

# final report

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## Collagen extraction

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## **Executive summary**

This report summarises the state-of art of collagen extraction and use of methods (from red meat sources) for foods, pharmaceutical, cosmetic and biomedical applications. In particular, the following items are addressed:

1. A summary of the patents on the topics and how it affects the Australian industry's freedom to operate.
2. The potential issues and opportunities for the red meat industry in the general area of collagen utilisation.
3. Recommendations on what direction/topics and effort MLA should have for research, development and commercialisation.

These views and recommendations are based both on the documentation provided by MLA, along with a personal appreciation of the markets and opportunities that exist within these markets

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# 1 Patents on topics and affects on Australian industry

The following table is a summary of the most applicable patents with the fields of application in food, pharmaceutical, cosmetic and biomedical (Tissue Engineering) arenas:

Company	Collagen type	source	Field	Extraction (E) / Use method (U)	# patents	Countries
Collagen corp (US) / Inamed / Allegan	I,IV,VI, VIII	Bovine, porcine, equine (skin+ bone)	TE	E + U	9+	US,CA,AU,DE,EP,JP,AT,WO
Devro Pty. Ltd. (AU)	I	Porcine (skin)	FD	E+U	9+	WO,AU,EP,CN,JP,US
CollTech Australia Ltd. (AU)	I, III	Ovine, porcine, equine, (skin) bovine, caprine, marsupial	CO/CC/TE	E+U	1	WO,AU,EP,KR,NZ,TW,CN,JP,US,ZA
Integra Lifesciences Corp (US)	I	Bovine, porcine, equine (skin+ bone)	TE/CO/CC	E+U	10+	WO,US,AU,DE,EP,JP
Biorex labs (UK)	I	Rat	TE	U	1	GB
Uni. Cambridge Tech. (UK)	I	Bovine, porcine, equine (skin+ bone)	TE	U	1	GB
J&J (US)	I	Bovine, porcine, equine (skin+ bone)	TE	U	1	EP,AU,BR,CA,GB
HSC Res. Dev. Ltd (CA)	I (+ elastin)	Bovine, porcine, equine (skin+ bone)	TE	U	1	CA
Ontario Inc. (CA)	I	Rat	TE	U	1	CA
Inst. Bioeng. (CN)	I	Bovine, porcine, equine (skin+bone)	TE	E+U	1	CN
Iso Tis N.V. (NL)	I	Bovine, porcine, equine (skin+ bone)	TE	U	1	EP
France Etat. Armement (FR)	I	Bovine, porcine, equine (skin+ bone)	TE	E+U	1	FR
Bio Material Kenkyushp (JP)	I	Bovine, porcine, equine (skin+ bone)	CC	U	1	JP
3M (US)	I	Bovine, porcine, equine (skin+ bone)	PH	U	1	JP,EP,AU,CA,DE,US
Sumitomo Bakelite (JP)	Gelatin e	Bovine, porcine, equine (skin+ bone)	CC	U	1	JP
4th Military Medical Univ. (CN)	I,IV	Bovine, porcine, equine (skin+ bone)	TE	U	1	CN
Pharma Concepts GMBH (DE)	I	Bovine, porcine, equine (skin+ bone)	PH	U	1	DE

Ruhland Nachf GMBH (DE)	I	Bovine, porcine, equine (skin+ bone)	TE	U	1	DE
Nippon Rikagaku Yakuhn (JP)	I	Chicken	CC	E+U	1	JP
Nippon Collagen Kogyo (JP)	I	Bovine, porcine, equine (skin+ bone)	FD	U	2	JP
Marudai Food (JP)	I	Bovine, porcine, equine (skin+ bone)	FD	U	1	JP
Redbrook Res. Ltd. (IE)	I	Bovine, porcine, equine (skin+ bone)	FD	U	1	GB,IE
Amraf Ltd. (UK)	I	Bovine, porcine, equine (skin+ bone)	FD	E	1	US
Stork Fibron BV (NL)	I	Bovine, porcine, equine (skin+ bone)	FD/PH/CO	U	1	JP,EP,NL
Nippon Meat Packers (JP)	I	Porcine (skin)	FD	U	1	JP
Kureha Chem. Ind. Co. Ltd. (JP)	I	Bovine, porcine, equine (skin+ bone)	TE/FD	E+U	5	JP,NL,GB,FR,DE, AU,CA,
Dr Suwelack Skin & Healthcare (DE)	I	Bovine, porcine, equine (skin+ bone)	TE/CO	U	1	JP,DE,EP

Abbreviations:

Use fields: TE – tissue engineering, FD – food, CO – cosmetic, PH – pharmaceutical, CC – cell culture

Countries: WO – World, US – United States, EP – Europe, CA – Canada, AU – Australia, DE – Germany, AT – Austria, JP – Japan, KR – Korea, TW – Taiwan, GB – Great Britain, BR – Brazil, CN – China, FR – France, IE – Ireland, NL – Holland, ZA – South Africa.

**1.1 Summary:**

The world market for collagen-based biomaterials, for example, urinary incontinence, corneal shields, facial aesthetic dermal fillers and implants, wound dressings and skin regenerating scaffolds (see for example Integra™ (<http://www.integra-ls.com/products/?product=46>) and surface modifiers for cell attachment, is significant and has excellent growth potential. The U.S. dermal filler market alone is projected to expand at a compound annual rate of more than 25% through 2011 in the U.S., and 20% throughout the rest of the world, reaching \$1.5 billion in global sales. See

[http://www.miinews.com/exec\\_summaries/Global%20Market%20for%20Dermal%20Fillers%20Executive%20Summary%20022106.pdf](http://www.miinews.com/exec_summaries/Global%20Market%20for%20Dermal%20Fillers%20Executive%20Summary%20022106.pdf)]. Other markets such as food and nutraceuticals (and to a lesser extent, pharmaceuticals) are also substantial but do not offer the value-adding potential of medical or cosmetic markets.

The above table represents a detailed summary of the patent landscape, in particular in the fields of applications into which MLA collagen products may be utilised. With regards to the opportunities for MLA and the industry's freedom to operate, the picture is fairly clear. There are significant existent players within the extraction and use fields for gelatine, collagen I and IV from

bovine, porcine and equine skin and bone. Considering that these would represent the majority of the collagens extracted from the industry represented by MLA, it would seem that there is little freedom for the MLA or its partners to make significant inroads into the markets as an independent seller of extracted (primary) or further processed collagen products associated with most of the fields listed in the above table. The field is particularly heavy in regards to patented processes for tissue engineered products and cell culture products. The greatest concern or opportunity obviously lies with Australian-based companies, CollTech Australia Ltd. and Devro Co Pty. Ltd..

## **1.2 TE / PH / CO:**

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Collagen Corp. (US)/Inamed/Allegan is the major player in the field of collagen-based (bovine or porcine derived) tissue engineered products, with a substantial patent portfolio in most 1<sup>st</sup> world countries throughout the globe. The company has approximately 22 subsidiary companies worldwide. Not all of them focus on collagen however (only about half!). This company is mostly focused on bone regeneration in the TE field. Opportunities may exist in collagen-based skin products, although this is also a fairly heavily contested market with Integra Lifsciences making significant inroads. Collagen is of course prevalent in many cosmetic formulations but in my opinion, MLA would only have the opportunity to be a provider of base/primary collagens or base materials for collagen extraction (e.g. hides, bones, muscle tissue), not final refined cosmetic products. This also is the case for the TE and PH fields.

## **1.3 FOOD:**

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There are substantial opportunities for MLA within the food market for meat-based or meat-like products. Numerous companies have patented methods for extraction and use of collagen (principally collagen I) as a food additive or as a full meat-based product. These patents have been awarded (in general) in Japan only. Kureha Chem. Ind. Co. Ltd. is one of the only Japanese companies who have chosen to patent both extraction and use methods for food applications beyond Japan, including Australia. This could pose a problem should the MLA not have patented or unpublished methodologies for extraction and use in this field. This field is of course the most likely field into which the products from MLA partners may be introduced with ease. Tissue Engineered products (along with pharmaceutical and cosmetic fields) are certainly required to meet far greater regulatory standards of production and use. This must be considered prior to MLA or its partners consider entering into these markets.

## **1.4 Recommendation:**

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MLA must define what technology exists within the company or its partners that may be patented as novel extraction or use methods. Without this information it is impossible for a solid position of 'freedom to operate' to be sensibly reached. In the absence of novel technologies, MLA must then assess the possibility of licensing technology from existing players in the field or of forming a joint venture with a producer of finished products (for example Collagen Corp (US), CollTech Australia Ltd., Devro Co. Pty. Ltd.) as a supplier of raw material for extraction or of extracted or refined collagens should this capability exist in MLA or its partners. This could indeed offer a viable option for achieving value-adding to otherwise waste streams with minimal investment in capital to achieve extraction and purification to levels required by the partner. This would of course be very case dependent but it is worth consideration.

One large advantage that MLA has as a potential supplier of collagen-based products or primary collagens are the lack of BSE safety concerns. With herds in Australia currently free of BSE and also with the international reputation of such high standards within the industry to avoid any introduction of such a devastating disease, there exists an opportunity to capitalize as a supplier of BSE free products to existing market players. This market edge is certainly being utilised by one new entry into the collagen market based in Western Australia, CollTech. This company has one current product for the cosmetic market, with a research product for life sciences market coming online in 4 quarter 2007 and a medical product for Wound care, Tissue engineering, Biomaterials, Drug Delivery and Injectables applications. This company utilises Ovine collagens I and III. Further details can be found at <http://www.colltech.com.au/>. Please also refer to Devro's website at [www.straliaweb.com.au/devro](http://www.straliaweb.com.au/devro).

With regards to the substantial regulatory hurdles for entry into the medical market (within Australia and throughout the globe), please refer to the recent review by Grady and Bordon 2003.

## **2 Potential issues and opportunities of collagen utilisation**

Besides the potential issues and opportunities listed in item 1 above, a few more opportunities are worth mentioning. I believe that an opportunity exists within the life sciences market for the supply of purified and well characterised collagen of numerous types. CollTech Australia Ltd. are certainly attempting to capitalise on this market sector (see <http://www.colltech.com.au/research.html>).

A perusal of the product listing offered by numerous Life Sciences companies which focus on commodity consumables and chemical, for example Sigma Aldrich, would suggest that collagens from a multitude of sources are in high demand. This is indeed the case from my personal experience. Collagen (I, IV) gels are now becoming common place within cell culture labs as a three dimensional model for organogenesis and is believed to be more representative of an in vivo growth environment. Indeed, definitive differences in cell behaviour are noted when cells are suspended within a collagen gel as opposed to being seeded on top of a surface coated with collagens. Further, collagens I, II, IV, V, VI, VIII are prime candidates often used to functionalise surfaces for enhanced cellular adhesion and expansion, in generic cell maintenance through to differentiation assays and within investigations of stem cell maintenance and differentiation. A highly purified source for each of these collagens would be welcomed by the sector. Recombinant collagens are certainly coming to the market but at prices much higher than extracted collagens.

However, again, given that I am unaware of the current technology available to MLA or its partners inhouse, it is very difficult to assess as to whether MLA has the capability to enter into this market as either an end product provider or as a primary provider to a company like Sigma Aldrich.

### 3 Recommendations for further research, development and commercialisation

A focus on establishing an IP position in each of the following two areas in order to determine the most appropriate position to take with regards to collagen utilisation:

- 1.) Extraction technologies: What technologies/methods are currently utilised within the industry to extract collagen? Are these technologies novel in their methodologies (patented or patentable)? Are they capable of isolating and purifying collagen variants (for example, collagen I versus collagen IV, all collagen types)? If the answer to all of these questions is NO, then MLA must invest effort into establishing connections with research laboratories with capabilities in this area to co-develop novel methods which will allow MLA to have a competitive edge. Alternatively, given the abundance sources of collagen, it could immediately joint venture with a company which has existing extraction technology and markets for supply of raw materials (hides, bones) or unpurified collagens from existing waste streams. Both avenues represent significant value-adding.
- 2.) Use technologies: What technologies/methods are currently utilised within the industry to process collagens, and if they exist, into what product slates/markets? Are these technologies novel in their methodologies (patented or patentable)? Again, if the answer to these questions is NO, then MLA must invest effort into establishing connections with research laboratories with capabilities in this area to co-develop novel methods for use of MLA collagens which will allow MLA to have a competitive edge. However, it is highly likely that any outcomes from such investment will be licensed to existing companies within each market (for example, CollTech or Collagen Corp) and hence it would be worth engaging with these companies sooner rather than later to establish a position with regards to opportunities to joint venture or co-develop new methods.