final report

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AL573 alginate peptide wound dressing – pre commercial trial & commercialisation

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1.0 ABSTRACT

IRL (Industrial Research Limited) in New Zealand and MLA have identified a bioactive from bovine / ovine eye lenses that significantly improve wound healing. In this project the technology was advanced to the stage of '*commercial-ready'* through; animal trials to validate the laboratory tests; critical analysis of key commercial drivers and impediments; identifying and targeting commercial partners with the capacity to commercialise the technology.

Currently, bovine and ovine eye lenses are considered to have little value and are largely sent rendering where they are worth less than 5¢ per head. Extraction of a bioactive from eye lenses for use in high value wound healing applications could significantly boost demand for lenses and preliminary calculations indicated that the value of lenses could be increased 10-fold to in excess of 50¢ per head.

Wound care is one of the most lucrative and rapidly expanding medical device market segments and the global size of the advance wound care market was estimated at $5.1 Billion in 2009 rising to $5.5 Billion by 2011. Growth in this market is driven by an aging population and the rapid increase in the incidence of diabetes. The wound care market was targeted in our development program due to the size, growth and unmet market need for compounds that stimulate wound-healing. Our review of the IP landscape also revealed gaps for compounds that stimulate wound healing.

From an extensive screening of the extracellular matrix from low-value animal co-products, six extracts were isolated with interesting biological activity. The lead extract, isolated from ovine and bovine eyes, was shown to stimulate angiogenesis and promote cell migration of endothelial cells and thus had the potential to stimulate wound healing. A clinically and commercially suitable method for the isolation and preparation of a wound dressing using this protein extracted from lenses was developed. Several formulations were tested and complications associated with formulation of the intact protein complex overcome by targeting the isolation and purification of the active ingredient which was subsequently identified as a small (573 Dalton) peptide (GAP573). Methods for the rapid purification of the peptide from eye lenses and its formulation into wound dressings were developed.

A combination device (termed AL573) based on an alginate gel incorporating GAP573 was tested an ethically approved pre-clinical animal study. AL573 demonstrated significantly faster wound-healing than Fibracol-Plus, a market leading wound-healing product. The mechanism by which GAP573 mediated its action was identified as *down-regulation of gap junction communication*, promoting cell migration and blood vessel formulation. Treatment with the GAP573 was also found to reduce inflammation and scarring.

In an analysis of manufacturing costs, de-novo synthesis of GAP573, using modern peptide synthetic methods, was found to be significantly less expensive, than extraction from bovine or ovine eye lens. In addition, the regulatory (e.g. FDA or TGA- approval) and commercial (e.g. establishment of a suitable supply chain) barriers were found to be lower as suitable GMP-approved peptide manufacturing facilities exist which are capable of scalable manufacture that meets regulatory requirements. Thus, using GMP-peptide synthesis for manufacture provides the best opportunity for the commercialisation of this technology. With no requirements for (co)products from the red meat industry MLA's focus was on licensing the technology.

For the wound-healing application (AL573) of the technology an analysis of the regulatory hurdles indicated that this product would be classified as a ‘combination device’ comprised of an existing device (alginate gel) and a therapeutic (GAP573). In Europe this would be a class 3 medical device and in US would be considered a ‘biologic’ and directed towards the FDA Office of Combination Products. For reimbursement in the US and Europe, a new code would be required as existing codes do not cover the mode of action for this device.

The market for advanced wound healing products is large and growing especially for the treatment of chronic ulcers. There is a particular need for combination products that combine existing materials with biologic molecules to accelerate healing and reduce scar formation. The IRL/MLA peptide in an alginate gel is a novel solution to this unmet market need. Given there are a number of large companies in the current wound healing space, a partnership for the next stage of commercialisation is being investigated.

2.0 EXECUTIVE SUMMARY

Strategy

A market analysis in 2002 identified wound healing as the potential target market as it was growing in double digit figures due to the high incidence of diabetes and population demographics. IP-landscape analysis of wound healing technologies was conducted to identify gaps and opportunities that also aligned with our expertise and match to an unmet market need. Development of compounds to stimulate angiogenesis and promote cell migration of endothelial cells specifically was thus targeted.

Market

The size of the advanced wound care market was approximately $US5.1 billion in 2009 and is estimated to be worth $US5.5 billion in 2011. The market is forecast to grow at 5-7% p.a over the next 4 years to a forecast market size of $US7 billion in 2015. There are a number of segments. There are 3 main types of product segments in the advanced wound care market – moist wound dressings, biologics and negative pressure wound treatment.

Combination products represent some of today's most promising areas in advancing patient care for instance drug eluting stents. Already approximately 15% of the advanced wound care market is made up of combination products and this percentage is forecast to increase. AL-573 combination product includes an alginate gel with a patented natural biologic (GAP573 peptide). Consequently this product is positioned in the right segment, and has promising preclinical results emphasising its significant promise as a future solution. The main players in the advanced wound healing space and consequently potential partners include: 3M HealthCare, B. Braun, Coloplast, Convatec, Covidien, Hartmann-Conco, KCl, Medline, Molynlyke Health Care, Smith & Nephew and Systagenix.

Discovery

An initial discovery programme led to the discovery of six extracts with interesting biological activity. The extracts were prepared from extracellular matrix from low value animal co-products. The strategy was to develop high-value end products from waste or low value co-products that would generate additional income for meat industry as the only potential supplier of the raw material.

The lead extract was from ovine and bovine eyes stimulated endothelial cell migration and angiogenesis and thus promoted wound healing.

Development

A commercially useful method for the isolation and preparation of a wound dressing using a purified extract from lenses was developed and evaluated in a number of preclinical tests. Several formulations were tested and complications associated with formulation overcome by targeting the isolation and purification of the 'active ingredient' which was subsequently identified as a small (573 Dalton) peptide that was named *GAP573*.

Methods were developed for the rapid purification of *GAP573* from eye lenses and its formulation into a wound dressing were undertaken. Testing of dressings incorporating the *GAP573*, in an ethically approved pre-clinical animal study, demonstrated significantly faster wound-healing compared to Fibracol-plus, a market leading wound-healing product. Treatment with the GAP573 was also found to reduce inflammation and scarring. The mechanism by which GAP573 mediated its action was identified as down-regulation of gap junction communication which promotes cell migration and blood vessel formulation.

Manufacture

The forecast costs of the extraction process were approximately double that of the synthetic material. There were also significant economies of scale for larger weights of the synthetic peptide which would most likely increase the cost differential between peptide from the synthetic supply and the extraction of the natural peptide.

Whilst the cost of the extraction process could be further optimised to reduce costs, the major portion of the cost of the extraction is the extraction of the lenses. It is possible that a process using customised automated equipment could reduce the costs significantly. However, at a reasonable profit per animal to the industry the cost would still be higher than sourcing a synthesised material.

De-novo synthesis of the specific bioactive molecule is thus significantly less expensive, less risky and more effective than extracting it from the bovine eye lens. Consequently synthesising the peptide became the recommended method of manufacture rather than from lens extraction. In light of this recommendation, and the lack of direct benefit to the Australian Red Meat Industry, MLA's strategy focused on licensing of this technology.

Intellectual property

The intellectual property is jointly owned by MLA and IRL. The initial platform patent is at a National phase. PCT Application PCT/AU2008/001319 was filed September 5, 2008 with priority from a provisional patent filed September 7, 2007 titled "Agents with Angiogenic and Wound Healing Activity". A second provisional patent application entitled "'Agents for Modulating Cell Signalling" was filed 12 September 2011.

The project included a review of the patent landscape using a contracted patent searcher which identified any relevant prior art. The results of the review are included in a separate confidential report.

Regulatory Pathway

The product is believed to be a combination device as it is combination of an existing device (alginate gel) and a therapeutic (the peptide which modifies cell communication by down regulating gap junction communication). In Europe this would be a class 3 medical device and in US would be considered a 'biologic' and thus directed towards the FDA Office of Combination Products who would most likely refer the submission to the Centre for Drug Evaluation and Research. The process towards regulatory submission and approval needs to be carefully planned. Understanding all parts of the process is critical. These issues include Good Manufacturing Practice (GMP), Quality Management Systems (QMS), Risk Management, Design Controls, Pre-clinical testing, Clinical Evidence and clinical trials

Reimbursement

It is likely that new codes would be required for the product and this process can be long and arduous. In the US there are multiple payors to consider including Medicare, Workers' Compensation, Private/Commercial Insurance, Champus/TRICARE and Medicaid. In Europe there is no harmonized system for reimbursement of medical devices. Each country has its own individual system with reimbursement decisions being made at the national level and in some countries, even at a regional and local level. There are two systems to consider: hospital/inpatient and ambulatory/outpatient. The hospital funding system is quite similar across different countries; the outpatient is totally different from country to country.

In the US for a new code to be issued the technology must be new, existing payment must be inadequate, technology must represent "Substantial Improvement" over previous therapies. In Europe, typically three files should cover most situations. 1) "Identification of the demand" which contains details on the manufacturer, contact person, type of request 2) "Medical & Technical File" details on product, pathology treated, indication, use,

epidemiology as well as details on the clinical benefits & risks, details on the current therapeutic strategy and the place of the device in this strategy, details on the improved benefit brought by the device compared to other validated competitors' device. 3) "Economic File" with impact of the device on healthcare system (patients + economic + use) based on clinical data, with pricing arguments such as International recommendations, level of pricing in other countries, FDA approval etc.

Commercialisation

The final phase of the preclinical commercialisation assessment focused on partners in the wound healing and the big pharma with the capacity to commercialise the technology. Activities in this phase included identifying and contacting partners, preparing review material including an Information Memorandum, one pager, web page (see www.gap573.com) and a PowerPoint presentation. Communications with potential partners included; face-to-face meetings at Ausbiotech 2011, email correspondence and phone conversations.

By comparison to similar projects there was a high level of interest in the technology. 40% of big pharma companies initially contacted agreed to meetings and/or requested further information, with an additional 25% companies expressing interest after follow-up when they were informed that the active ingredient could be synthesized rather than extracted from animal sources. For the specialist wound healing companies, 45% expressed interest in the technology and wanted to undertake a more in-depth review of the information provided.

Discussions with a number of companies are continuing with a view to licensing the technology. For some companies the technology is either at a too early stage of development or is not in their immediate area of interest. Feedback from companies in the wound healing space indicates that considerable value can be added to the technology by completing phase 1 clinical trails.

3.0 CONTENTS

4.0 BACKGROUND

4.1. A specific bioactive from bovine eye lenses has been isolated and identified to significantly improve wound healing and has been selected for the MLA's bioactive hit list. Recent developments and associated testing has opened opportunities for new products and new approaches to manufacture. This project had the objective of providing key commercial information required to formulate a commercialisation strategy.

4.2. Specifically this project reviewed the technology and its potential applications, summarised the patents submitted and reviewed other patents in the field, compared the manufacturing process of the peptide using extraction from the bovine eye lens and using synthesis in a GMP facility in a range of volumes, looked at the regulatory and reimbursement path to market for a wound healing product incorporating the peptide, and finally the commercial opportunity the peptide presents - with a focus on wound healing applications (including market size and competitive companies and products).

4.3. In summary, this project provided the data essential to the development of a commercialisation strategy that provides the highest likelihood of commercial success.

5.0 PROJECT OBJECTIVES

5.1. Specifically the project involved focussing on six specific areas:

- **Technology** including summarising the mode of action, potential applications and pre-clinical data.
- **Patenting** including patents submitted and a review of competitive IP.
- **Manufacturing** including summarising an extraction process and then costing the process for both the lens extraction from cows at an abattoir and the specific peptide extraction using a batch process. This costing would then be compared to a number of quotations from a range of peptide synthesising companies who have GMP accreditation.
- **Regulatory** including defining the class of device and the regulatory pathway in Europe and the US.
- **Reimbursement** overview in both Europe and the US including the approach, decision makers, information required and timing issues.
- **Commercial** including market size and growth, segmentation, competitors and their product portfolio and hence potential strategic partners.

6.0 METHODOLOGY

6.1. Questions were formulated for each key area of commercialisation and were then systematically addressed. These included:

Technology

- What is the background of the technology and what does it do?
- What are the potential applications and what data is required to complete an initial proof of concept?
- What testing has been performed and what are the results?

Patenting

- What patents have been submitted?
- What other patents have already been lodged or approved by other groups in a similar field?

Manufacturing

- What is the process for extraction of the peptide from bovine lenses and how practical is it, both from a manufacturing and cost perspective?
- How easy is it to synthesise the peptide in volume? What companies can manufacture a synthetic version and at what cost?
- From the answers to these questions, is bovine lens extraction or synthesis from raw materials the preferable method for manufacture?

Regulatory

- With respect to a wound healing application, will the regulatory pathway be pharmaceutical, biologic or a medical device? And if a device, what class is it?
- What are key issues to consider in development from a regulatory perspective?

Reimbursement

- What is the approach for reimbursement in the US and Europe?
- Is it different for different areas?
- Who makes the decision? Who is the submission made to?
- What information is needed? e.g. health economics, comparison to existing devices/pharma etc
- Are there existing reimbursement codes for this type of pharma e.g. from competitors?
- Is there different or additional clinical work to device approvals by regulatory authorities?
- At what stage is the submission made relative to regulatory submissions?
- How long does it take?

- What are the key issues to understand for reimbursement when planning product development?

Commercial

- What is the market size for wound healing products?
- What competitors are in this space and in what specific segments?

6.2. From the answers to these questions, an Information Memorandum was prepared which provided the background to a webpage, a one page handout and presentation to potential partners.

6.3. Initial communications were held with companies with the goal of forming partnerships for the next stage of commercialisation and/or understanding what else is needed for a formal partnership, license agreement or spin-out company to be established.

7.1 RESULTS

7.1. Technology

What is the background of the technology and what does it do?

Industrial Research Limited (IRL), a government research institution in New Zealand, and Meat and Livestock Australia (MLA) initiated a research partnership in 2002 the purpose of which was to identify biologically active compounds in the waste streams from meat processing works. An extract from the bovine lens was identified with the ability to stimulate endothelial cell migration (angiogenesis) and wound healing. The active ingredient of this extract was identified as a novel peptide called *GAP573.* The IP around the lens extract, mode of action and peptide sequence has been captured in two patent families with Dr Keryn Johnson of IRL as the inventor.

The accelerated healing and therefore faster closure rate found with **GAP573** is due to modulation of gap junction communication. The patented **GAP573** peptide has some homology to proteins involved in cell to cell communication. The peptide is small 573 Da and appears to be able to cross the plasma membrane and get to the intracellular site of action and modulate cell to cell communication.

What are the potential benefits for wound healing applications?

GAP573 when used in combination with an alginate gel has the potential to:

- Promote faster healing, by
    - promoting cell migration,
    - promoting blood vessel formation,
- Reduce inflammation, and
- Reduce scarring.
- Potential pain reduction

In addition the new technology

- can be made synthetically, using simple well defined techniques, at low cost
- is based on an animal-sourced biologic and therefore is likely to have few side-effects
- satisfies a large unmet medical need which is poorly served by current devices

What are the potential applications and what data is required to complete an initial proof of concept?

Given the size and unmet market needs of the chronic wound segments, the development work to date has focussed on combining *GAP573* with alginate dressings. Wounds with an underlying complication of poor blood flow would be suitable for treatment with this peptide. In addition to chronic non-healing wounds the quality of healing is good which provides a suitable cosmetic benefit with reduced inflammation and scar reducing properties a focus on elective cosmetic surgery could also be of significant value.

It is clear however that the platform technology has potential application in a range of areas including:

- A spray formulation for wound healing. This is due to a powder-formulation which stabilises the peptide and allows its slow release.
- Acute wounds. A single dose within four hours of injury has been shown to be most effective. Therefore the peptide could be used in the acute setting or following elective surgery to reduce inflammation and scarring as well as accelerate healing.
- Combination with other wound dressings. The peptide can also bind salts and it has been prepared in a salt complex form with gauze material with for topical application.
- A topical cream. *GAP573* has been formulated into a cream for topical application on skin for a cosmetic type application. The gap junction modulator activity may also enhance penetration into the skin via topical administration due to its ability to reduce cell to cell communication.
- Eye wounds. Ocular targets are also a potential application especially as the *GAP573* is derived from a bovine eye lens. The scar prevention would be very useful in glaucoma surgery to prevent scar formation and blockage of the channel that is cut into the eye to enable fluid movement. Scaring of this wound generates blockage of the channel. Currently this surgery is treated with mitomycin C. A high number of patients do not respond appropriately to the current treatment.

What testing has been performed and what are the results?

Validation of *GAP573*'s ability to stimulate angiogenesis and wound healing has been performed in a number of preclinical models[1] including:

- Bovine aorta endothelial cell (BAEC) migration assays
- Rat aortic ring model (organ culture model of angiogenesis) – 28% promotion of angiogenesis by GAP573 relative to control was demonstrated.
- An ethically approved rat dorsal excisional full thickness wound model- two full thickness wounds 8mm in diameter were made on the dorsal surface of the rat and each animal received GAP573 topically on days 1, 3, 5, 7 and 9. The rate of wound healing accelerated between days 7 to 9 for the test wounds compared to the control wounds over the same time period (fig 1). In addition, complete wound closure was achieved earlier than the control wounds. The faster closure rate suggests that the wound healing process is stimulated at a number of points along the wound healing cascade leading to faster wound closure.

[1] *These results are described in WO2009/029991A1*

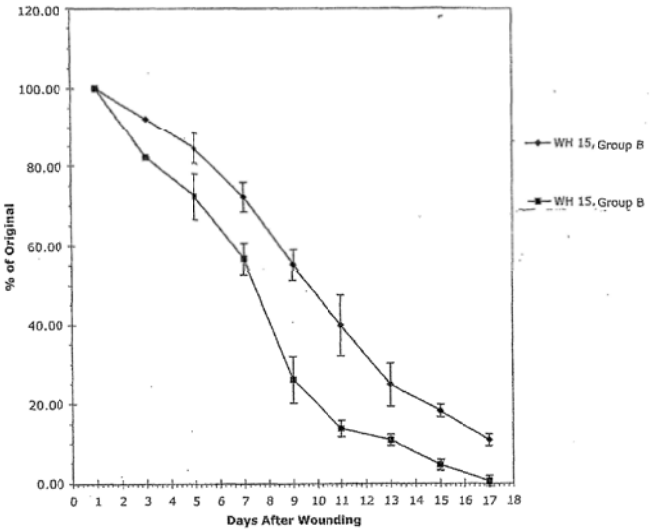


Fig 1. Rat wound healing study.

In addition in a rat study terminated after five days immunological analysis of the junctional zones (healing regions) demonstrated enhanced angiogenesis for the GAP573 treated wounds.

- Pig pilot trials[2]

Pig trials are accepted by the US FDA as a suitable model for the evaluation of wound healing products and the trials described below were independently carried out at Massey University veterinary facilities by Estendart Limited. The trial was ethically approved.

AL-573 wound dressings were manufactured by mixing alginate with *GAP573* peptide. The AL-573 dressing containing GPA573 peptide was compared to the market leading combination dressing Fibracol Plus (Systagenix) using a pig model. Briefly, dressings (18 cm) were applied to wounds (2 cm diameter) along the side of the pig at various time points. Biopsies were taken on days 3, 9, 14, 24 and 42 and the wound area, closure rate, wound gape, number of blood vessels, scar area, cellular content of scars measured. In addition DNA, PBS-extractable protein, 6M urea extractable protein and GAG levels, collagen extraction and immunohistochemical analysis of CD34, CD68, TNF alpha levels, smooth muscle cell actin, E-Cadherin, and Ki 67 were also analysed. This analysis was performed to build up a picture of the wound healing potential of AL-573 wound dressings containing *GAP573* produced and evaluated in this study. The analysis of pig wounds at the various time points provides a snapshot of the wound healing cascade during the inflammatory phase, proliferation phase (which includes angiogenesis) and wound contraction, closure and scar remodelling phases.

In summary, AL-573 wound dressings incorporating *GAP573* had 23% faster healing compared to alginate dressing alone. Fibracol Plus healing rate was 1% slower than

[2] *Industrial research Limited Report No. 2479, "Pre-clinical testing of protein and peptide wound dressing prototypes in pig pilot wound healing study". Complete results can be disclosed under a CDA*

alginate alone. Assuming similar results in humans, the GAP573 alginate dressing would save 2.5 days of care (for a wound of 1000 mm^2).

7.2. Patenting

What patents have been submitted?

PCT Application PCT/AU2008/001319 was filed September 5, 2008 with priority from AU provisional Application Ser. No. 2007904857 filed September 7, 2007 titled "Agents with Angiogenic and Wound Healing Activity" and published as WO2009/029991 on March 12, 2009. National phase applications have been filed in the following countries: USA, Europe, Australia, New Zealand and Japan

This patent describes a method for treating a wound, promoting angiogenesis and/or endothelial cell migration using an effective amount βB2 crystallin protein or an angiogenic fragment of the protein. The crystallin is usually in its monomeric form. Various forms and methods of making and using them are claimed.

A provisional entitled 'Agents for Modulating Cell Signalling' was filed on 12 September 2011.

This patent provides a method for modulating gap junction communication in mammalian cells, comprising treating the cells with an effective amount of a peptide having a specific amino acid sequence.

What other patents have already been lodged or approved by other groups in a similar field?

A patent search was undertaken using appropriate key words by a specialised contractor. The identified patents were reviewed for relevancy and the results were included in a patent review document. Several closely related patent were identified by the IP searches and comments addressing the various patent were made in defence of our IP families. Removal of claims related to alpha A crystallin protein were undertaken at national phase as this protein had already been identified as having wound healing potential in a number of publications.

7.3. Manufacturing

What is the process for extraction of the peptide from bovine lenses and how practical is it, both from a manufacturing and cost perspective?

The eyes are a normal part of the carcase that is treated as waste and rendered. The extraction process costed included removing the lens from 1000s of cow eyes in the abattoir until an amount of about 100kgs is reached (typically one days supply from a large abattoir). The lenses would then be frozen prior to transportation to a dedicated extraction facility. The peptide is then extracted and precipitated using a wet chemical process using multiple steps. These steps would be performed in a large extraction tank.

A number of significant risks were identified with this process including practicality and cost of process, reliability of supply and quality control. It was also identified that there would be minimal reduction in cost from increasing the batch size. Normally volume efficiencies are important to take advantage in any type of manufacturing.

How easy is it to synthesise the peptide in volume? What companies can manufacture a synthetic version and at what cost?

There are numerous companies around the world that specialise in the synthesis of peptides for multiple uses including medical applications. Five (5) companies were contacted that had the capability to supply suitable volumes and with Good Manufacturing Practice (GMP) facilities. Quotations were then received for the supply of various amounts of peptide.

From the answers to these questions, is bovine lens extraction or synthesis from raw materials the preferable method for manufacture?

It is clear from an analysis of the complexity and risks associated with the extraction process and the volume discounts in the supply of synthetic peptide, that synthesis is the recommended method for manufacture of the peptide.

The estimate for manufacturing 40g of peptide using the extraction process was twice that of the synthetic material. There were also significant economies of scale for larger weights of the synthetic peptide which would most likely increase the difference in cost of peptide from the synthetic supply versus the extraction method.

It is important to note that the cost of the extraction process could be further optimised to further reduce costs. Potentially the number of steps could be reduced which would decrease the cost of the process. However, the major portion of the cost of the extraction from the natural source appears to be arising from the extraction of the lenses. It is possible that a process using customised automated equipment could reduce the costs significantly. However allowing for a reasonable profit for the red meat industry per animal the cost is still more than the cost of the synthetic material.

Not only is it estimated that the synthetic route to manufacturing is significantly lower cost compared to extraction, it also has other benefits. These include:

- Competitive price point obtained.
- Faster to market as no new manufacturing facility will be required and many existing peptide manufacturing facilities are GMP-approved, meaning that they are suitable for biomedical applications.
- Supply chain is simpler – peptide manufactured in one commercially and GMP proven facility. These suppliers already exist whereas the whole extraction process would need to be developed and proven.
- Minimal Quality assurance/Quality control steps.
- More options for selection of supplier, or backup suppliers. Therefore less risk in losing continuity of supply.
- No risk with respect to infectious agents such as BSE.
- Easier and less costly Product Insurance.
- Likely further reductions in the costs of synthesis with introduction of new technologies and increasing competition.

These reasons make it easier from a licensing strategy point of view. The technology becomes saleable and there are no limitations in being able to address a significant portion of the market(s).

7.4. Regulatory

With respect to a wound healing application, will the regulatory pathway be pharmaceutical, biologic or a medical device?

An alginate gel is a medical device and in Europe, based on the information provided, the peptide would be classified as a pharmaceutical. Together they would be classified as a class 3 medical device.

In the USA, when the peptide is an alginate gel it would be a combination product but given its principle mode of action is the peptide, the FDA Office of Combination Products advised it would be referred to the Centre for Drug Evaluation and Research and therefore be treated as a new pharmaceutical.

What are key issues to consider in development from a regulatory perspective?

The following flow diagram gives and overview of the process. Understanding all parts of the process is critical. These issues include Good Manufacturing Practice (GMP), Quality Management Systems (QMS), Risk Management, Design Controls, Pre-clinical testing, Clinical Evidence, clinical trials

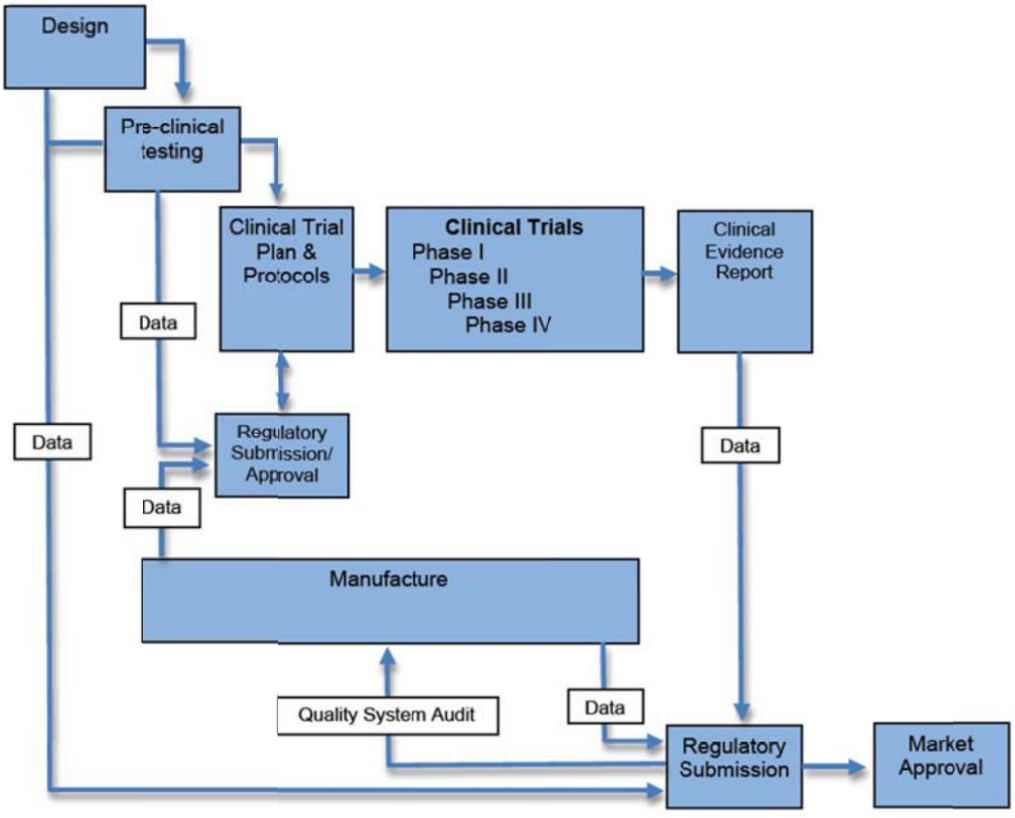


Figure 1: Generic Regulatory Process Overview

7.5. Reimbursement

What is the approach for reimbursement in the US and Europe?

The U.S. payer community is made up of a number of payers including Medicare, Workers' Compensation, Private/Commercial Insurance, Champus/TRICARE and Medicaid. Many payers utilize the Medicare model as a basis for their coverage and payment methodologies. HCPCS II codes are used for supplie , Durable Medical Equipment, drugs and medical devices. The most common codes utilized for drugs are J-codes and A-codes are the most common codes utilized for medical and surgical supplies.

In Europe there is no harmonized system for reimbursement of medical devices. Each country has its own individual system with reimbursement decisions being made at the national level and in some countries, even at a regional and local level. Although there is no harmonized system of reimbursement in Europe manufacturers may have to face similar expectations from authorities, in terms of demonstration of medical benefit and relevance of cost for healthcare system. All the reimbursement systems across Europe are facing budget concerns, this is why, both demonstration of medical and economic benefit is crucial.

Is reimbursement different for different areas?

Typically reimbursement is uniform across the whole of the US. However each European country has its own system with reimbursement decisions being made at the national level and in some countries, even at a regional and local level. There are two systems to consider: hospital/inpatient and ambulatory/outpatient. The hospital funding system is quite similar across different countries; the outpatient is totally different form country to country.

Who makes the decision? Who is the submission made to?

The U.S. payer community is made up of a number of payers including:

Payor Category	Funding Source	Eligibility
Medicare (CMS)	Federal Government	• Over the age of 65 • Disabled • End Stage Renal Disease
Workers' Compensation	Employers	• Work related injury or illness
Private/Commercial	Individual Premiums	• Employees/Families • Individuals
Champus/TRICARE	Federal Government	• Active Military/Families • Retired Military/Families • Disabled Veterans
Medicaid	State and Federal Government	• Low Income

Each payer functions to a great extent as an independent entity—making their own coverage, benefit and payment determinations. The definition of “medically necessary” and “experimental or investigational” will vary by payer.

For inpatient/in-hospital, devices, all the Western European countries have adopted Diagnosis Related Group (DRG) system. A DRG is a code that covers a wide range of diagnoses and treatments. This code will be used for the prospective payment of medical services provided during the hospitalization. Those DRG systems are the basis of the in-patient settings, coding and tariffs with national and/or regional specificities. Each patient, at discharge, is associated to a DRG code, with a specific tariff. A tariff is determined for each DRG, taking into account expenses related primarily to patient hospitalization, including diagnostic, medical and surgical procedures as well as MDs (single use consumables, implants, equipment). The DRG gathers all the different costs. The medical staff has the opportunity to use different device in order to treat the patient, but has to always keep in mind the threshold of the DRG tariff. This means that if they spend more money in something they must spare it somewhere else.

With respect to outpatient/ambulatory in Europe the reimbursement environment is totally different from country to country. Some countries have some specific positive list with dedicated reimbursement coding and tariff for trademark name product, some other propose generic description with a single tariff for all similar products. The tariff could be fixed at national level, fixed and adapted locally/regionally or even free.

What information is needed? Eg health economics, comparison to existing devices/pharma etc

In the US, new technology payment opportunities exist for new technology which meets specific criteria including: Technology must be new. Existing payment must be inadequate. Technology must represent “Substantial Improvement” over previous therapies ie must be beneficial over current treatment approaches eg easier, faster, cheaper and/or better.

In Europe the information varies from country to country but typically three files should cover most situations. 1) “Identification of the demand”: details on the manufacturer, contact person, type of request… 2) “Medical & Technical File” details on product, pathology treated, indication, use, epidemiology…details on the clinical benefits & risks, details on the current therapeutic strategy and the place of the device in this strategy, details on the improved benefit brought by the device compared to other validated competitors’ device. 3) “Economic File”: impact of the device on healthcare system (patients + economic + use) based on clinical data. pricing arguments such as International recommendations, level of pricing in other countries, FDA approval…

Are there existing reimbursement codes for this type of pharma eg from competitors?

In the US currently there is no established code which accurately and adequately describes a drug which is based on a peptide salt formulation, modulates/regulates biomechanical pathways and/or designed to improve the rate and quality of wound healing, scar reduction and wound closure.

Whereas in Europe there are devices with specific codes but they do not appear to have the same mode of action as GAP573.

Is there different or additional clinical work to device approvals by regulatory authorities?

The approval requirements for the FDA and the requirements for the payers are quite different. FDA approval is required to market and sell the product, request coverage from a payer and request a new or modified code. The goal is to have as much reimbursement planning done in advance of FDA clearance, so upon FDA clearance the reimbursement strategies are implemented.

Approval Requirements	
FDA Clearance	• Does the clinical data support the claims? • Is the new technology safe and effective for its intended use(s)?
Payors/Purchasers	• Does the technology improve health outcomes? • How well does the new technology work compared to the current standard of care? • How much does this treatment cost compared to the current practice? • Is the extra cost justified by the gain in quality or clinical outcomes? • Are there savings without reducing the quality of care? • When should the treatment be used? • What is the profile of the patient who would benefit the most?

In Europe, the level of expectation is different regarding the regulatory approval and reimbursement. For regulatory authorities there is a need to demonstrate the safety and performance, for reimbursement authorities it is important to demonstrate efficacy safety and even in some countries clinical effectiveness.

At what stage is the submission made relative to regulatory submissions?

Once regulatory submissions are made reimbursement approval requires an additional 4 tasks: writing and submitting the code application, Medical Society advocacy and support, Development of key messages/presentations and a presentation to a Work Group. There needs to be FDA approval before a new Code is issued.

The regulatory submission for CE-mark should be done as soon as the relevant data is available. The duration of this process will depend on the complexity of the file. This also applies to reimbursement approvals.

How long does it take?

In the US, it is a lengthy process for a new code – it can take years. It is recommended to plan and execute the reimbursement strategy, while undertaking the regulatory process.

What are the key issues to understand for reimbursement when planning product development?

- It should be part of the planning process and addressed during product development not as a separate task at the end of the development process.
- Collect economic data as part of the clinical trial so that an economic and cost effectiveness analysis can be completed. Results can be utilized to demonstrate the

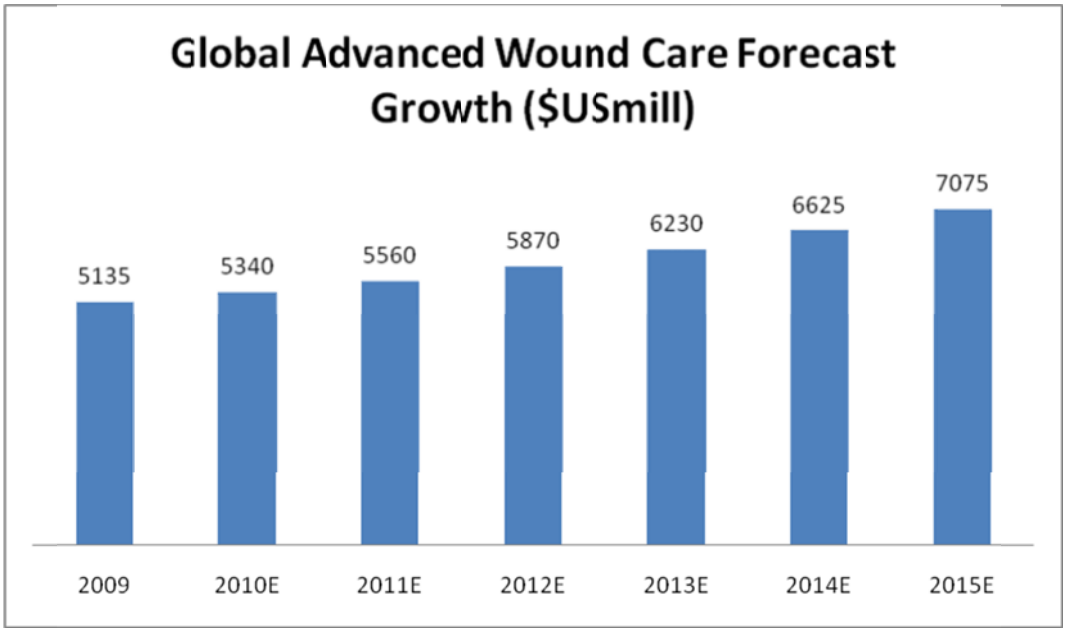
benefit and value of the therapy in a publication strategy, code application, sales messages, etc.

- Once the clinical trial has started, identify which physicians have relationships with society members who are in leadership positions (i.e. American College of Surgeons, American Society of General Surgeons, Wound Healing Society (WHS), Symposium for Advanced Wound Care (SAWC) and European Tissue Repair Society (ETRS) etc.)
- Develop a plan to work with the physicians to initiate a dialogue with Specialty Society CPT/Health Policy Advisors to educate them on the new technology, clinical outcomes, potential savings, value, etc. The goal is to gain their support and collaboration for submitting new code applications.
- The key issue is your capability to bring enough data to be able to negotiate first with hospital for inpatient use and then with authorities to get registration for ambulatory care

7.6. Commercialisation and Partnering

What is the market size for wound healing products?

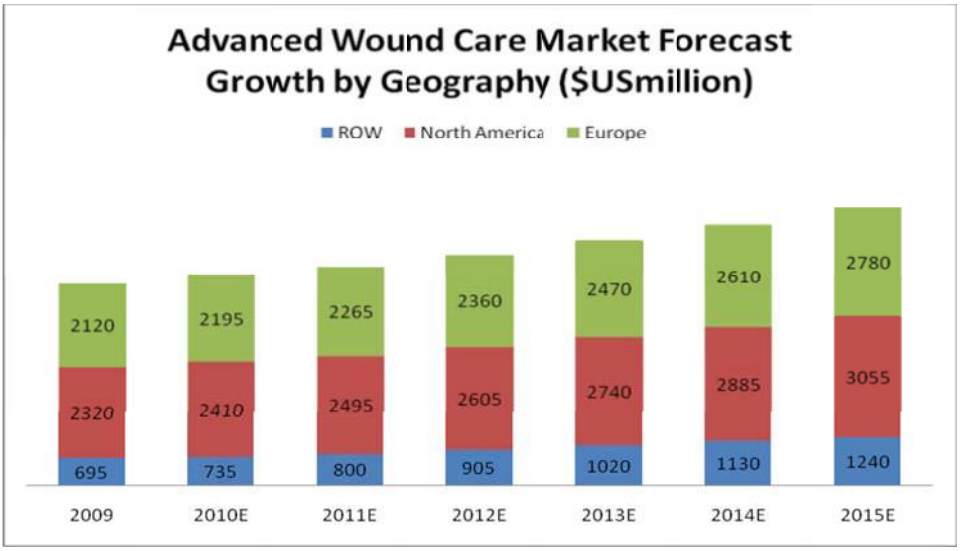
Globally[3], the size of the advanced wound care market was approximately $US5.1 billion in 2009 and is estimated to be worth $US5.5 billion in 2011. The market is forecast to grow at 5-7% each year over the coming 4 years. This equates to a forecast market size of $US7billion in 2015. The market details including size and forecast growth and geographies and product category segments[6] are shown in the following sections.



[3] The Global Advanced Wound Care Market to 2015 November 2010 Espicom Business Intelligence

Geographical segments

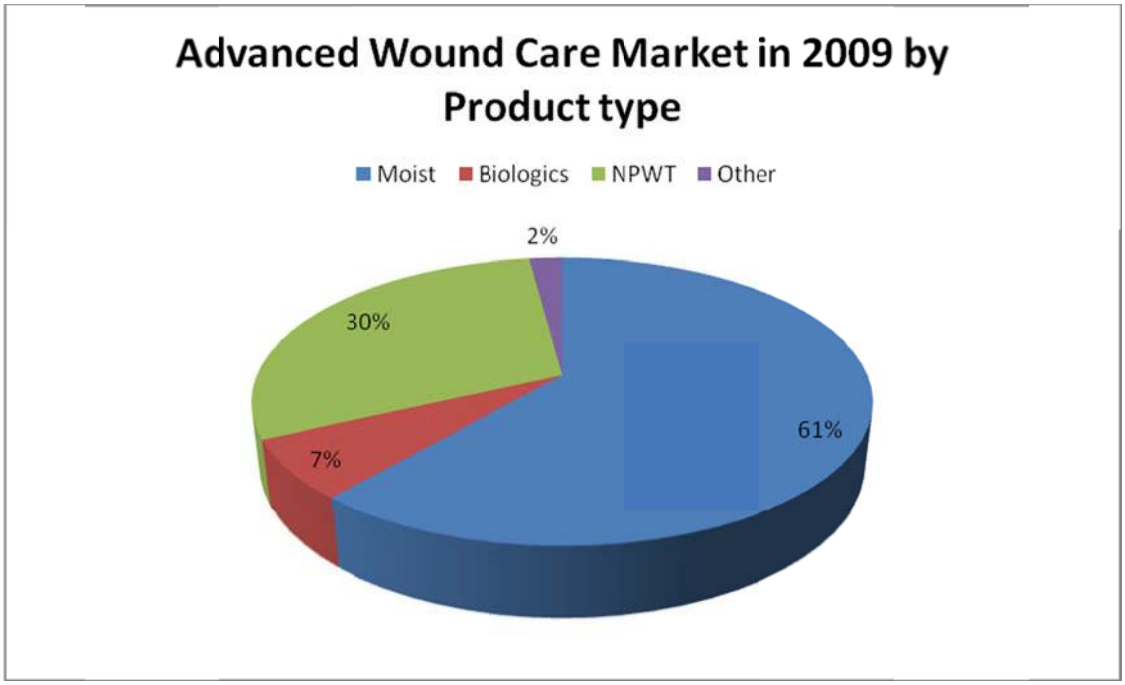
In 2009, healthcare costs for wound care in the US alone were estimated at $20 billion, with more than $4 billion spent on wound care products to treat an estimated 3 to 5 million chronic wounds[4]. Approximately $2.3 billion of these products are for treating chronic wounds – so called advanced wound care products. This equates to 45% of the global market. According to U.S. healthcare statistics, the average cost of treating a wound ulcer is $5,000 to $25,000, depending on the severity and the patients' response to treatment. It is projected to increase to $6.3 billion by 2014, which represents a CAGR of 12.5%. The size of the European market was estimated to be a similar amount.

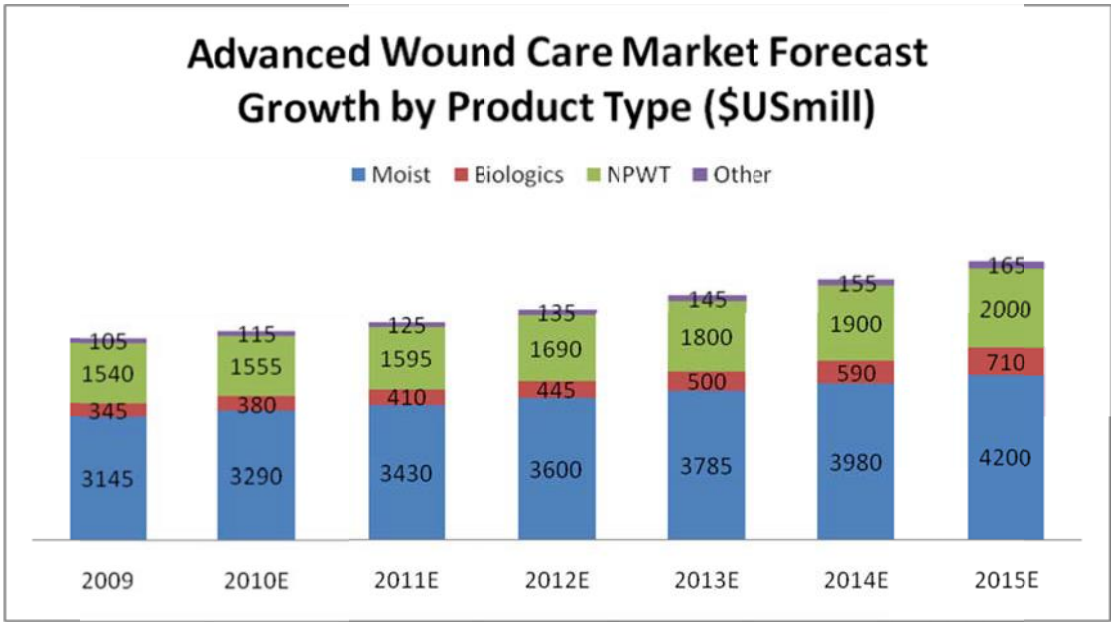


[4] Drug-device Combinations: The Global Market Report Code: PHM045B Published: January 2010 BCC research

Product segments

There are 3 main types of product segments in the advanced wound care market – moist wound dressings, biologics and negative pressure wound treatment. The relative market share is broken down in the following pie chart and the forecast growth by product type in the following bar chart.





The cornerstone of the advanced wound market is moist wound dressings which includes hydrogels, hydrocolloids, foams, transparent films and alginates. Moist wound healing is intended to provide the moisture required for cell growth. The wound exudate serves as a transport medium for a variety of bioactive molecules such as enzymes, growth factors and hormones. The different cells in the wound communicate with each other via these mediators, helping to co-ordinate the healing process. Wound exudate also provides the different cells of the immune system with the conditions to destroy invading pathogens such as bacteria, foreign bodies and necrotic tissue, reducing the rate of infection.

Device therapies are dominated by Negative Pressure Wound Treatments (NPWT) or topical negative pressure and vacuum-assisted therapy, which involve the application of controlled levels of sub-atmospheric (negative) pressure to a wound to accelerate debridement and promote healing. The aim is to use negative pressure to create suction, which drains the wound of exudate and influences the shape and growth of the surface tissues in a way that helps healing.

Much of the growth dynamic is coming from the biological dressing segment of the market. Biological dressings improve healing rates, thus shortening hospital stays and reducing costs. Examples of biological dressings are artificial skin, collagen-based dressings as therapeutic agents, and various growth factors. Besides the always-improving synthetic dressing materials, newer technologies in treatment include the xenogeneic tissue scaffold, bilayered human dermal substitutes, recombinant growth factors, endoscopic subfascial ligation of venous perforators, and endovascular arterial repair techniques.

Combination products

Combination products represent some of today's most promising areas in advancing patient care for instance drug eluting stents.

There are numerous drivers of these technologies, the principle one being the broad need and desire for enhanced outcomes in safety and effectiveness. Combination products increasingly incorporate cutting-edge, novel technologies that hold great promise for advancing patient care. Combination product technology can also enable safer and more effective technologies due to local administration and individualized therapy.

The development of combination products in advanced wound care is no exception. Already approximately 15% of the advanced wound care market is made up of combination products and this percentage is forecast to increase.

MARKETS FOR BIOLOGICAL WOUND CARE PRODUCTS THROUGH 2014 ($ BILLIONS)[5]

Market Segment	2008	2009	2014	CAGR%, 2009-2014
Total advanced wound care ($ billions)	3.4	3.5	6.3	12.5
%Share as combination products	15.0	15.0	25.0	-
Value of combination products	0.51	0.53	1.6	24.7

AL-573 combination product currently in development includes an alginate gel with a patented natural biologic (GAP573 peptide). Consequently this product:

- is positioned in the right segment, and
- has promising preclinical results emphasising its significant promise as a future solution.

What competitors are in this space and in what specific segments?

The following pie chart shows the breakdown of the US market by competitors[6]. Kinetic Concept's (KCI) leadership in the advanced wound care market is largely driven by their long standing dominance of the NPWT market. Their other main presence is in the biologics (active therapies) segment with skin graft substitutes. Market players like Systagenix, Smith & Nephew, 3m, and Convatec have established strong brand reputation through various forms of advanced dressings. The market is fragmented with a wide number of specialty developers who have expertise in various forms of advanced dressings.

[5] Drug-device Combinations: The Global Market Report Code: PHM045B Published: January 2010 BCC research
[6] U.S. Advanced Wound Care Market N71A-54 August 2010 Frost & Sullivan

8.1 DISCUSSION AND CONCLUSIONS

8.1. Technology

A collaboration between MLA and IRL has developed an advanced wound care dressing which combines a moist alginate gel with a patented, animal-derived (but synthetically manufactured) peptide – *GAP573*. The peptide mediates wound healing though down regulation of gap junction communication and thus promotes healing through stimulation of angiogenesis resulting in a reduction of inflammation and scaring and acceleration of wound closure rates. A number of *in vitro* and preclinical models[7] have been used to validate *GAP573*'s ability to stimulate angiogenesis and wound healing. In pig trials *GAP573* when incorporated into an off-the-shelf alginate gel demonstrated significantly (23%) faster wound healing compared to alginate alone or Fibracol Plus, a market leading combination product. *AL573* wound dressing is designed to accelerate healing of chronic wounds with poor blood flow such as venous leg ulcers, foot ulcers or pressure ulcers. The accelerated wound healing has a number of benefits including:

- less complications due to faster closure rate
- cost effective treatment - Lower costs from the reduced number of dressing changes, reduced nursing care contact time and less time in hospital
- getting people back to their normal life faster – at home and/or at work

8.2. Patenting

- The intellectual property is jointly owned by MLA and IRL.
- Initial platform patent is at a National phase. PCT Application PCT/AU2008/001319 was filed September 5, 2008 with priority from a provisional patent filed September 7, 2007 titled "Agents with Angiogenic and Wound Healing Activity".
- A second provisional patent application entitled 'Agents for Modulating Cell Signalling' was filed on the 12th September 2011.
- A patent landscape report reviewed relevant patents which were identified from a search using appropriate key words.

8.3. Manufacturing

The forecast costs of extraction process were approximately; double that of the synthetic material sourced from a range of suppliers (under GMP). There were also significant economies of scale for larger weights of the synthetic peptide which would most likely increase the difference in cost of peptide from the synthetic supply versus the naturally produced extracted peptide.

It is important to note that the cost of the extraction process could be further optimised to further reduce costs. Potentially the number of steps could be significantly reduced which would decrease the cost of the process. However, the major portion of the cost of the extraction from the natural source appears to be

[7] *These results are described in WO2009/029991A1*

arising from the extraction of the lenses themselves. It is possible that a process using customised automated equipment could reduce the costs significantly.

Forty grams of peptide at 2mg per 100cm^2 bandage would be used to produce 20,000 bandages. It is believed chronic ulcers would be the best initial application which has a prevalence of about 1.5 million cases per year in the US. If it is assumed that each patient has 3 bandages per treatment to achieve success then 40g of peptide can treat about 7,000 patients which are only about 0.5% of the addressable market in the US.

8.4. Regulatory Overview

The product is a combination device of an existing device (alginate gel) and a therapeutic (the peptide which down regulates gap junction communication). In Europe this would be a class 3 medical device and in US would be directed towards the FDA Office of Combination Products who would most likely refer the submission to the Centre for Drug Evaluation and Research. The process towards regulatory submission and approval needs to be carefully planned. Understanding all parts of the process is critical. These issues include Good Manufacturing Practice (GMP), Quality Management Systems (QMS), Risk Management, Design Controls, Pre-clinical testing, Clinical Evidence and clinical trials.

8.5. Reimbursement in US and Europe

It is expected that new codes would be required for the product and this process can be long and arduous. In the US there are multiple payors to consider including Medicare, Workers' Compensation, Private/Commercial Insurance, Champus/TRICARE and Medicaid. In Europe there is no harmonized system for reimbursement of medical devices. Each country has its own individual system with reimbursement decisions being made at the national level and in some countries, even at a regional and local level. There are two systems to consider: hospital/inpatient and ambulatory/outpatient. The hospital funding system is quite similar across different countries; the outpatient is totally different form one country to another.

In the US for a new code to be issues the technology must be new, existing payment must be inadequate, technology must represent "Substantial Improvement" over previous therapies. In Europe, typically three files should cover most situations. 1) "Identification of the demand": details on the manufacturer, contact person, type of request… 2) "Medical & Technical File" details on product, pathology treated, indication, use, epidemiology…details on the clinical benefits & risks, details on the current therapeutic strategy and the place of the device in this strategy, details on the improved benefit brought by the device compared to other validated competitors' device. 3) "Economic File" with impact of the device on healthcare system (patients + economic + use) based on clinical data, pricing arguments such as International recommendations, level of pricing in other countries and FDA approval.

8.6. Commercial

The unmet market need for *AL573* wound dressing is large and is predicted to grow at 5- 7% over the next 4-years. The global advanced wound care market was approximately $US5.1 billion in 2009 and is forecast[8] to grow to $US5.5 billion in 2011 and $US7billion by 2015. Key drivers for growth are the aging population, the need for reduce health care costs and the growing prevalence of obesity and diseases such as diabetes that increase in the number of people with chronic wounds such as foot ulcers.

GAP573 provides a platform technology that due to high flexibility in its ability to be formulated provides for a range of other potential applications including sprays, topical creams, treatments for eye wounds and drug eluting stents.

In summary, *AL573* is an advanced wound care dressing that is a simple to use and manufacture medical device used for the treatment of chronic wounds. The device addresses a large, growing and unmet market need. The dressing is based on a synthetically produced but animal-derived peptide, *GAP573,* which mediates its effect by down regulation of GAP junction communication. This novel mode of action provides opportunities to develop generic technology with healthcare applications beyond wound healing.

The next stage of commercialisation should involve partnering with an established wound healing company or a big pharma company for the commercialisation for a number of applications. These discussions have been initiated and are currently at an early stage.

[8] The Global Advanced Wound Care Market to 2015 November 2010 Espicom Business Intelligence