406633-A	Scar reduction	Not specified	Scarless composite biological material containing hyaluronic acid	WANG Z (WANG-Individual)
US2001041684-A1; US6573249-B2	Components for topical purposes	Not specified	Treatment of burns, wounds or decubitus ulcers using a cromolyn compound which can control release of chymase and tryptase and promote healing without scarring	LEZDEY J (LEZD-Individual); LEZDEY D (LEZD-Individual); ALPHAMED PHARM CORP (ALPH-Non-standard)
WO200123532-A; WO200123532-A1; AU200074379-A	Preservation of cells for tissue and gene therapy	Not specified	Cryopreserved amniotic cells, useful for growing tissue or in gene therapy, can be stored in viable condition for a long time	TSAKAS S (TSAK-Individual); LINARDOS N (LINA-Individual)
WO9944582-A; EP1058554-A; WO9944582-A2; US5989577-A; AU9928003-A; US6113932-A; BR9908447-A; EP1058554-A2; JP2002505270-W	Cell growth media - wound healing	Not specified	Composition comprises an intractable natural or synthetic vernix composition, useful for promoting e.g. wound healing, skin flexibility or for skin moisture retention or delivery	CHILDREN'S HOSPITAL MEDICAL CENT (CHIL-Non-standard)
EP333328-A2; WO8907425-A; EP333328-A; AU8932183-A; AU640609-B; EP333328-B1; DE68911178-E; CA1330418-C; ES2060750-T3; US5612028-A	Tissue generation	Human or animal	Medical use of amniotic cells or tissue - for tissue regeneration, implant treatment, production of useful substances, detoxification of body fluids and skin or scalp treatment	GENETHICS LTD (GENE-Non-standard)
WO2006091546-A2	Eye injury	Not specified	Treatment of a disorder or injury in an eye, comprises administration of amniotic fluid free of amniotic membrane particulate matter to the eye to ameliorate symptoms associated with disorder or injury	UNIV JOHNS HOPKINS SCHOOL MEDICINE (UYJO)
US2003235580-A1; WO2004000164-A2; AU2003243781-A1; AU2003243781-A8	Human amniotic epithelial cells. Skin repair and wound treatment	Not specified	Delivering a molecule to a patient, useful for treating chronic wounds, comprises administering amniotic epithelial cells capable of delivering the molecule, to the skin of the patient	ZHANG F (ZHAN-Individual); AMNIOTECH INC (AMNI-Non-standard)
WO2003042405-A; WO2003042405-A2; EP1442115-A2; AU2002363659-A1; JP2005509422-W; US2005124003-A1	Cell techniques	Not specified	Producing a population of cells enriched for pluripotent foetal stem cells, useful for enzyme replacement and gene therapy, comprises selecting c-kit positive cells from chorionic villus, amniotic fluid or placenta sample	CHILDRENS MEDICAL CENT (CHIL-Non-standard); ATALA A (ATAL-Individual); DE COPPI P (DCOP-Individual)

WO2004093890-A2; CN1533797-A; CN1679637-A	Inflammation,cancer etc(Western - Chinese)	Fowl	Pharmaceutical compositions comprising bioelements like enzymes and factors, for treating e.g. various cancers and tumors, Parkinson's disease, inflammation or swelling of glands, cystis and pemphigus	WANG J (WANG-Individual)

11.9 Appendix 9 Patents for amniotic membrane

Patent Number	Application	Species	Title	Assignee
WO2007009062-A2; US2007021704-A1	Wound healing.(Dried amniotic membrane)	Not specified	Treatment of leg ulcer e.g. venous leg ulcer and diabetic leg ulcer, involves contacting the ulcer with a collagen biofabric	ANTHROGENESIS CORP (ANTH-Non-standard); HARIRI R J (HARI-Individual); SMIELL J M (SMIE-Individual)
WO2006094247-A2	Scarring, inflammation	Human	Amniotic membrane extract prepared by homogenizing frozen amniotic membrane to provide amniotic membrane homogenate having soluble and insoluble membrane extract, useful for preventing e.g. inflammation	TISSUETECH INC (TISS-Non-standard)
US2004048796-A1	Eye disease	Human	Preparing collagen biofabric from placenta having amniotic membrane and chorionic membrane, useful for drug delivery, involves separating amniotic membrane from chorionic membrane and decellularizing amniotic membrane	HARIRI R J (HARI-Individual); KAPLUNOVSKY A M (KAPL-Individual); MURPHY P A (MURP-Individual)
WO2007009061-A2; US2007021762-A1	Eye disease	Not specified	Ocular plug for occluding and repairing discontinuities in sclera or delivering biologically active compounds to sclera or eye e.g. during vitreo-retinal surgery, comprises cap and shaft made of biodegradable composition	ANTHROGENESIS CORP (ANTH-Non-standard); LIU Q (LIUQ-Individual); RAY C D (RAYC-Individual) LIU Q, RAY C, RAY C D

11.10 Appendix 10 Patents for placenta (cosmetic applications)

Patent Number	Application	Species	Title	Assignee
RU2275186-C2	Cosmetic	Unknown	Cosmetic product for face and neck skin care	MIKROGEN MED IMMUNIBIOLOG ASSOC (FGUP-Soviet Institute); KANYGINA EH L (KANY-Individual); SAVKINA M A (SAVK-Individual)
SU1792702-A1	Shampoo	Not specified	Mixture for manufacture of hair shampoo - uses alcoholic extract of placenta as bioactive component, and sulpho:ethoxylate(s), alkylolamide(s) of fatty 10-13C acids and tri-ethanolamine salt of lauryl sulphate as surfactants	TASHK VACCINES SERA RES INST (TSVA-Soviet Institute)

11.11 Appendix 11 Patents for placenta (tissue engineering applications)

Patent Number	Application	Species	Title	Assignee
WO2006138552-A2	Tissue engineering using cells from placenta or other tissues	Human	Tissue engineered cartilage useful for treating cartilage damage, comprises nanofibrous polymer support having several polymer nanofibers, and several chondrocytes dispersed throughout polymer support	US DEPT HEALTH & HUMAN SERVICES (USSH)
WO2005038012-A2; EP1649013-A2; US2006154367-A1; AU2004281371-A1	Tissue Engineering	Human	New postpartum-derived cell capable of self-renewal and expansion in culture and that can differentiate into a cell of an osteogenic or chondrogenic phenotype, for diagnosing or treating bone or cartilage disorders, e.g. rickets	ETHICON INC (ETHI)
CN1537465-A; CN1277489-C	Immunity, senility	Ovine	Functional food containing ewe placenta, and its preparation	DALIAN LIGHT IND COLLEGE (DALI-Non-standard); DALIAN INST LIGHT IND (DALI-Non-standard)
WO2005001079-A2; US2005058629-A1; EP1641917-A2; AU2004252570-A1	Tissue engineering	Human	New postpartum-derived cell that self-renews and expands in culture, and provides trophic support to a soft tissue cell, useful for treating a soft tissue condition, such as hernia, ulcer, burn, surgical wound or vascular disorders	ETHICON INC (ETHI); HARMON A M (HARM-Individual); HARRIS I R (HARR-Individual); KIHM A J (KIHM-Individual); MISTRY S (MIST-Individual); MESSINA D J (MESS-Individual); SEYDA A (SEYD-Individual); YI C (YICC-Individual); GOSIEWSKA A (GOSI-Individual)
KR2004064004-A		Human	Usage of amnion as cell culturing matrix or basement membrane and method of manufacturing cell treatment thereby	BIOLAND LTD (BIOL-Non-standard)
CN1466955-A; CN1176668-C	Cardiovascular, immunity ,memory and skin	Ovine	Composite biological active capsule and method for preparing the same	YU J (YUJJ-Individual)
CN1468632-A; CN1199688-C	Growth hormone extraction	Ovine, bovine equine, porcine	Preparing growth hormone for ovarian functional cell comprising crushing animal brain, homogenizing, freeze-thawing to leach out active matter, superfiltration and freeze drying to obtain animal tissue powder	YU J (YUJJ-Individual)
WO2004006961-A1; AU2003249805-A1; EP1536837-A1; JP2005536496-W; US2006127873-A1	Tissue repair	Human	Composition useful for e.g. soft tissue repair comprises solution of isotonic neutral chitosan and cross-linking solution containing aldehyde or aldehyde-treated hydroxy-containing polymer	BIO SYNTECH CANADA INC (BIOS-Non-standard); HOEMANN C (HOEM-Individual); CHENITE A (CHEN-Individual); BUSCHMANN M (BUSC-Individual); SARREQI A (SARR-Individual); SUN J (SUNJ-Individual)
WO200263962-A; EP1367892-A; WO200263962-A1; US2002160510-A1; EP1367892-A1; AU2002243980-A1; NZ528035-A	Tissue engineering	Human	Manufacturing tissue matrix for implantation into a patient, by collecting embryonic stem cells from placenta which has been treated to remove residual cord blood; and seeding stem cells onto or into a tissue matrix	HARIRI R J (HARI-Individual)

WO200246373-A; EP1349918-A4; WO200246373-A1; US2002123141-A1; AU200220209-A; EP1349918-A1; KR2003081345-A; JP2004523220-W; ZA200304341-A; MX2003005014-A1; US2005272148-A1; US7045148-B2; AU2002220209-B2	Cell collection	Human	Collecting embryonic-like stem cells from drained placenta by perfusion technique which utilizes either or both of umbilical artery and umbilical vein developed on recovery of human placenta following exsanguination	HARIRI R J (HARI-Individual); ANTHROGENESIS CORP (ANTH-Non-standard); HARIRI R (HARI-Individual)
JP2002020299-A	Energy augmentation, menopause treatment, skin beautification and liver function improvement (Chinese medicine)	Human	Placenta-containing sublingual tablet for absorbing biological active component of placenta by human body, useful for energy augmentation, menopause treatment and liver function improvement, comprises component of placenta	FINE KAGAKU KENKYUSHO KK (FINE-Non-standard)
CN1329908-A	Preparation (Chinese medicine)	Human	Recovery pill and its preparation process	GU M (GUMM-Individual)
WO200204599-A2; AU200173362-A; US2002150974-A1; AU2001273362-A8	Burn and wound treatment, tissue culture. (Polypeptide)	Any	Novel placental polypeptides comprising multiple epidermal growth factor-like domains, designated as Zneu2 polypeptides, useful for stimulating epidermal tissue growth e.g. in burn treatment and wound healing	ZYMOGENETICS INC (ZYMO); HOLLOWAY J L (HOLL-Individual); HEFFERNAN J K (HEFF-Individual); TAFT D W (TAFT-Individual)
CN1541667-A	Nerve disease, burns, itching , cancer	Fowl	Active enzyme biological medicinal composition for treating Parkinson's disease, nerve disease, itching, cancer, and burns and scalds comprises placenta, umbilical cord and protein of hatched fowl egg	WANG J (WANG-Individual)

11.12 Appendix 12 Bioactives in amniotic fluid

This table contains bioactives reported in amniotic and allantoic fluids. It is extensive, but not exhaustive. The bioactives and their concentrations for the 2 fluids are reported separately since they come from different compartment of the amniotic sac and contain different activities. However, collection of ruminant amniotic fluid may lead to pooling of the fluids, which change their volumetric ratio during gestation. The reader should note that many of the reported components and their concentrations are from human amniotic and/or allantoic fluids.

Bioactive	**Concentration in Amniotic Fluid**	**Concentration in Allantoic Fluid**	**Claimed activity**	**Species**	**Gestational Period**	**Reference**
9 alpha, 11 beta-prostaglandin F-2			Contracts uterine smooth muscle; upregulated by bacterial cell wall and proinflammatory cytokines	Human		Mitchell *et al*., 2005. J Clin Endocrinol metab 90(7):4244-4248
Activin	3.2 ng/mL	189 ng/mL	Growth factor, role in inflammation, wound healing	Ovine	20-124 days	Foulds, *et al*., 1998. Biol. Reprod. (59): 233-240.
Activin			Growth factor, role in inflammation, wound healing			Phillips *et al.,*1999. J Endocrinol 162:111-116
AF mesenchymal progenitor cells (MPCs)			Foetal cartilage engineering, *in vitro*	Ovine		Kunisaki *et. al.,* 2006. Stem Cells & Dev 15(2):245-253
Albumin				Human	5-13 weeks	Gulbis *et al*., 1992. human Reprod 7(6):886-889
Albumin				Human	10-14 weeks	Stewart *et al*., 2001. Electrophoresis 22:1136-1142
Alpha-1-acid glycoprotein (AGP)				Human	2nd/3rd trimester	Orczyk-Pawilowicz *et al.,*2006. Clinica Chimica Acta 367(1-2)
Alpha1-antitrypsin				Human	10-14 weeks	Stewart *et al*., 2001. Electrophoresis 22:1136-1142
alpha-1-fetoprotein			Metabolism error; Disease involving nervous system			Stibler & Kristiansson 1991. Acta Paediatrica Scandinavica 32-38 Suppl. 375
Alpha-fetoprotein			In normal foetuses, AFP binds the hormone estradiol.		28-37 weeks	*Shahin & Raslan 2007. Gynecologic Obstetric Invest 63(4):195-199
Alpha-fetoprotein				Human	5-13 weeks	Gulbis *et al*., 1992. human Reprod 7(6):886-889
Alpha-fetoprotein	1.25-5 µg/ml			Human	midtrimester	Keel *et.a/.,* 1991. Molec Reprod Dev 30(2):112-118.

Bioactive	Concentration in Amniotic Fluid	Concentration in Allantoic Fluid	Claimed activity	Species	Gestational Period	Reference
Annexin A5 (AF-AnxA5)					15-24 weeks	Van Eerdenet *et al*., 2006. Am J. Obstet. Gynecol 194(5):1371-1376
Antioxidant enzymes (several)			Defence agaist ROS (esp early pregnancy)			Gianazza *et al.,* 2007. Proteom Clin Appl 1:167-175
Bactericidal/permeability-increasing protein			Antimicrobial, broad spectrum			Cited Underwood *et al.,* 2005. J Perinatology 25: 341-348
Beta-1-glycoprotein (SP1)	88-610iu/l			Human	10-23 weeks	Kelly *et al.,* 1994. Early Human Dev 37(3):175-178
beta2-microglobulin				Human	13-20, 27-34, 36-42 weeks	Oliveira *et. al.,* 2002. Braz. J. Med. Biolog Res. 35(2):215-222.
bFA1 (soluble glycoprotein); (bovine Dlk-1)				Bovine		Vuocolo *et al.,* 2003. Comp Biochem Physiol B-biochem & Molec Biol. 134(2):315-333
Calprotectin			Antimicrobial, broad spectrum			Cited Underwood *et al.,* 2005. J Perinatology 25: 341-348
Cathelicidin [LL-37]			Antimicrobial, broad spectrum	Human	term	Yoshio *et al.* 2003. Ped res 53:2, 211-216
CD38, soluble form (sCD38)			Involved in lymphocyte activation, adhesion to endothelium	Human		Funaro *et al.,* 1996. Int Immun 8(11): 1643-1650
Chitinase 3-like protein-1 (human cartilage glycoprotein 39)			Growth factor/CT remodelling	Human	16-18 weeks	Gianazza *et al.,* 2007. Proteom Clin Appl 1:167-175
Chymotrypsin			5-100-mu-g/L	Human	17-18 weeks	Carrere *et al.,* 1992. J Ped Gastroenterol nutrit 14(2):198-203
C-reactive Protein (CRP)				Human	midtrimester	Helliwell *et al*., 2006. J. Clin Endocrinol Metabolism 91(2):597-605
Cystatin C			Enzyme inhibitor	Human		Kristensen *et al*., 2007. Molec Human Reprod 13(3): 189-195
EGF				Rat	day 19-22	Morikawa *et al*., 1994. Bil Neonate 66(2-3):100-105
EGF				Human	late pregnancy	Varner *et al*., 1996. J. Soc Gynec Invest. 3(1):17-19

Bioactive	Concentration in Amniotic Fluid	Concentration in Allantoic Fluid	Claimed activity	Species	Gestational Period	Reference
EGF	*30pg/ml			Human	newborn	Kelly et al., 1997. Ach Disease Childhood 76(3):F158-162 Sp. Iss. SI, May
EGF				Rat	d13 and 18-22	Ribeiro *et al*., 2005. PNAS USA 102(22):8048-8053
Epidermal Growth Factor (EGF)				Human		Hirai *et al*., 2002. J Ped Gastroent Nutrition 34(5):524-529
Erythropoietin				Ovine	late gestation	*Brace *et al.,* 2006. Am J. Obstet Gynec 195(1):246-254
Erythropoietin	14mU/ml in diabetic. 6.3mU/ml in controls			Human		Teramo *et al.,* 2004. Diabetologia 47(10): 1695-1703
Foetal fibronectin				Human	14-38 weeks	Negidhi *et al.,* 1995. Int J. Gynec Obstet 49(1):17-20
Foetal Immunoglobulins				Human		Quan *et al*.,1999. Am J. Reprod Immunol. 42(4):219-225
Fibroblast growth factor (FGF)				Human		Hirai *et al*., 2002. J Ped Gastroent Nutrition 34(5):524-528
Fibroblast Growth Factor (FGF-2)				Human	Term	*Hill *et al*., 1995. J Clin Endocrinol Metab 80(6):1822-1831
Fractalkine (FRK)			CX3C chemokine with chemoattractant activity for T cells, monocytes and NK cells; may contribute to immunodefence during pregnancy	Human	2nd/3rd trimester	Shimoya *et al.,* 2003. Molec Human Reprod. 9(2):97-101
Gamma-globulin				Human	10-14 weeks	Stewart *et al*., 2001. Electrophoresis 22:1136-1142
G-CSF (= granulocytopoietic growth factor)			topical intestinal growth factor (mouse)	Human	Healthy term/preterm.	*Cited Underwood *et al.,* 2005. J Perinatology 25: 341-348
G-CSF (= granulocytopoietic growth factor)				Mouse		^ Gersting *et al.* 2004. Ped Res 55(5): 802-806
Glycodelin			Immunosuppressive, morphological marker of differentiation, contraceptive	Human		Jeschke *et al.,* 2005. Anticancer Res 25(3A):1581-1589.

GRO alpha/MGSA			New member of chemokine superfamily CXC(alpha)		A range of ages	Cohen et al., 1996. Am J. Reprod Immunol 35(1):23-29
Growth Hormone						Bona et al., 1994. Panminerva Medica 36(1):5-12.
Heparin-binding EGF-like growth factor (HB-EGF)	0.2-230 pg/ml			Human	Term/preterm	Michalsky et al., 2002. J Ped Surg 37(1): 1-6
Hepatocyte growth factor (HGF)					2nd trimester	*Ohnishi et al., 1999. Human Reprod 14(10):2625-2628
Hepatocyte growth factor (HGF)						Hirai et al., 2002. J Ped Gastroent Nutrition 34(5):524-528
Hepatocyte growth factor (HGF)				Human	<37 weeks	Kumazawa et al., 2003. Acta Medica Okayama 57(1):25-32
Human neutrophil peptides 1-3 (HNP 1-3).			α-defensins, antimicrobial, broad spectrum/antibacterial	Human	Term	Yoshio et al. 2003. Ped Res 53:2, 211-216
Human chorionic gonadotrophin (hCG)	Beta-hCG; 6.7kIU/l, Intact hCG; 1.7kIU/l, Free alpha-subunit; 0.26mg/l			Human	1st trimester	Iles et al., 1992. J Endocrin 135(3):563-569
Human Chorionic Gonadotropin, Beta Subunit				Human	28-37 weeks	Shahin & Raslan 2007. Gynecologic Obstet Invest 63(4):195-199
Human neutrophil peptides 1-3 (HNP 1-3).			Antimicrobial	Human	>37 weeks	Akinbi et al., 2004. Am J Obstet Gynec 191(6):2090-2096
Hyaluronic acid/ GF Gyaluronic acid stim-activator						Karacal et al., 2005. J Surg Res 129 (2): 283-287
Hyaluronic acid/ GF Gyaluronic acid stim-activator			neochondrogenesis			Ozgenel et al., 2004. Br J Plastic Surg 57 (5) 423-428
IgA				Chicken	d14	Bencina et al., 2005. Avian Pathol. 34(6)
IgA				Human		Quan et al.,1999. Am J. Reprod Immunol. 42(4):219-225
IGF-1				Human	early pregnancy	*Wathen et al., 1992. Early Human Dev. 28(2):105-110

IgG				Human		Quan *et al.*,1999. Am J. Reprod Immunol. 42(4):219-225
IL						Greig **et al**., 1995. Am J. Obstet Gynec 173(4):1223-1227
IL						Heybourne *et al*., 1994. Am J. Obstet Gynec 171(1):55-59
IL-10				Human	term, preterm labor, throughout pregnancy, midtrimester	Dudley *et al*., 1997. J Reprod Immunol 33(2):147-156
IL-10, IL-12, TGF-beta, IL-11	LOW			Human	14-16 weeks	
IL-11				Human		Srivastava *et al*., 1996. Am J. Reprod Immunol 36(3):157-166
IL-15	Not recorded			Human	14-16 weeks	Mazzucchelli *et. al.,* 2004. Am J. reprod. Immun 51(3):198-203.
IL-16				Human	mid trimester	Athayde *et al*., 2000. Am J. Obstet. Gynecol. 182(1):135-141 Part 1
IL-1beta				Human		Srivastava *et al*., 1996. Am J. Reprod Immunol 36(3):157-166
IL-1RA				Human		Srivastava *et al*., 1996. Am J. Reprod Immunol 36(3):157-166
IL-6	950pg/ml			Human	14-16 weeks	Heikkinen *et al.,* 2001. Scand J Imm 53(3):310-314
IL-6				Human		Srivastava *et al*., 1996. Am J. Reprod Immunol 36(3):157-166
IL-8	606pg/ml			Human	14-16 weeks	Heikkinen & Alanen 2001. Prenatal Neonatal medicine 6(4):214-218.
IL-8						Maheshwari *et al*., 2002. Cytokine 20(6);256-267
IL-8				Human		Srivastava *et al*., 1996. Am J. Reprod Immunol 36(3):157-166

IgG				Chicken	d14	Bencina *et al*., 2005. Avian Pathol. 34(6)
IgG				Human		Quan *et al.*,1999. Am J. Reprod Immunol. 42(4):219-

						225
immunoglobulin-G				Human	5-13 weeks	Gulbis *et al.*, 1992. human Reprod 7(6):886-889
Insulin-like growth factor (IGF)-binding protein-1 (IGFBP1)			Regulates activity of IGF in early pregnancy	Human		Sala *et al.,* 2005. J. Biol Chem 280(33):29812-19
Insulin-like Growth Factor (IGF-1* #, IGF-2)					2nd trimester	Ohnishi *et al.,* 1999. Human Reprod. 14(10):2625-2628
Insulin-like Growth Factor (IGF-1* #, IGF-2)				Human	2nd trimester	Kubota et al., 1992. Endocrinologica 127(4):359-365
Insulin-like Growth Factor (IGF-1* #, IGF-2)				Human		Hirai *et al., 2002.* J. Ped. Gastroenterol. Nutrition 34(5):524-528
Insulin-like Growth Factor (IGF-1* #, IGF-2)				Avian	6d>	Karcher *et al.,* 2005. Comp. Biochem Physiol A-Molec. Integrative Physiol 142(4):404-409
Interferon gamma-inducible T-cell alpha chemoattractant (ITAC)				Human	midtrimester	Malamitsi-Puchner *et al.,* 2006. J Soc Gynecologic Invest. 13(1):25-29
Interleukins						
Lactoferrin (LF)			Antimicrobial, broad spectrum	Human	>37 weeks	Akinbi *et al.,* 2004. Am J Obstet Gyn 191, 23090-6
L-type prostaglandin D synthase (PGDS)				Human		Helliwell *et al*., 2006. J. Clin Endocrinol Metabolism 91(2):597-606
Lysozyme (synom. Muramidase)			Antimicrobial, broad spectrum/antibacterial	Human	Term	*Yoshio *et al.* 2003. Ped res 53:2, 211-216
Lysozyme (synom. Muramidase)				Human	>37 weeks	Akinbi *et al.,* 2004. Am J Obstet Gyn 191, 23090-6
Macrophage colony-stimulating factor (M-CSF)			Immunological function in maintenance pregnancy & foetal growth	Human	Healthy term/preterm.	*Cited Underwood *et al.,* 2005. J Perinatology 25: 341-348
Macrophage colony-stimulating factor (M-CSF)	Median 4815 pg/mL			Human	Term	^ Hayashi *et al.,* 2006. Am J reprod Imm 55(3): 266-231
Matrix metalloproteinase 3 (MMP-3)			CT breakdown?	Human	several gestational stages (no change in conc)	Park *et al.,*2003. J Perinatal Med 31 (1):12-22
MCP-2					preterm labour	*Jacobsson *et al*., 2005. Acta Ostetricia Gynecologica Scandinavica 84(6):566-571
MCP-3					preterm labour	*Jacobsson *et al*., 2005. Acta Ostetricia Gynecologica Scandinavica 84(6):566-571

MIP-1 alpha				Human		Srivastava et al., 1996. Am J. Reprod Immunol 36(3):157-166
MMP-1, -2, -3, -7, -9	MMP-2 &-3 expressed constitutively, MMP-9 barely detectable until labor, MMP-7 increases during pregnancy			Human		Weiss et al., 2007. Frontiers in Bioscience 12:649-659
MMP-2				Rat	days 18-20	Lei et al., 1995. Biol Reprod 53(2):339-344
MMP-2						Riley et al., 2000. J Reprod Fert. 118(1):19-27
MMP-9				Rat	days 18-20	Lei et al., 1995. Biol Reprod 53(2):339-344
MMP-9						Riley et al., 2000. J Reprod Fert. 118(1):19-27
Monocyte Chemotactic Protein-1 (MCP-1)						Denison et al., 1998. Human Reprod. 13(8):22922-2295
Monocyte Chemotactic Protein-1 (MCP-1)					preterm labour	Esplin et al., 2005. J Maternal-Foetal Neonatal Med 17(6):365-373
Mucins:FM-1, FM-2				Human		Hanisch & Peterkatalinic 1992. Eur J. Biochem 205(2):527-535
N-acetyl-beta-D-glucosaminidase (NAG)				Human	13-20, 27-34, 36-42 weeks	Oliveira et. al., 2002. Braz. J. Med. Biolog Res. 35(2):215-222.
Nerve Growth Factor						#Marx et al., 1999. Am J Obstet Gynec 181(5):1225-1230
Neurotrophic Factor						#Marx et al., 1999. Am J Obstet Gynec 181(5):1225-1230
Neurotrophin-3						#Marx et al., 1999. Am J Obstet Gynec 181(5):1225-1230
N-formyl-methionyl-leucyl-phenylalanine (fMLP) receptor ligands			Inflammatory peptide	Human	all	Biondi et al., 2005. J Reprod Immun 68(1-2):71-83

Non-glycosylated SP-A	700+/-333ng.ml(-1)			Rat	d21	Sakai *et al.,* 1994. Eur Resp J. 7(1):88-93
Oct-4 expressing stem cells, Stem Cell Factor			Pluripotent stem cells	Human	14th week	Prusa *et al.,*2003. Hum Reprod 18/7:1489-1493
Parathyroid Hormone-Related Protein (PTHrP)	Mid-gestation: 21pmol/l. Term: 19pmol/l			Human	mid-gestation, term	Dvir *et al*., 1995. Eur J. Endocrinol 133(3):277-282
Phospholipase A (PLA) inhibitory protein (PLIP-1, PLIP-2)				Human		Moom *et al.,* 2000. Biol Pharmaceutical Bull. 23(10):1163-1166
Prolactin				Human	28-37 weeks	Shahin & Raslan 2007. Gynecologic Obstet Invest 63(4):195-199
Prolactin			*may have role in growth and maturation of gut mucosa during ontogeny	Rat		Bujanover *et al*., 2002. J. Ped Endocrinol Metab. 15(6):789-794.
Prolactin				Rhesus	130-166 days	Bethea *et. al.,* 1998. Bil Reprod 58(6):1385-1393.
Protein C (PC), Protein S (PS), Thrombomodulin (TM)			Anticoagulant system		1st stage of labour	Uszynski *et al*., 2006. J Perinatal Med 34(4):289-292
Psoriasin [S100A7]			Antimicrobial, broad spectrum			Cited Underwood *et al.,* 2005. J Perinatology
Psoriasin [S100A7]			immunobiological (chemokine-like activity?)		3rd trimester	Porre *et al.,* 2005. Mol Hum Reprod. 11 (2): 87-92
Secretory component (SC)-like protein(s)			Anti-phospholipase A(2) activity	Human	3rd trimester	Bennett *et al*.,1999. J Soc Gynecologic Investigation.6(6):311-317.
secretory Ig (S-Ig)				Human		Quan *et al*.,1999. Am J. Reprod Immunol. 42(4):219-225
Secretory leucocyte protease inhibitor			Antimicrobial, broad spectrum	Human	37 weeks	Akinbi *et al.,* 2004. Am J Obstet Gyn 191, 23090-6
sIL-2R				Human		Srivastava et al., 1996. Am J. Reprod Immunol 36(3):157-166
SRIF (=Somatostatin?)						Bona *et al*., 1994. Panminerva Medica 36(1):5-12.
Stem Cell Factor				Human		Srivastava *et al*., 1996. Am J. Reprod Immunol 36(3):157-166

Thrombin activatable fibrinolysis inhibitor (TAFI)	53 ng/ml		antifibrinolytic	Human	term	Uszynski *et al*., 2007. Thrombosis Res 119/2: 241-245
TIMP-1			Tissue remodelling, growth promoter, anti-angiogenic factor, apoptosis modulator			Gianazza *et al.,* 2007. Proteom Clin Appl 1:167-175
Tissue factor (TF) = tissue thromboplastin/coagulation factor III	Mean conc= 9996pg/ml		Initiates extrinsic coagulation pathway (oncogenesis?)	Human	term	*Uszynski *et al.,* 2001. Eur J Obstet Gynec Reprod Biol 95:163-166
Tissue factor (TF) = tissue thromboplastin/coagulation factor III						Lockwood *et al.,* 1991. Am J Obstet Gynec 165(5): 1335-1341
tissue inhibitor of matrix metalloproteinases (TIMPs)						*Riley et al., 2000. J Reprod Fert. 118(1):19-27
TNF-alpha				Human		Srivastava *et al*., 1996. Am J. Reprod Immunol 36(3):157-166
Transferrin				Human	5-13 weeks	Gulbis *et al*., 1992. human Reprod 7(6):886-889
Transferrin				Human	10-14 weeks	Stewart *et al*., 2001. Electrophoresis 22:1136-1142
transferrin			Metabolism error; Disease involving nervous system			Stibler & Kristiansson 1991. Acta Paediatrica Scandinavica 32-38 Suppl. 375
Transferrin			Involved in iron transport			van Rooijen *et al.,* 1998. Glycobiol. 8(11):1053-1064
Transforming Growth Factor alpha (TGF-alpha)				Human		Hirai *et al.,*2002. J Ped Gastroent Nutrit 34(5):524-528
Transforming Growth Factor beta (TGF-beta)				Ovine	early	Dore et al., 1995. Biol Reprod 53:143-152
Transforming Growth Factor beta (TGF-beta)			Wound healing; enhanced fibroblast collagen lattice contraction; fibroblast-populated collagen lattice (FPCL) contraction	Rat	14d	Levinson *et al.,* 2001. J Surg Res 100(2):205-210
Trypsin			5-100-mu-g/L	Human	17-18 weeks	Carrere *et al.,* 1992. J Ped Gastroenterol nutrit 14(2):198-203
Type IIA Secretory Phospholipase A(2) Inhibitory Protein				Human		Moon *et al*., 2000. Biol Pharmaceut Bull. 23(10):1163-1166

Uterine Milk Protien (UTMP)		present	Binds activin.	Ovine	20-140 days	McFarlane *et al*., 1999. Endocrinology 140:4745-4752.
Uteroglobin/Clara cell 10-kDa protein (CC10)			Anti-inflammatory, immuno-modulatory			Gianazza *et al.,* 2007. Proteom Clin Appl 1:167-175
Xanthine				Human	10-14 weeks	Stewart *et al*., 2001. Electrophoresis 22:1136-1142

11.13 Appendix 13 Bioactives in placenta

This table contains bioactives reported for placenta (choriodecidua) in the scientific literature. While the table is extensive, it is not exhaustive and further literature searches and indeed future analysis are likely to reveal more compounds.

The reader should note that many of the reported components and their concentrations are from human placenta which as described in section 1, is quite different in structure to ruminant placentas.

* Decidua = maternal; Chorion= foetal; Trophoblast and Syncytiotrophoblast = foetal.

Bioactive	Concentration	Claimed activity	Species	Layer	Gestational Period	Reference
15-Hydroxy-prostaglandin dehydrogenase (PGDH)		Abrogates prostaglandin activity	Human	Placenta		Sato, *et al.,* 2006. Am. J. Obst. & Gyn.(195) 1396-8
Arginase-I (A-I) and arginase-II (A-II)		converts L-arginine to urea and ornithine	Human	trophoblast		Ishikawa, *et al.,* 2007. Placenta 28:133-8.
Annexin 1 (=Lipocortin 1)		protien involved in inflamation	Human	choriodecidua		Sato, *et al.,* 2006. Am. J. Obst. & Gyn.(195) 1396-9
Annexin 5		Unkown, possible role in the inhibition of blood coagulation	Human	chorion		Sato, *et al.,* 2006. Am. J. Obst. & Gyn.(195) 1396-10
Apolipoprotien		Binds to Apolipoprotein-A-I	Human	Placenta		Enholm, *et al.,* 1991. Biochimica et Biophysica Acta 1086:255-260.
Cortisol			Human	Decidua		http://en.wikipedia.org/wiki/Decidua
CRF			Human	Decidua		http://en.wikipedia.org/wiki/Decidua
Cytokines			Human	Decidua		http://en.wikipedia.org/wiki/Decidua
Estrogen			Human	Placenta		http://en.wikipedia.org/wiki/Placenta
GnRH			Human	Decidua		http://en.wikipedia.org/wiki/Decidua
growth factor			Human	Decidua		http://en.wikipedia.org/wiki/Decidua
hCG			Human	Trophoblast (cells forming the outer layer of the		http://en.wikipedia.org/wiki/Trophoblast

				blastocyst)		
IL-1 beta		Pro-inflamatory cytokine	Human	Placenta		Holcberg, *et al.,* 2007. J. Repro. Immuno. (74) 15-23.
IL-1 beta	<5 ng/mg		Human	Amnion	all	Elliot, *et al.,* 2001. Am. J. Repro. Immun. 46:260-267.

IL-1 beta	<1 ng/mg		Human	choriodecidua	all	Elliot, *et al.,* 2001. Am. J. Repro. Immun. 46:260-267.
IL-6	743 pg/uL	Pro-inflamatory cytokine	Human	Maternal	pre-term, (32-36 weeks)	Holcberg, *et al.,* 2007. J. Repro. Immuno. (74) 15-23.
IL-6	192 pg/uL	Pro-inflamatory cytokine	Human	Foetal	pre-term, (32-36 weeks)	Holcberg, *et al.,* 2007. J. Repro. Immuno. (74) 15-23.
IL-6	963 pg/uL	Pro-inflamatory cytokine	Human	Maternal	term	Holcberg, *et al.,* 2007. J. Repro. Immuno. (74) 15-23.
IL-6	88 pg/uL	Pro-inflamatory cytokine	Human	Foetal	term	Holcberg, *et al.,* 2007. J. Repro. Immuno. (74) 15-23.
IL-6	83 ng/mg wet wt/24-hr	Pro-inflamatory cytokine	Human	choriodecidua	term	Sato, *et al.,* 2006. Am. J. Obst. & Gyn.(195) 1396-7
IL-8	10 ng/mg	neutrophil chemoattractant	Human	Amnion	all	Elliot, *et al.,* 2001. Am. J. Repro. Immun. 46:260-267.
IL-8	3.5 ng/mg	neutrophil chemoattractant	Human	choriodecidua	all	Elliot, *et al.,* 2001. Am. J. Repro. Immun. 46:260-267.
IL-10	400 pg/mg wet wt/24-hr	Pro-inflamatory cytokine	Human	choriodecidua	term	Sato, *et al.,* 2006. Am. J. Obst. & Gyn.(195) 1396-7
IL-10			Human	Placenta		Sato, *et al.,* 2006. Am. J. Obst. & Gyn.(195) 1396-10
IL-15			Human	Decidua		http://en.wikipedia.org/wiki/Decidua
Insulin-like growth factor-binding protien 1 (IGFBP1)			Human	Decidua		http://en.wikipedia.org/wiki/Decidua
Insulin-like growth factor-II (IGF-II)		may play a role in decidual angiogenesis and placental differentiation.	mouse	Trophoblast	d 5.5-10.5	Pringle and Roberts, 2007. Placenta 28:286-297.
Leptin			human	Trophoblast		Henson, *et al.,* 1999. J. Clin. Endocrinol. Metab. 84:2543-2549.
Leptin		Inhibits uterine muscle contractions.	baboon	Trophoblast		Henson, *et al.,* 1999. J. Clin. Endocrinol. Metab. 84:2543-2549.
Neurokinin B (phosphocholine)			Human	Placenta		http://en.wikipedia.org/wiki/Placenta
Peroxisome proliferator-activated receptor gamma			mouse	Placenta	d11.5	Suwaki, *et al.,* 2007. Placenta 28:315 323

Pregnancy protien 14 (PP-14)			Human	Decidua		http://en.wikipedia.org/wiki/Decidua
Progesterone			Human	Syncytiotrophoblast		Henson.1998. Human Reproduction Update 4:389-405
Prolactin			Human	Decidua		http://en.wikipedia.org/wiki/Decidua
Prostaglandin E2	1.7 pg/mg wet wt/24-hr	Pro-inflamatory cytokine	Human	choriodecidua	term	Sato, et al., 2006. Am. J. Obst. & Gyn.(195) 1396-7
Relaxin			Human	Decidua		http://en.wikipedia.org/wiki/Decidua
Renin		circulating enzyme that activates the renin-angiotensin system by producing angiotensin I from angiotensinogen.	Human	Decidua		Shaw, et al., 1989. J Clin Invest. (83): 2085-92. quoted in Sato
Smad ubiquitin regulatory factor 2 (Smurf2)		E3 ubiquitin ligase	Rhesus	Placenta	d12	Yang, et al., 2007. J. Histochemistry and Cytochemistry 5:453-460
Somatomammotropin			Human	Placenta		http://en.wikipedia.org/wiki/Placenta
Sterylsufatase			Human	Placenta		Dibbelt, et al., 1991. Biological Chemistry 372:173-185.
TNF-alpha	365 pg/uL	Pro-inflamatory cytokine	Human	Maternal	pre-term, (32-36 weeks)	Holcberg, et al., 2007. J. Repro. Immuno. (74) 15-23.
TNF-alpha	46 pg/uL	Pro-inflamatory cytokine	Human	Foetal	pre-term, (32-36 weeks)	Holcberg, et al., 2007. J. Repro. Immuno. (74) 15-23.
TNF-alpha	225 pg/mg wet wt/24-hr	Pro-inflamatory cytokine	Human	choriodecidua	term	Sato, et al., 2006. Am. J. Obst. & Gyn.(195) 1396-7
TNF-alpha	425 pg/uL	Pro-inflamatory cytokine	Human	Maternal	term	Holcberg, et al., 2007. J. Repro. Immuno. (74) 15-23.
TNF-alpha	20 pg/uL	Pro-inflamatory cytokine	Human	Foetal	term	Holcberg, et al., 2007. J. Repro. Immuno. (74) 15-23.
Vascular endothelial growth factor (VEGF)			Human	Decidua		http://en.wikipedia.org/wiki/Decidua
VEGF			mouse	Placenta	d 11.6	Suwaki, et al., 2007. Placenta 28:315 324
Carcinoembryonic antigen (CEA)		mediators in remodeling of diverse human tissues, and modulators of cell proliferation and differentiation.	Human	trophoblast	all	Vićovac, et al., 2007. Placenta. 28:85-96.

Nitric oxide synthase (NOS)			Human	trophoblast		Ishikawa, et al., 2007. Placenta 28:133-8.

11.14 Appendix 14 Bovine offal yields supplied by Hans/Swickers

Offal Products	% of Cold CCS. Wt
Brains	0.05%
Tongue	0.40%
Head Meat	0.60%
Papillae	0.20%
Head Bone	4.70%
Fore Tendon	0.30%
Small Intestine	1.90%
Large Intestine	1.90%
Spleen	0.30%
Reticulum	0.20%
Rumen	1.70%
Omasum	1.20%
Abomasum	0.60%
Liver	1.80%
lung	1.40%
Heart	0.50%
Kidney	0.20%
Aorta trim	0.10%
Thin Skirt	0.20%
Thick Skirt	0.50%
Tendon Shin	0.20%
Penis	0.20%
Testes	0.20%
Oesophagus	0.10%
Kidney Fat	3.50%
Blood	5.00%
Trachea	0.10%
Pancreas	0.10%
Thymus	0.00%

Total Offals	**28.15%**
Slaughter Internal Floor Trim	
Fat	0.30%
Trim	2.20%
Total	**2.50%**
Slaughter Floor External trim	
Horn	0.05%
Beef feet	2.50%
Bung	0.10%
Hide Trim	0.10%

Face Pieces	0.50%
Hide Trim	13.00%
Total	**16.25%**

11.15 Appendix 15 “China free” story

7/11/2007 - **In the ongoing controversy surrounding ingredients derived from China, one dietary supplement company has taken the bold move to label its products as "China-free".**

Food for Health International has announced it will start labeling boxes for its dietary supplements with a sticker that reads "safe" and "China-free" following highly publicized discoveries of contaminated food imports from China.

The move begs the question whether such labeling is in fact a thinly disguised means for domestic producers to muscle out the highly competitive sector of Chinese ingredients, or even whether it is blatant xenophobia. The Orem, Utah-based manufacturer claims this is not its aim, but that it is looking to distinguish itself from synthetic vitamin ingredients, which it says stem mainly from China.

Food for Health, which supplies dietary supplements through Internet marketing, says its products are more costly than most vitamin and mineral supplements on the market because they are organic and derived from 'whole foods'. It says 90 percent of vitamin ingredients sold in the US are synthetically derived, but that consumers are not aware of this. But they are increasingly aware of Chinese ingredients contamination scares.

"If I just put 'no synthetic' on the label it would not get the message through in the same way as 'China-free'," Food for Health president Frank Davis told NutraIngredients-USA.

Chinese food and cosmetic imports have been put under a negative spotlight as the result of contamination cases involving products from pet food to toothpaste in recent months.

In April, wheat gluten products imported from China for use in pet food were found to have been contaminated with banned chemical melamine and were blamed for the deaths of hundreds of dogs and cats. This uncovered a host of other cases that have left manufacturers who buy ingredients from the country under pressure to demonstrate they are sourcing responsibly, as well as giving those companies who do not source from the country the opportunity to differentiate themselves as 'risk-free'.

"I am certainly not trying to wage a war with China," said Davis. *"I import materials from China, just not nutritionals."*

The current challenge with Chinese-derived ingredients has left a no-man's land of confusion somewhere in between the resource-constrained US Food & Drug Administration (FDA) and anticipated consumer reaction.

"As consumers, all we can do is if it says "made in China', avoid it," Michael Doyle, director of the Center for Food Safety at the University of Georgia, told CNBC in a televised interview Friday.

In the dietary supplement industry, many companies have been publicizing they source domestically, or have been promoting themselves as sourcing responsibly and as overseeing their entire supply chain.

This has in turn created business opportunities for dietary supplement testing bodies to promote their services as third party auditors who can go over a company's international supply chain with a fine tooth comb, as well as test products for contaminants.

If companies follow First Health's lead, the fear directed at products sourced from China is not likely to subside.

First Health will print stickers on their product boxes that fold over one of the top edges - saying "safe" on the top half of the two-inch sticker, and "China-free/synthetic-free" where it folds over.

"We're going to put it on our product within the week," said Davis.

The company's mainstay has been a line of products some might say also capitalizes on media driven consumer fears - household emergency food supplies for disasters. It sells these products through major retailers

Appendix 16 Table of extent of use of complementary medicine

Country or region	Extent of Use

Africa	Used by 80 percent of the population for primary health care
Australia	Used by 49 percent of adults
China	Accounts for 30 to 50 percent of total health care. Fully integrated into the health system 95 percent of Chinese hospitals have Traditional Medicine (TM) units.
India	Widely used 2,869 hospitals provideTM.
Indonesia	Used by 40 percent of the total population. Used by 70 percent of the rural population.
Japan	72 percent of physicians practice TM
Thailand	TM integrated into 1,120 health centres
Vietnam	Fully integrated into the health care system 30 percent of the population is treated with TM.
Western countries	CAM and TM not strongly integrated into the health care system.
France	At least 75 percent of the population has used CAM at least once.
Germany	77 percent of pain clinics provide acupuncture
United States	29 to 42 percent of the population uses CAM

Source: World Health Organization, 2002.

Appendix 17 List of placental derived products listed with TGA

Label	Product	Sponsor
147834	YOUNGO PLACENTA EXTRACT 2500mg capsule bottle	Youngo International Pty Ltd
200500	NATURES NATURALS SHEEP PLACENTA EXTRACT capsule	Natural Pharmaceuticals Australia Pty Ltd
150277	NPA NATURAL HEALTH PRODUCTS SHEEP PLACENTA EXTRACT 2750mg capsule bottle	Natural Pharmaceuticals Australia Pty Ltd
151735	3GHP PINK LADY SHEEP PLACENTA capsules bottle	THIRD GENERATION HEALTH PRODUCTS AUSTRALIA P/L
152213	WEALTHY HEALTH SHEEP PLACENTA 2500mg capsule-hard bulk	Bargain Health Food Supplies Pty Ltd
152482	OAK NATURAL HEALTH PRODUCTS Sheep Placenta with Vitamin C capsule-hard bottle	Sunny International Corporation Pty Ltd
154152	ELIER SHEEP PLACENTA capsule-hard bottle	MEILI'S GROUP PTY LTD T/A ELIER HEALTH PRODUCTS
162209	WEALTHY HEALTH BIO-PLACENTA 3000 capsule - soft bottle	Bargain Health Food Supplies Pty Ltd
163517	SHEEP PLACENTA VITALIZING CREME COMPLEX	Nature's Hive Pty Ltd
164509	SHEEP PLACENTA EXTRACT capsule - hard bottle	HARMEX PTY LIMITED
171616	GREENCARE SHEEP PLACENTA SOFT GEL CAPSULE bottle	Greencare Australia Pty Limited
176114	NATURE'S CARE PLACENTA 3000mg capsule bottle	Nature's Care Manufacture Pty. Limited
176119	NATURE'S CARE PLACENTA 5000mg capsule bottle	Nature's Care Manufacture Pty. Limited
186300	Aussia Sheep Placenta capsule-soft bottle.	Aussia Australia Pty Ltd
188715	Sheep Placenta 3000mg capsule-soft bottle	Homart Pharmaceuticals Pty Ltd
188773	Typical Sheep Placenta 3000mg capsule-soft bottle.	United World Enterprises Pty Ltd
197025	Sheep Placenta 3000mg	Aulong Development Pty Ltd
205231	Placenta 1000mg	Lanopearl Pty Ltd
206275	Sheep Placenta 3000	H C L Manufacturers Pty Ltd
207112	Biosis Sheep Placenta 2000mg capsule	Australia Natural Pharmaceutical Pty Ltd

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