APPENDIX A

BUSINESS CASE

BY

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Executive Summary

NacreTech is a material and manufacturing platform based upon research that is being developed within Victoria University of Wellington. It relies on the further development of a unique biomaterial, which has the potential to be used as a scaffold for bone growth.

The biomaterial consists of a flexible polymer matrix which is strengthened through the crystallisation of a secondary compound into the matrix surface. The combination of the matrix and the secondary compound is hypothesised to allow for a rigid, but not brittle, material with similar strength to bone. A specific porous macrostructure is considered to be crucial for supporting bone growth while retaining strength. This combination of features is considered to give the NacreTech biomaterial a competitive advantage.

Traditional methodologies are unable to create the detailed porous structure. Hence a bottom up process such as 3D printing is considered to be the best method of manufacture as it can allow the biomaterial to be tailored for many different applications

Discussed in detail is a potential initial application of the biomaterial as a bioactive bone screw. Currently most available bioactive bone screws are made with poly-lactic acid (PLA) as a base material, which results in the following identified problems: weak material strength resulting in breakage, fast degradation rates resulting in incomplete healing or holes left in the bone and harmful acidic by-products which impede healing, lack of reliable clinical data and trust by surgeons.

The bone screws produced by the NacreTech product platform are anticipated to overcome these existing problems, due to the attributes of the material. Specifically, the porous macrostructure will increase bone growth rates, while the base material reduces the rate of degradation.

The vision of the NacreTech platform is not a single market application, such as bioactive bone screws, but a range of different product lines. The ability to 3D print will enable adaptive manufacturing of the biomaterial for new applications without the expense of developing a new production process. Initially, the product line could easily expand to produce bolts, pins, plate systems, and other bioactive implants for use in orthopaedic applications.

The long term vision is the manufacture of personalised orthopaedic implants. This can be achieved due to the 3D printing which allows for the tailoring of the porosity, strength, degradation rates and design to meet the needs of the patient and the orthopaedic surgeon.

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Introduction

The NacreTech biomaterial platform concept has been developed towards commercialisation as part of the Masters of Advanced Technology Enterprise (MATE). The goal of the MATE course is to provide the participants with practical experience in the commercialisation of university or other advanced research.

The initial project presented to the student participants was from the research laboratory of Professor Kathryn McGrath at Victoria University of Wellington (VUW). The research is based upon a method of producing a material referred to as synthetic nacre. A team was formed around this material with the purpose of determining a market application and planning subsequent development of the enterprise.

The purpose of this document is to provide the initial findings of the NacreTech team. It is recognised that the material is still in the early stages of development. As such, the focus of this document is providing a potential market application, the immediate next steps in the product development and initial legal considerations.

Base Research

The initial research was to mimic the chemical process by which molluscs, oysters, and mussels produce a material within their shells called nacre. Nacre is a naturally formed composite of calcium carbonate, in the form of aragonite, structural protein, and chitin; an example of the resulting material is the semi iridescent inside lining of a mollusc shell (Munro, Green, & McGrath, 2013).

The initial research provided to the team was the method of producing a material similar to nacre which the research team called synthetic nacre. At a basic level this material is a composite of a chitin/chitosan natural polymer scaffold and calcium carbonate in the form of aragonite crystals; the primary difference from the natural form is the absence of proteins and contaminants creating a material that is potentially suitable for medical applications.

The research group developed this material using a combination of known chemical processes which resulted in the surprising and novel formation of the aragonite integrated into the polymer scaffold. Additionally a process to 3D print the chitin scaffold followed by the mineralisation has been shown to work in the laboratory. There are limitations are on the maximum wall thickness of the material which is restricted by limits of diffusion. During experimentation samples have been made in microspheres, films, and printed rings all < 1mm at their maximum thickness.

Team Summary

Research Group

The research group, as lead by Professor Kathryn McGrath, including Dr Natasha Evans provided a support role helping the teams understanding of the research and advice on concept feasibility. The research group would also be responsible for the progression of the material to meet the target product profile.

Business Mentors

The mentors, Jennifer Anderson and Melissa Yiannoutsos from Kerasi limited, provided advice to the team regarding the commercialisation of the research.

Victoria Link

Victoria Link (VicLink) is the commercialisation branch of Victoria University of Wellington. Anne Barnett is a Senior Commercialisation Manager at VicLink who supported the NacreTech team during the MATE program.

Christina Houlihan - Biological, intellectual property and regulatory aspects

The role of Christina Houlihan within the team was initially to investigate the hypothesis that the biomaterial is capable of performing its function as a biomaterial. This was envisaged to involve determining what results are needed to confirm that the biomaterial is capable of undergoing osteoconduction and that it is non-toxic, investigating who would be capable of developing and performing these tests and then potentially arranging completion of said tests.

In the second quarter of the year (June-July), it became very clear that sample was not going be able to be produced and therefore no biological testing was going to be completed this year. As a result, the role within the team changed to focus on the patent strategy and regulatory considerations. This involved taking into consideration what biological testing needs to be completed (as per the previous role) but also to investigate the longer term obstacles associated with obtaining clinical testing results. The patent strategy role involved performing a freedom to operate search (patent landscape), developing a patent strategy which aligned with the overall business strategy and considering appropriate filing dates, locations and methods.

Issues

Due to the specialisation and experience required in the patent and regulatory industry, formulation of specific actions in order to obtain a patent or regulatory approval was not considered to be a part of the role. In addition, as the biomaterial is still in the early stages of development, it was considered too early in the commercialisation of the biomaterial to bring such specialists into the team.

Outcome

In view of the recognition of the early stage of development, the patent strategy and regulatory considerations were considered at a high level and incorporated advice from industry professionals.

Thomas Sobiecki - Biomaterial design, mechanical, and manufacturing aspects

The role of Thomas Sobiecki within the team initially was to learn the process of fabricating synthetic nacre - followed by fashioning specimens and prototypes for mechanical testing as part of proof of concept. A literature review into the current orthopaedic biomaterials and characteristics of nacre identified limitations, effect, and advantages. This review influenced the decision to choose bone screws as an application and later in the development of the target product profile.

While working with the VUW research group the current early stage development status of the material was discovered. This forced a role shift to building the technical targets for the biomaterial and reducing the proof of concept testing component to developing a preliminary plan. Investigating the technical targets evolved to include much of the biological aspects of tissue engineering design and the specialised macrostructures needed for osteoconduction to occur.

As a result of understanding the tissue engineering design aspects it became apparent in the second half of the yearlong project that 3D printing, or another additive process, would be required (as opposed to being an option among many) for fabrication. This eventually led to the development of the single material and adaptive manufacturing system concept, i.e. the NacreTech product manufacturing platform. Additionally the test design recommendations around non-standard degradation were included in the proof of concept planning.

Issues

Due to the early stage development of the material the role evolved from developing specimens and prototypes for testing to developing the technical targets for the material to meet in the future. By not completing any full design, test, evaluate loops the concept and specifications have not been validated.

Outcome

A design concept and technical targets have been developed for a biodegradable osteoconductive load bearing biomaterial which given further development the synthetic nacre material may meet. The single material and manufacturing system concept has been developed to allow targeting a larger market from the single material using 3D printing.

Michael Mettrick - Market research, strategy, and business model development

Within the team, Michael Mettrick's role was to develop the understanding of the market aspects, both customer needs and aspirations, as well as identify how their needs are being met by current competitors. Once the existence of unmet market expectations had been established, the focus switched to the strategic level identifying and developing the optimal business model.

The decision by the team to focus on orthopaedic bone screws guided the primary market research and showed a need to further understand the operating environment. The primary research phase entailed end user interviews with orthopaedic surgeons and nurses. These interviews led to a second round of secondary research to investigate the findings and help the team better understand the end users viewpoints and needs. The next step was to identify the specific surgical application for NacreTech to target as its first product.

Issues

Part way through June 2014 it became evident that the material development was not at a stage where specific applications could be considered. This early stage of material development impacted the market research because we could not target a specific surgical application of the bone screw.

Outcome

Unable to ascertain the material limitations and parameters required to isolate specific material applications caused a shift in focus. Initially the intention was for gathering further detailed market research. Later the role changed to developing the business strategy and gaining further knowledge about the competitive environment. The strategy development was directed towards establishing the best foundation for NacreTech to meet the needs of the users and also the goals of the material owners (VicLink).

Key Decision Points

January

- 6 week intensive course
- Meeting with Anne Barnett of VicLink
- Choose project
- Developed business model canvas
- Formed team

February

- Defined decision making process

March

- Brainstormed potential material applications including: artificial reef, filtration for mining, environmental shotgun pellets, insulator, bone-carving, medical applications, tiles
- Investigation into medical market looking at orthopaedic bone substitute
- Identified strength as a potential advantage (narrowing to load bearing orthopaedic bone substitutes)
- Research indicated that there is market saturation of void fillers with approximately more than 12,000 on the market

April

- Cost per gram for raw materials informed decision to focus solely on medical applications
- Met with Anne Barnett- NacreTech supplied Memorandum Of Understanding (MOU)
- Research team believed mechanical testing would be done by mid-year
- Research team informed the project team about the limitations on manufacturing size leading to the decision to focus on bone screws
- Identified that the screw shape would be technically difficult to manufacture and would provide a good test case for the manufacturing process

May

- Laboratory observations begin regarding learning the process to synthesise the material
- Initial freedom to operate search conducted
- Primary market research started- Interviews indicated a need for active and strong biodegradable bone screws, this need is not perceived as been meet by current products, degradation rate and half-life were questioned informing aspects of the TPP investigation

June

- 3D printer failure delaying compression testing
- Interview with regulatory professionals regarding CE mark and FDA regulatory systems. In particular, FDA specialist suggested a drug master file or that a 510k may be possible
- Further secondary research is started
- National phase entry of patent

July

- Meeting with Professor Kathryn McGrath regarding further material development. Intention of the research team to focus on 3D printing of hydrogels

- Found further research confirming that the current screws are not up to requirements and also find out about screws becoming loose in a competitors screw- used primarily for ACL reconstructions
- Determined that 510k application for FDA approval was not possible due to the material being new to medical applications
- Further manufacturing limitations determined such as the maximum material thickness is less than first understood
- Testing degradation in buffer solution confirmed chitin scaffold did not degrade. Surface reaction occurred transforming the calcium carbonate into calcium phosphate.
- Started developing business case and business model

August

- First major market research report gained- medical device market is growing fast especially the relevant sections of the market
- Determined that the bioactive bone screw would be a class III device requiring clinical trials
- Identified 'Bioretec' as potential model company to mimic and gained their investment prospectus

September

- Obtained copy of second major market research report: Biomaterials a global market overview. Confirmed target markets are growing
- Morgo conference. Group discussion regarding business model and strategy

October

- Top up freedom to operate search identified the Stryker patent
- Confirmation that regulatory aspect will in fact inform some of the organisation strategy, not just cause minor hurdles
- Reconfirmed that further applications for the material are intended in the long run i.e. not just bone screws. This will boost the potential returns as ground regulatory work will have been completed
- Australia Biotech Conference, attended by Michael. Provided information around production, business model, market penetration may be the issue not technology, crowd funding investment model. Informal meeting with Anne Barnett.

November

- Preparation for presentation
- Met with Anne Barnett to discuss our findings

December

- Presentation

January

- Third patent landscape search is performed and nothing significant identified

Market Overview

Introduction

NacreTech intends to bring the next generation of biodegradable materials to the orthopaedic and trauma markets. NacreTech has focused on a potential application of the biomaterial as bone screws. A combination of primary and secondary research established that current bone screws have both technical and reputational problems. Therefore, significant opportunity exists for NacreTech's biomaterial to address these market needs.

The long term goal for NacreTech is to further advance the biomaterial medical market through the production of medical devices with the ability to support natural bone recovery.

Marketing Position

Biomaterials are slowly gaining penetration into the long established medical device marketplace (Industry Experts, 2011). This slow penetration has been limited by both technical and reputational problems. Current biomaterials are used in a wide variety of medical applications from bandages to valve stents, and void fillers to glues. The production of bone screws is intended to be NacreTech's initial market niche.

The biomaterial and intended development schedule of the bone screws are planned to overcome the known technical problems with current materials and products. It is recognised that the initial price of the biomaterial bone screw will be priced above existing bone screws; however, there is the potential for reduced total cost of care and significantly improved outcomes. The intended technical development meant that there is the potential to disrupt the current marketplace for biomaterial bone screws.

The Product

The intended product of NacreTech is orthopaedic biodegradable, load-bearing bone screws. Bone screws are a form of internal fixation used by orthopaedic surgeons to support the bone during the healing process. Internal fixation is largely used in orthopaedic surgeries where serious or critical damage to the bone has occurred. NacreTech has focused on the orthopaedic and trauma markets as the primary proof of concept. Other applications such as orthodontic and Craniomaxillofacial (CMF) will be considered once material development has been completed. In addition, the specific surgical application of the bone screw will depend on the outcome of material development.

Global Market

Globally health expenditure as a percentage of Gross Domestic Product (GDP) is increasing. This global growth is relevant because it represents a market opportunity where consumers are purchasing in increasing volumes which will support business growth. Furthermore it also presents opportunities for products that intend to reduce the overall cost, such as biodegradable bone screws that don't need to be removed. The global nature of this increase in health expenditure is shown below (World Health Organization, 2014) in **Error! Reference source not found.**Figure 1.

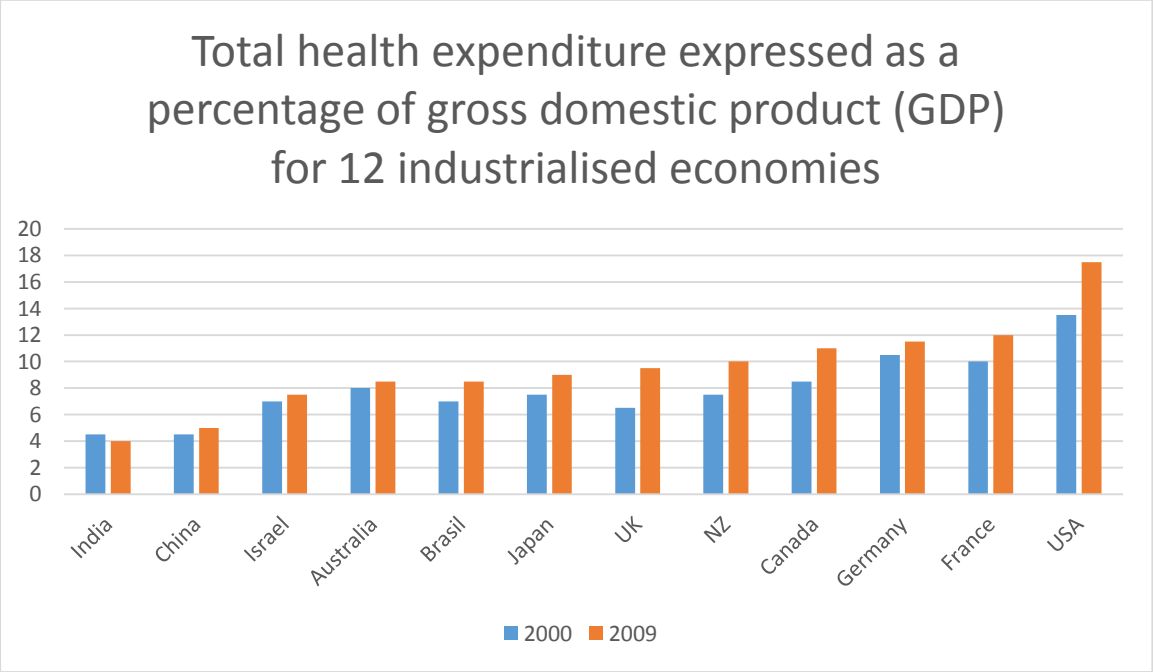

Figure 1: Total health expenditure expressed as a percentage of gross domestic product (GDP) for 12 industrialised economies (World Health Organization, 2014)

Global Medical Device Market

The market segment NacreTech is targeting is medical technology, specifically medical devices for use in orthopaedics and trauma markets. The global medical technology market was valued at over $325 billion USD in 2014, with the expectation that by 2018, total sales will total $440 Billion USD (Industry Experts, 2011). This expected valuation indicates a Compound Annual Growth Rate (CAGR) of 4.5%.

Size of the Orthopaedic Market

Globally, the orthopaedic market accounts for approximately $30.2Bn USD in sales turnover (Industry Experts, 2011). The CAGR of 3.1% indicates that growth is still happening for the overall orthopaedic market. Biomaterial components of the orthopaedic market are growing fast; for

example, within the United States geographic region, orthopaedic biomaterials grew at a CAGR of 11.12%.

Size of the Trauma Fixation Device Market

NacreTech is initially targeting a subset of the orthopaedics markets, the market for trauma fixation. This global market for trauma fixation is estimated at over $6.1 Bn USD (Transparency Market Research, 2013), just under $3Bn USD of that is within the US market. The same United States market sees approximately 41 million visits annually to the emergency department for trauma, of these admissions almost half underwent surgery (Vanderson, 2010).

Synthes, Stryker, and Smith & Nephew collectively dominate the Trauma fixation market supplying 70% of overall market share (Orthoworld, 2010). A large number of SMEs account for the other 30%.

Target Markets

The United States and Europe make up the largest percentage of the global market and have been identified as NacreTech's target markets. The United States accounts for 40% of the global medical technology market and Europe for 30% (MedTech Europe, 2012).

Effect on NacreTech: Analysis of Global Operating Environment

NacreTech is looking to enter the high market growth, orthopaedic fixation market. High market growth, low market share is expected initially and the intention is to quickly grow the business to high market share within the growing market (Morrison & Wensley, 1991). The expectation is that obtaining significant market penetration will be easier within a growing market (Solomon, 2008).

Market Research: Competitive Environment

Approximately 400 organisations from around the world have been identified as selling or developing bioactive materials (Industry Experts, 2011). It is worth noting that the majority of these applications of biomaterials are not focused on the orthopaedic and trauma markets. Most biomaterial selling companies are focused on the larger wound care and cardiothoracic markets.

Only 37 organisations were found to target orthopaedics. Of these 37, only seven were identified as direct competitors selling load bearing bone screws. It is also worth noting that 25 organisations were found to sell bioabsorbable interference screws, which are primarily used in anterior cruciate ligament (ACL) reconstruction. Interference screws are not direct replacements for bone screws, but it is possible that some may be adapted to the bone screw market if they can meet the technical requirements.

Significant Players in the USA and European Markets for Bioactive Bone Screws

Biomet

Biomet is the largest of the identified direct competitors within the current marketplace. In 2014, Biomet had a turnover of approximately $3.2 billion USD and targets the entire orthopaedics and trauma market (Forbes.com, 2014). Biomet is in the process of being purchased by Zimmer, a slightly larger orthopaedics device manufacturer. There are regulatory antitrust concerns about the acquisition, as the EU's antitrust regulators believe that competition would be reduced in some markets due to the size and near monopoly. Biomet has a competitive advantage resultant from their large size and considerable resources.

Bioretec

Originating from Finland, Bioretec develops, manufactures and distributes bioactive medical devices. These devices are solely within the area of bioactive fixation devices (predominantly screws and pins). Last year, Bioretec had a turnover of $681 USD million and were in a growth phase having just completed another round of investment (Anonymous, 2014). With reference to their technical focus and business model, Bioretec are the company the team is trying to mimic; they have built almost their entire company around the concept of bioabsorbable medical devices. Bioretec also has a competitive advantage resulting from their specialisation in the area of biomaterial bone screws.

Conmed

From the United States of America, ConMed manufacture surgical devices. They specifically target general surgery, orthopaedic, sports medicine, gynaecology, gastroenterology, anaesthesiology and pulmonology. Last year ConMed had a turnover of approximately $750 million USD (2014) (ConMed Corporation, 2014). Unfortunately for ConMed recent growth has plateaued and their corporate

management is under threat from activist investors, whom want them to divest or be acquired by another company. ConMed has a completive advantage resulting from a company specialisation in surgical equipment.

Takiron

From Japan, Takiron are a conglomerate focused upon the use of plastics technology. Takiron had a combined turnover of approximately $600 million last year from their diverse portfolio of industry specific companies (Markets.ft.com, 2015). We have not found recent reports of success or failure. Takiron have used their knowledge of plastics to combine the base polymer with another ceramic material. The diversity of Takiron is also a competitive advantage as they not reliant on success any one industry.

Sinobiomaterials Co, Harbin Haiousi Business Co and Gunze trading limited.

Three Chinese companies Sinobiomaterials Co, Harbin Haiousi Business Co and Gunze trading limited have been identified as selling bioabsorbable bone screws from the Chinese market. Currently only very limited information is available about each of these companies beyond product lines. We do know that they have a variety of plastics based products, and also capabilities with multiple types of plastic compositions. Sinobiomaterials Co, Harbin Haiousi Business Co and Gunze trading limited are thought to have a competitive advantage based on their locations within China where there is often considerable government support (Peng, 2012).

Market Research-User Perception

Once secondary market research had been conducted to understand the current literature and operating environment a round of primary market research interviews were carried out. The intention of the interviews was to find out if there was an unmet need with regards to orthopaedic bone screws that could potentially be solved with the application of our material. These interviews were followed by more information gathering and a final survey to quantify the outcomes. The phased processes that we tried to follow was that recommended by literature (Adams, 2010; Zikmund, Ward, Lowe, Winzar, & Babin, 2010).

User Engagement

Interviews were carried out with a small but highly representative sample of senior orthopaedic and trauma surgeons and senior orthopaedic nurses from Wellington Hospital in Wellington, New Zealand. These interviews were qualitative and exploratory in nature with both specific and open-ended questions being asked (Bryman & Bell, 2007). The line of questioning was left largely open to enable freedom within the conversation to induce and explore interesting and useful comments (O'leary, 2010). The interviews were 30 - 45 minutes in length and conducted in May and June 2014.

Significant Findings

One orthopaedic consultant described the current bioactive materials as having limitations, they were either "Strong but not bioactive enough, or bioactive and not strong enough."

The surgeon went on to say that because of this "Bioactive materials are generally not considered for load bearing applications in adults".

This indication of a lack of market penetration for bioactive materials was very interesting to find out, mostly as a lot of the available secondary information does not support this position. Our secondary research indicated that while there had been problems with earlier bioactive materials the current generation were in general, found to meet their clinical objectives, indeed they often produced superior clinical results to the traditional metal based medical devices. Early bioactive screws were found to have problems with some screws loosening over time (Gefen, 2002). These secondary findings pointed away from a focus on the technical aspects holding back biomaterials and instead, user perceptions inhibited market penetration.

A focus upon the degradation process also became pertinent during one of the interviews. The surgeon wanted to know the degradation time and rate was including the half-life strength of our material if it was potentially going to be used in orthopaedic applications. Once mentioned it became apparent that the degradation properties would be very relevant to the user requirements.

Desirable degradation properties have since been added to the biomaterial technical requirements based upon this conversation. Metal implants were also said generally to be removed if possible, this supported the available literature (Hanson, van der Werken, & Stengel, 2008).

The final noteworthy findings are that surgeons are responsible for selecting the medical device that are used during surgery. The interviewed surgeons most commonly find out about new technologies from the sales people that visit them in the hospital.

A follow up survey was also created and circulated but rates of completion were so low they were statistically invalid, however useful information was still gathered that supported the findings from the conducted interviews.

Findings from Ausbiotech 2014

Attendance at the Ausbiotech 2014 conference in late October led to an informal discussion with a representative from the Therapeutic Goods Association (TGA). The TGA regulate the medical device market for Australia. The TGA representative described how he had recently been the TGA investigator for one of our direct competitors products, their bio-absorbable bone screws had flown through the clinical trial with outstanding results. Having previously investigated other similar products for the TGA he said that the ease of gaining regulatory approval was common as recent products had all been successful in the clinical trials. From TGAs perspective there are no major problems with current biomaterial products.

The TGA representative also talked about how these products have only managed small scale market penetration; not because of the technical aspects but instead because of the attitudes of the surgeons that selected the medical devices. The TGA representative described how the actions of the surgeons are justified, and described further that surgeons are specifically trained and instructed in such a way as to instil an air of self-confidence and belief that they are ‘all knowing’. This air of ‘knowing all’ has the advantage that patients are soothed and that trust is boosted in the surgeon. According to ‘Seeing what others don’t’ by Klein (2013) a disadvantage to ‘knowing all’ is that you are not open to insights and innovations. Klein describes how when someone has the perception of ‘knowing all’ they play it safe and relying on existing processes instead of being open to new ones. The playing it safe mentality would therefore inhibit the market penetration of cutting edge medical devices.

Strategic Analysis

A PESTEL analysis is included to cover and identify macro-environmental factors that are expected to or may possibly impact the business (Wheelen & Hunger, 2006). Efforts have been made so that the Strength, Weakness, Opportunity and Threat (SWOT) analysis is useful and relevant to business strategy as suggested by Piercy and Giles (1989).

PESTEL Analysis for Bioactive Bone Screws

Political

Globally there is a strong focus upon limiting or reducing overall healthcare costs. In New Zealand centralisation of bulk purchasing for public hospitals is currently occurring through Health Benefits Ltd. Bulk purchasing means that prices centrally negotiated (Summers, 1989). Funding and support is available to some start-ups in New Zealand, these businesses embody the desire to increase national GDP (Raine, O'Reilly, Teicher, New Zealand, & Ministry of Science and Innovation, 2011). The implementation of Obamacare in the US is progressing towards collective bargaining for medical devices when they are sold within the country (Gleckman, 2014). The Trans Pacific Partnership Agreement (TPPA) which is currently under negotiation may also impact the international medical device market, currently these negotiations are secret so the potential impact is unknown.

Economic

Strong global economy. Risk of war in Eastern Europe does threaten some economic stability, as does the current Arabian conflict. Internationally there is interest in health economics and bringing down the overall cost of healthcare.

Socio/Cultural

The broad variety of international markets makes this area overly generalistic. Nonetheless, globally there is an increasing awareness of, and, acceptance for bioactive materials among the general public (medicaldevicedevelopments, n.d.). Desire for a bone substitute that is as suitable as an allograft but one that does not require additional surgeries to extract from the patient (Truumees & Herkowitz, 1999). Globally there is an increase in health awareness(Nielsen, 2015). Indications of change with regard to the amount of evidence that is required to support device efficacy.

Technological

There are a lot of competing technologies and research institutes/companies in the field of biomaterials (Industry Experts, 2011). Therefore it is a very competitive, technologically focused marketplace. Patients were found to generally be accepting of technological advancement but medical professionals were found to be lagging(Or & Karsh, 2009; Yarbrough & Smith, 2007).

Environmental

Minimal impact on the environment identified. The one exception for this is regarding the sourcing of large quantities of chemically uniform chitin for the manufacturing process.

Legal/Regulatory

Proposed changes to the Food and Drug Administration (FDA) and EU medical device regulatory systems may increase examination costs to prove efficacy and safety of proposed devices.

SWOT Analysis of NacreTech

Strengths

- Novel material has had a patent application that has been filed in multiple markets, this application creates the foundation for the intellectual property strategy.
- Development work is already underway to meet the Biomaterial Technical Properties (BTP).
- Intended products look to meet the needs of the global interest in health economics and overall cost/benefit analysis.

Weaknesses

- Lack of funding relative to the required investment.
- Current lack of dedicated team taking over once the MATE program concludes.
- NacreTech does not currently have a presence in the market.
- NacreTech does not currently have a science advisory group, or board of governance.
- Costs required to meet the BTP are expected to be considerable. Development costs are also expected to be considerable.
- May not be possible to meet the BTP within a reasonable time as it relies on a number of factors aligning.
- Current base material has not been used in internal medicine, potentially causing delays or blockages. Proof of concept testing and clinical trials are expected to be required, as are the associated costs.
- Possibility that even after, considerable development the current material may not be able to meet the requirements of the BTP.
- Currently only one single patent lodged to protect the material from imitation and theft.
- Additional capabilities and resources are needed within the development team.
- An inexperienced team.
- Physical distance from intended markets. Coming from New Zealand but targeting markets on the opposite side of the world.
- End product is expected to cost more than alternative products, especially metallic screws.

Opportunity

- Market research indicates global demand would be considerable for the type of product proposed.
- Limited number of identified direct competitors.
- BTP for massively scalable product/s.
- Opportunity for multiple spin-offs or pivots within the medical device market.
- Multiple potential markets.
- Chosen marketplaces are undergoing considerable growth.
- Market research shows potential influential consumers are enamoured with the concept.
- Potential to replace current biomaterial screws.
- First mover advantage with 'new generation' biodegradable material (Markides Constantinos & Sosa, 2013). A recent patent could potentially threaten this and enable second mover advantages instead.
- Build relationships with potential customers during the product development process. Surgeons whom are involved with the development will have increased buy-in as well as providing legitimacy and credibility to the development process. As indicated by the market research, surgeons select the devices that they use therefore purchasing behaviour will be influenced.
- Opportunities to licence the material to leading medical device manufacturers.
- Opportunity to expand patent portfolio to strengthen legal position.

Threat

- Another incumbent company is preparing to enter the market with a similar product material.
- Imitation.
- Incumbents are generally large established companies.
- Potential for material scarcity as supplier specific properties are expected.
- Biomaterial screws currently have a poor reputation.
- Potential that medical screws used for other applications may be adapted and fill our market niche.
- Organisation that owns material (VicLink) has other projects that will be competing for attention and finance.
- High regulatory and development costs are expected.

Strategic Plan and Exit Strategy

Introduction

Strategically there are a few incoming decision points and suggestions at both the strategic and operational levels. Each decision point could lead NacreTech in a variety of different directions. The overarching strategy being suggested is the dynamic model of strategy as proposed by Moncrieff (1999). In essence the mission of NacreTech's strategy is value creation; it is believed that through the use of a dynamic' model that the maximum value can be created. The dynamics model uses a combination of both deliberate-planned processes and also emergent adaptions to the current operating environment.

Strategic Planning

As proposed by Moncrieff, the strategic intent (also known as planned strategy) is a combination of the vision of senior management/stakeholders, their analysis of both current resources and capabilities and the current operating environment. The analysis, the vision and the resultant plan are all affected by the assumptions and beliefs of the person doing the analysis. It is the implementation of the plan that leads to both new emergent strategies and strategic learning. This strategic learning in turn influences the future strategic intent as well as emerging opportunities. In essence the strategic plan for NacreTech is to create a plan, implementing it and learn from how it worked as well as integrating new information.

It is also worth noting that since NacreTech is intending to sell a medical device, medical devices generally have requirements such as clinical trials and regulatory approval. These requirements as outlined within the regulatory section and are expected to dictate some of the specific milestones for NacreTech. It is within these milestones, that the above strategy is primarily intended to influence NacreTech's overall direction.

It is recognised that the key impeding decision point and associated suggestion depends on the choice of business model. There are two different business models that are primarily being considered, licensing and independent spin-off subsidiary. The suggested path for NacreTech is to pursue both of these options sequentially. If it is possible at a relatively early stage of material development to license the material to a company operating in a different market segment, then it is recommended that NacreTech capitalise on the market opportunity. Licencing at a relatively early stage will limit potential risk and curtail the investment and reduce the time to see a return on investment.

If licencing is unsuccessful or considered undesirable, it is recommended to follow the traditional biotech development pathway. The traditional pathway would have NacreTech launch as an independent company to commercialise and sell products from the developed biomaterial platform. The exit plan for this longer pathway is to sell the firm to a large biotech company. The alternatives are to list on the share market or pursue an acquisition by a venture capital organisation. As discussed below raising a portion of capital through targeted 'crowd funding' to support the spin-off may be desirable, as long as it does not inhibit other forms of investment.

Identified Action Points and Suggestion:

1. *Governance and Science Advisory*

   The intention here is to create a team to support the translation from science lab to commercial reality. A board of governance is suggested to be made from the stakeholders who have vested interests in NacreTech (IP owners, investors, VicLink etc.). Furthermore a science advisory panel should be made up from subject matter and commercialization experts.

2. *Develop Product and Capabilities in-house, or find external resources*

   This project relies upon the commercialization of science. In particular further research and development is needed to meet the specific requirements of the biomaterial target profile. Currently development is underway within Victoria University of Wellington, but offsite development by a third party may be required. The decision to outsource development or not needs to be made in conjunction with decision 4 and 5.

3. Identification of a Physical Location for Development and Production

   Manufacturing is envisaged to rely on 3D printer technology. 3D printer technology can reduce the costs associated with the expansion of a product line. Scalable 3D printer technology can limit labour costs. Instead of 'racing to the bottom' looking for cheap labour in the international manufacturing market there is the ability to keep production physically located with development teams. This locality means the processes used in manufacturing are able to be continuously improved as new developments are realised (Ashkenas, 2012). The down side is finding a suitable location that has both development and production space available.

4. Time Frame Considerations

   The key action to be made with regards to the future of NacreTech is deciding the timeframe for realizing the return on investment, in particular the choice of exit strategy. Both short-

term and long-term options are viable. The pathway for short-term return on investment focuses on licensing of the material to interested parties. The alternative long-term pathway traces the normal business creation process that most biotech start-ups follow. The long-term pathway is expected to require full development of both the technology and the business. The longer pathway means greater overall value is expected to be created but it is expected to take longer to see these significant return on investment. Return on investment is expected to take the form of dividends to shareholders or returns from being acquired by another competing company. Five and six below expand upon these two pathways.

5. Licencing Business Model

Licensing of the technology to a medical device maker may be possible to either one that wants to develop capabilities in next generation biomaterials, and already has compatible capabilities, or one that has resources they want to defend.

It has been identified that the largest orthopaedics company (Stryker) has recently patenting a chemically similar material, this application has opened a range of strategic options to NacreTech. We have identified two primary avenues of action. The first option is to license the use of our material to one of Stryker's competitors, these companies will be wanting to remain competitive with the newer generation of materials; this will enable fairly early acquisition of the material. At a slightly later stage licensing of the material directly to Stryker may be possible. Our material would enable Stryker to strengthen their position with regards to diversity of resources/capabilities and also stop their competitors from having similar capabilities. The licensing of the materials to one or more companies within the medical device market can be seen as the safe option; a return on the investment and research can be realized with minimal risk.

6. Extrapreneurship Business Model

Conversely there is the longer term, high risk, high reward option. This entails setting up NacreTech as a subsidiary/spin-off company to directly compete within the medical device market (Johnsson & Hagg, 1987). This means further investment into developing the entire supply chain from development and design all the way though to sales and reimbursement. The intention is to emulate the success of Bioretic within the marketplace for bio-absorbable bone screws. It must also be mentioned that licensing of the material to medical device company or companies does not rule out the viability of a spin-off company but does affect

the company tactical options it is worth remembering that network effects could potentially support the business (Robinson & Stuart, 2006).

If a business is created to realize the potential of the material, the recommendation is to pursue alternative business models such as 'crowd funding' for a small portion equity (Belleflamme, Lambert, & Schwienbacher, 2013). Bioabsorbable bone screws have traditionally had problems with market penetration. Early generation products caused problems to the reputation of bioabsorbable bone screws (see market research), there is also indications that because of the reputation of the earlier generation bone screws the newer 'better' bone screws are having trouble with market penetration. One of the intentions with the suggestion of crowd funding is to aid market penetration. Further reasoning for suggesting crowd funding is given in the section below.

7. Alternative Applications

With the extrapreneurship business model it is expected that eventually there will be the opportunity to diversify the product range beyond just bone screws. The recommendation is that this step in growth for the business is not rushed and instead the focus is retained until the organisations resources and capabilities can organically support the expansion and diversification (Schaper, Volery, Weber, & Lewis, 2011).

Reasoning for Suggesting Crowd Funding

Interviews indicated that there is still an interest in the concept and the possibility of better healthcare that biodegradable bone screws offer. There may be an opportunity such as crowd funding to capture this interest and use it to help fund and develop the venture as well as aid development of the products that the market wants (Belleflamme et al., 2013).

The concept of crowd funding is inspired by the success of 'BrewDog' an independent craft beer brewery from Scotland. BrewDog successfully managed to combine the collection of investment/funds and also increased the vested interest of consumers as well as influencing their purchasing behaviour (Boyce, 2013). Both the investment and customer behaviour modification are beneficial to the business. BrewDog managed to achieve this is by crowd funding a small proportion of the equity in the business to consumers. Crowd funding has supported and enabled BrewDog during extremely rapid growth, averaging 285% growth annually over the past 5 years (Brinded, 2014).

This concept of crowd funding is intended to bring a number of benefits (Ahlers, Cumming, Guenther, & Schweizer, 2012). There is the intention to target professionals within the medical industry (specifically surgeons) with this application of crowd funding. The reasons for this specific targeting are multiple. Firstly this will facilitate engagement with surgeons who have a vested interest in the success of the project, this engagement will enable testing and development with intended users giving them a product made to their specifications and needs. User engagement will increase the legitimacy of the product and increase awareness within the target market (Suchman, 2012). The ethical implications and potential conflict of interest arising from these prospective relationships would also need to be addressed and developed so that the integrity of all parties can be maintained (Torr-Brown, 2013).

The desire is to engage with surgeons for more than just the standard development process. This engagement will boost their perception of NacreTech and associated product lines. By increasing communication and overall legitimacy with the surgeons, market penetration may increase at a faster rate than that achieved by the incumbents in the market. Finally surgeons are traditionally high net-worth, but time poor, and an investment of this nature is intended to tap into both their financial and philosophical aspirations (helping patients) as well as using their specialist knowledge.

The main concern identified with crowd funding is in regard to future investment where venture capital may be put off by the more complicated ownership structure. This concern helped reinforce the specific targeting of the investments, the hope is that by targeting the end users in such a way

the positive benefits will outweigh the negatives. The second way to reduce unintentional harm to the business from crowd funding is to limit the size of this type of funding to specific and small amounts of total equity.

Biomaterial Concept

Introduction

To develop a biomaterial suitable for biodegradable load bearing osteoconductive orthopaedic implants the material needs to be developed from its current status to meet the target product profile. Here is an explanation of the complexities faced to reach a number of key targets and the adaptive material concept. This is followed by a detailed table of specific targets and the set of current limitations affecting the target product profile.

Porous Structure

For the biomaterial to gain high quality osteoconductive properties the porous macro structure needs to meet certain targets for pore size and interconnectivity. There is an ideal macro pore size of 200 to300µm (though there is disagreement in the literature (Zhou, Ma, Li, & Yao, 2011)); if the pores are too small then the osteoblast cells may block passage further into the biomaterial's pore network; if the pores are too large then the cells may treat it as a flat surface instead of a 3D structure and the strength of the material is drastically compromised (Zhou et al., 2011).

A material with isolated pores is not sufficient as they need to be connected to each other – that is have open and conductive pores - to allow blood vessels to propagate through the biomaterial (Rouwkema, Rivron, & van Blitterswijk, 2008). As bone growth is a very intensive process these blood vessels help determine how osteoconductive the biomaterial is by supplying nutrients; the more interconnections there are the better the result.

Strength

To meet the requirements to act as a biomaterial for load bearing implants the strength of the material needs to have an upper limit of 230MPa in compression; this is the approximate maximum strength of cortical bone and required for load bearing implants (Pilia, Guda, & Appleford, 2013). Due to bone being adaptively responsive to force or load (Sikavitsas, Temenoff, & Mikos, 2001) the strength should be near, in a similar manner to pore size, an ideal point in the middle; too strong and the biomaterial will cause stress shielding, where the surrounding natural bone is reabsorbed, as metal implants do currently; too weak and breakage will occur.

Current biomaterials on the market, such as Biomatlante's MBCP Wedges ("MBCPTM Wedges - Biomatlante," n.d.), gain good osteoconductive properties by directly increasing porosity; more and more pores are squeezed into the same volume until they overlap creating interconnectivity.

However this complicates reaching strength targets since there is an inverse relationship between porosity and strength – the more porosity, and improved osteoconduction, the less strength and vice versa (Karageorgiou & Kaplan, 2005).

The proposed method to help lessen the effect of this relationship is to design a sparse network of connected pores. Consisting of pores connected by narrow tunnels (50 to 100µm in diameter) this will help the biomaterial retain more material while still having highly interconnected pores for the purpose of osteoconduction. How successful this porous macro structure is has not been tested within the literature reviewed for this report.

Combining strength and porosity requires balancing two inversely related properties with their own individual ideal targets.

Degradation

For the implant to be absorbed by the human body over time it needs to be biodegradable – this means the strength of the biomaterial changes over time as well. The rate or profile at which this degradation occurs is a key property that needs to be balanced with strength and porosity; they are all interrelated variables. As for strength and pore size there is a target rate of degradation in the middle; too fast and the new bone will grow incorrectly and be easily damaged; too slow and the biomaterial will impede the healing process. The ideal situation would be where the rate of degradation matches the rate of new bone growth within the patient (Raghunath, Rollo, Sales, Butler, & Seifalian, 2007).

Joining all the above features:

For good osteoconduction there is an ideal porous structure required in the biomaterial. This macro structure inversely affects strength which has an ideal target as well. Due to degradation the strength of the biomaterial changes over time; there is an ideal rate at which this occurs.

Variable Feature Targets

There is a balancing act between the three properties to reach an optimal point compromising osteoconduction, strength, and degradation for a given application. This is achieved in some way by all biodegradable osteoconductive biomaterials available and a key target for the synthetic nacre is to improve on this by allowing the optimal point to be adapted, or changed, as required by surgeons and patients (Figure 2).

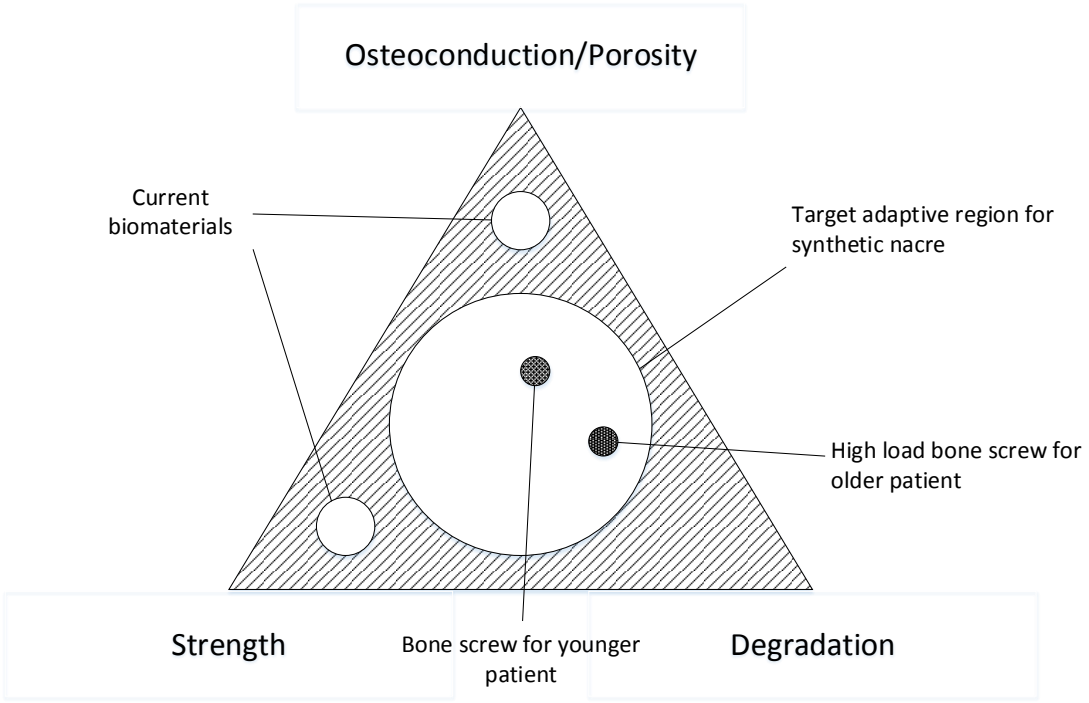

FIGURE 2 CONCEPTUAL DIAGRAM COMPRISING DIFFERENT BIOMATERIAL FEATURES

Gaining this ability is an important improvement since each optimal point is only useful for a limited number of applications and patient types as illustrated by (Lew, Othman, Ishikawa, & Yeoh, 2012) regarding the various bioceramics used in the body. Depending of the type of implant, bone, and patient the ideal targets for porosity, strength, and degradation will change. A bone screw for a leg bone will have different optimal point balancing strength and porosity than a bone screw for an arm repair surgery. The rate of new bone growth changed depending on the age of the patient; for example the ideal rate of degradation for an implant in a 50 year old will be different than that for a 20 year old.

In summary enabling tailored material properties for individual implant and patient types will support a broad range of orthopaedic implant applications; turning synthetic nacre into a platform biomaterial.

Biomaterial Target Profile

The target profile has been developed to detail the feature parameters which the biomaterial should have to allow for good osteoconduction and strength. It has been established from medical literature research articles and analysis of competing products. While it is not considered to be a set measure or comprehensive list the porous structure and mechanical targets include the key aspects which should not be ignored.

#	Feature	Target	Minimum
Porous structure*			
	Interconnectivity	100% via ~50µm tunnels	>70% via ~40-100µm channels
	Macro pores	200-300µm	150-500µm
	Micro pores	~5µm pores within the struts between macro pores	~1-10µm
	Wall thickness**	200-400µm	<400µm
Mechanical targets			
	Elastic modulus (Joukainen, 2008)	±1GPa of target bone area ranging from ~10-30GPa for cortical bone	>10GPa to improve on synthetic plastics and <<200GPa to improve on stainless steel
	Compressive strength (Pilia, Guda, & Appleford, 2013)	±10MPa of target ranging up to ~230MPa	It will be dependent on the final application but >150MPa will improve on competing products.
	Tensile strength***	130MPa	±20MPa to match bone and be on par with PEEK material (Katti, 2004).
	Shear strength***	50-65MPa	~40-100MPa
	Fatigue (Teoh, 2000)	No susceptibility to fatigue	Strength under shear stress remains above 40MPa
Surface properties			
	Wettability (Vandrovcová & Bacakova, 2011)	Strongly hydrophilic	Sufficient for cells to propagate during osteoconduction testing
	Topography (Vandrovcová & Bacakova, 2011)	Nanoscale (100nm) surface roughness of ~40Ra	Nanoscale roughness
Thermal properties			
	Thermal contraction/expansion coefficient (Holmes, 2011)	$\sim 27 \times 10^{-6} mm/C°$; Or near that of the surrounding bone.	Similar enough not to displace set bone (application specific).
	Thermal conductivity (k) (Holmes, 2011)	0.41 to 0.510 or similar to the surrounding bone	~0.13 or similar to PLA
Degradation			
	Strength half-life	±2 weeks over a range with an upper limit of 12 weeks – based off the enzymatic hydrolysis taking twice as long to degrade the biomaterial vs. non-enzymatic hydrolysis (Venkatesan & Kim, 2010).	>6 weeks or the current strength half-life of competing materials
	Debris released (Böstman & Pihlajamäki, 2000)	0	Slow enough that an adult body can absorb the released

		debris before it builds up which can cause a cascade inflammatory reaction
Specific targets for implant types		
Screw coaxial torsion strength (dependent of design and screw diameter)		Sufficient, when combined with specialised tools, not to break during insertion. For example ASTM F543 requires 3.5mm metal screws to withstand 2.3Nm.
Fixation strength (dependent of screw design and application)		>1200N for interference screws (Kousa et al., 1995)
Plate stiffness	Target bone resist 50% of force after initial healing period	
Plat controlled plastic deformation	0 – targeting locking plates as unlikely to have plastic deformation with ceramic component	

TABLE 1 BIOMATERIAL TARGET PROFILE

*Specific targets adapted from (Zhou, Ma, Li, & Yao, 2011), (Lee, Kasper, & Mikos, 2014), and (Hing, Annaz, Saeed, Revell, & Buckland, 2005).
**Based on the diffusion limit of oxygen *in vivo* of 100-200µm (Rouwkema, Rivron, & van Blitterswijk, 2008).
***Adapted from (Turner, Wang, & Burr, 2001) and dependent on direction with lower requirements for perpendicular forces.

Summary

Within the market the compromise between osteoconduction and strength has not been solved; the biomaterial target profile, in particular the sparse network macrostructure, has been developed to fill this gap. As such if the synthetic nacre can incorporate the porous structure and strength characteristics detailed then it is perceived to be of interest for further investment.

Proof of Concept

Overview

When the synthetic nacre biomaterial has completed development and meets the target product profile a set of formal tests should be carried out before proceeding. The recommended order (based on technical risk, the critical path in material development, and cost) in which features or properties should be developed and tested begins with the porous structure and follows the flow chart below.

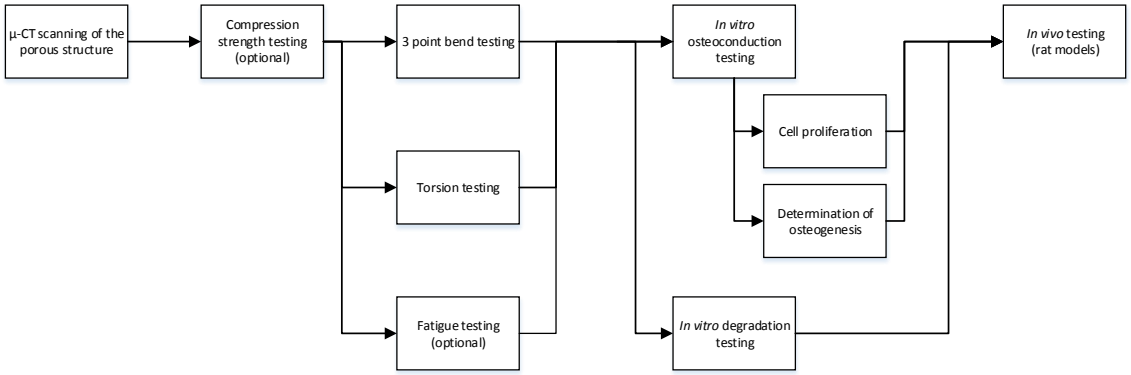

FIGURE 3 PROOF OF CONCEPT TESTING FLOW CHART

Mechanical

The purpose of the mechanical testing is to determine whether the synthetic nacre biomaterial can incorporate a target porous structure, desirable to later achieve osteoconduction, and strength similar to natural cortical bone. Furthermore *in vitro* degradation testing will help determine whether it is able to maintain these desired strength properties for sufficient time, without debris, to enable complete healing in adults. Currently the material is without any porosity which is required both for the desired porous structure and to be able to manufacture specimens for all further testing.

Porous µ-structure

Porosity with specific characteristics has been identified as a requirement before proceeding with strength or biological testing. There are several categories of pores mentioned in the material target profile but the presence of the macro level pores within the desired size range is the minimum requirement to support the proof of concept stage.

#	Feature	Target	Minimum
1	Macro pores within range:	200-300µm	150-500µm
2	Interconnecting tunnels	60µm	50-100µm
3	Interconnectivity	100%	>70%

TABLE 2 POROUS µ-STRUCTURE FEATURE TARGETS

There are various testing methods that can be utilised depending on availability and cost. During the development stage while implementing a porous structure SEM (Scanning Electronic Microscopy) and diffusion testing could be used to test for the presence, size, and interconnectivity of pores. For the final decision to continue to the next test µ-CT scanning is suggested to get a precise model of the porous structure; this should return a result similar to Figure 4. ASTM F2450, Standard Guide for Assessing Microstructure of Polymeric Scaffolds for Use in Tissue Engineered Medical Products, may help provide information to build appropriate analysis procedures from a 3D scan.

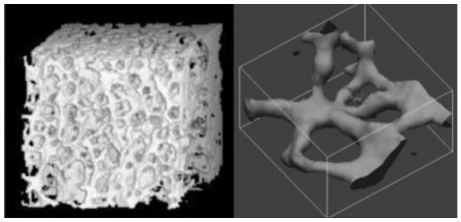

FIGURE 4 IMAGE ADAPTED FROM (KHERLOPIAN, ET AL., 2008)

SEM/diffusion testing can be completed at VUW and there are µ-CT scanner machines at the universities of Auckland and Otago ("NZ National Testing Facilities," 2014).

Cost: $200 for a simple scan to $2000.00 per scan for a large sample with analysis (Zamparo, 2011).

Strength

Research conducted into bone biomaterial market suggests that there is a gap for a biodegradable material, having good osteoconduction such that it requires a porous structure, with good mechanical properties. A positive strength in compression result is suggested before performing other tests. The end manufacturing process will include sterilisation via gamma irradiation – as this will cause cross-linking and make the material stronger it may not be necessary to include this process for these tests.

For each test:

- Use 10 specimens or more for statistical relevance.
- Test biomaterial at 37°C while the biomaterial is wet; if possible test *in situ* with specimen in soaking water or buffer solution.

- Use the manufacturing of specimen shapes as a test that the 3D printer has the minimum capability requirements.

All tests can be completed in a universal testing machine in a temperature controlled cabinet; one of which is available at Callaghan Innovation or in various New Zealand universities other than VUW ("NZ National Testing Facilities," 2014). For the proof of concept a preliminary basic compression testing is optional while the 3 point bending and torsion tests, which will also provide a compression strength value, are required by regulations and should follow the relevant standards such as ASTM D7264 and F543. These two are important as torsion, or twisting, and bending are the two most common modes of failure for bone and implants (Väänänen, 2009). Additionally a standard fatigue test for biomaterials will need to be conducted either at this point or a later date such as after the initial biological testing.

Costs are in order of $20 to $200 per specimen with the exception of fatigue testing which is related to the number of cycles or duration.

In vitro Degradation Testing

Currently there are no standards for testing biodegradable biomaterials where the breakdown mechanism is enzymatic hydrolysis. This test has been adapted from other standards (ASTM F1635) and testing procedures suggested in literature, primarily (Azevedo & Reis, 2005); as such this test can be adjusted with appropriate care.

Two profiles or rates are to be measured: the degradation, or remaining material; and strength, recording how the load bearing capabilities of the biomaterial change. This is essentially a repeated series of previously mentioned μ-CT scans and standard based mechanical testing over a period of time of up to a minimum of 6 months. Allowing for early termination in the event the material has completely degraded the time point at which testing ends will depend on whether complete specimen degradation occurs in a reasonable fashion. The mechanical strength testing should be performed *in situ* where possible or immediately upon specimen removal from the buffer solution used to degrade the biomaterial; this should ensure the wet strength, not dry, is tested.

The buffer solution should mimic the internal environment of the human body that the final implant will be expected to be in. Due to synthetic nacre being a composite including a natural polymer component, chitin/chitosan, the standard phosphate buffer solution used by competing products to test degradation rates is not sufficient; the enzyme lysozyme needs to be included.

Additionally to mimic the blood flow and fluid dynamics within the body the container containing the enzyme and phosphate buffer solution need to be cycled two times per minute.

Biological

The purpose of the biological testing is to determine whether osteogenic cells (bone cells) will grow on the biomaterial. The first stage is the *in vitro* testing: this involves determining whether the cells are capable of growing within the biomaterial and providing initial evidence support the statement that bone cells are capable of replacing the biomaterial with natural bone matrix. The second stage is the *in vivo* testing: this involves confirming that the biomaterial is degraded within the body and replaced with natural bone matrix; it also confirms a rate of degradation.

Currently there has been one test performed on the film form of the biomaterial. This test was performed using osteoblast cells which were incubated for 72 hours. The results showed that there was no immediate toxic effect to the osteoblast cells. The test did not demonstrate whether bone growth occurred due to the short incubation period. However, materials comprising chitin have been shown to support the growth of osteogenic cells and display osteoconductive features (US 13/801,044, 2013)(Di Martino, Sittinger, & Risbud, 2005). As such the current assumption is that the biomaterial is capable of osteoconduction and is non-toxic to osteogenic cells.

In vitro Testing

The *in vitro* testing is estimated to take a period of 6 to 12 weeks to perform; the first aspect is to examine cellular proliferation of osteogenic cells. There are standard methods of determining cell proliferation such as AlamarBlue assays, PicoGreen dsDNA assays, or MTS assays. The AlamarBlue assay involves incubating the cells with a reagent which produces a colourmetric change (from blue to red) when incubated with live cells. The colourmetric change is measured using either the fluorescence or absorbance spectra wherein the percentage of colour change indicates cellular proliferation (“alamarBlue®—Rapid & Accurate Cell Health Indicator,” n.d.). It would appear that the use of either AlamarBlue assays or PicoGreen assays are common tests utilised when determining osteoconductive capabilities of biomaterial scaffolds (Brey, Chung, Hankenson, Garino, & Burdick, 2010; Fang, Wan, Tang, Gao, & Dai, 2009; Musson et al., 2013; Subha N. Rath et al., 2012)

The next stage is to determine that the cells have adhered successfully to the biomaterial scaffold. This can be achieved using a combination of FDA/PI staining, fluorescent microscope, and scanning electron microscope. The FDA/PI is an assay which investigates the amount of live cells in a sample compared to dead cells. In particular, the cells are exposed to a compound called fluorescein diacetate and then propidium iodide. The viable cells are labelled green while the non-cells are

labelled red. The biomaterial samples will then need to be examined under fluorescent microscope and scanning electron microscope. The scanning electron microscope can also show the proliferation of the cells throughout the entire 3D structure of the material(Subha N. Rath et al., 2012; Jones & Boyde, 1977).

The last stage is to confirm that the biomaterial scaffold is osteoconductive and the cells begin the mineralisation process. Typical methods of determining whether osteogenic cells is by utilising reverse transcriptase polymerase chain reaction (RT-PCR) to ascertain the expression of genes associated with the regulation of osteogenesis (bone growth). The more common genes associated with osteogenesis that are measured are alkaline phosphatase, osteocalcin, osteopontin, RUNX-2 and collagen type I (Brey et al., 2010; Chen et al., 2012; Conserva, Foschi, Cancedda, & Mastrogiacomo, 2013; Fang et al., 2009; Thibault, Scott Baggett, Mikos, & Kasper, 2010).

Beyond Proof of Concept

A number of additional tests can or are required by regulation to be performed before the synthetic nacre biomaterial can gain pre-market approval. Following is an incomprehensive discussion of a number of future testing that may be undertaken and the various outcomes required.

Fixation Testing

Fixation is a known problem within orthopaedic implants and a potential advantage for the synthetic nacre material is the characteristic surface reaction that occurs in phosphate buffer solution. The calcium carbonate component of the biomaterial is dissolved and precipitated back as calcium phosphate (Ni, 2003), the same chemical composition as bone, and may form a chemical bond with nearby natural bone.

It is possible to test this and the fixation strength of the biomaterial before animal trials; this may be desirable to do so due to the lower cost and to build more medically relevant data and confidence around the future product. Fabricated bone screw specimens are inserted into natural bone, either cadaver or more available bovine bone, and placed in buffer solution over a number of days and the pull out strength measured at different time points. It may be possible to show that the surface reactions chemically bonds the implant to the surrounding bone holding the implant more firmly until osteoconduction occurs.

Animal models

The ISO 10993 standing for biocompatibility has a number of requirements for animal studies including to limit the number of and harm to the animals involved. Two different species are

required and rats and sheep are suggested to combine toxicology, degradation, and mechanical testing within the same trial.

Rats will be used for toxicology and testing that degradation is complete and osteoconduction occurs, as the biology of rats is very different from humans the rate at which degradation and osteoconduction occurs cannot be extrapolated.

Sheep are the second species as they, along with pigs, provide good models suitable for testing the repair of critical sized defects with load bearing implants (Peric et al., 2014). While pigs provide a closer model to humans sheep are suggested due to being more available and less expensive.

From the two trials, of which rats should be completed first, the biocompatibility testing should be completed as well as extrapolated profiles and effectiveness of the osteoconduction, degradation, and strength capabilities.

Comparison to Controls

To support market claims and for the purposes of filing patent documents appropriate controls need to be selected. In particular comparisons need to be made to existing products and the material described in US2014/0271914 to ensure healing times and efficacy is improved in the NacreTech biomaterial.

Manufacturing and Scale Up

Manufacturing and Material System

Meeting the requirements for tailored material properties described in the material target product profile a concept has been described for a material and manufacturing system. Once developed, this system will use 3D printing, or potentially another high resolution rapid prototyping manufacturing method, to fabricate any number of different implant designs using tailored synthetic nacre biomaterial. Design trade-off curves for the different biomaterial features, such as porosity, strength, and degradation, will be developed allowing the synthetic nacre to be tailored as needed by implant designers or even surgeons directly. The combination will form a system that allows multiple implant product lines with a range of different material properties to be manufactured using the same equipment and processes – greatly simplifying and reducing the cost of production (Yildirimer & Seifalian, 2014).

3D printing, particularly a variant similar to Fusion Deposition Modelling (FDM), was selected as the most viable method to obtain the adaptive requirements of the material as it has been shown in the lab by VUW researchers to work in concept. It currently works by printing the chitosan scaffold followed by the various chemical processes required to manipulate the material properties and perform the mineralisation of the calcium carbonate. 3D printing using FDM also has the benefit of future proofing the material and manufacturing by enabling developing technologies such as the inclusion of living cells, different materials, and drugs to be incorporated into the scaffold once they become available (Yildirimer & Seifalian, 2014).

Scale up of 3D Printing

A well-known challenge is the manufacturing scale up of 3D printing (The Economist, 2013) therefore a basic model was developed to test the costs and production quantities associated with using it. One advantage the current process has is that unlike plastic FDM the chemical process for printing the chitosan requires no heating element; this could potentially ease the incorporation of multiple printing heads in the same machine to increase production rates.

In the final configuration the basic model (Figure 5, Page 49) was used to estimate that 20 3D printing machines could produce 25,000 bone screw units annually; the bone screws were estimated by 4mm in diameter and 16mm in length cylinders. Depending on the target breakeven point and units manufactured per year, 100,000 units over 4 years estimated here, this will produce cylinders at a little over $446 each including overheads.

Manufacturing Target Profile

#	Feature	Target	Minimum
3D printing			
	Resolution	30µm or enabling control over pore shape as well as wall thickness	< 200µm or the maximum wall thickness in the porous structure
	Deposition speed	> 1000µm/s for higher production rates	> 100µm/s
	Printing heads	> 10 for higher product rates	1
	Per printer capital cost	< $10,000	< $30,000
	Printer working life	> 1 year	> 6 months
Sterilisation			
	Gamma irradiation	In addition to sterilisation used for crosslinking to make the material stronger	Used for bulk sterilisation as other methods, such as autoclaving, are not suitable for the biomaterial

TABLE 3 MANUFACTURING TARGET PROFILE

Raw Material Limitation

Natural polymers, including chitin/chitosan, have different characteristics depending on the source of the raw material and the process used during extraction and processing. With limited sources already a guaranteed supply from the same source needs to be acquired; since moving to a different source may change the properties (Aranaz et al., 2009) of the final material and/or may require changing the manufacturing process.

Intellectual Property Strategy

Patent Landscape

There are three key aspects to the biomaterial which has been developed. First is the use of chitin as a scaffold which is mineralised with calcium carbonate (aragonite) to form the initial biomaterial. Second is the manufacturing methods utilised to produce a 3D biomaterial and incorporate the internal porous structure. Third is the use of the chitin and calcium phosphate combination in bone growth applications. These are the key areas which the intellectual property landscape is focused on and explored.

The use of chitin as a scaffold which is mineralised with calcium carbonate is well known in the art. The IPRP for the initial patent application cited Hosoda & Kato (2001), US2004/0131562, Kato, Suzuki, & Irie (2000), Zhang & Gonsalves (1995), Wu, Cheng, Yao, Chen, & Shao (2011) which all disclose chitin that has been crystallised with calcium carbonate. The scaffold structure of the chitin in these documents has been electrospun or is in film form. It is further important to note for future patents that the inventor's publications disclose the method of manufacturing the material and therefore any crystalline structure formation, such as aragonite (Munro & McGrath, 2012), (Munro et al., 2013).

The methods disclosed above result in 2D forms of the chitin and calcium carbonate combination. There has been some investigation to incorporate a porous structure into a chitin scaffold. In summary, these methods are non solvent-solvent exchange (Pakavadee Ratanajiajaroen, & Masahiro Ohshima, 2012), gas bubbling, freeze-drying (Yin et al., 2003), injection moulding (Fernandez & Ingber, 2014) or porogens (Chevalier, Chulia, Pouget, & Viana, 2008). These methods result in internal material structures that have the incorrect pore structure when compared to the current invention (biomaterial). New developments in the manufacture of chitin have been investigated in the area of 3D printing however the current resolution of that particular 3D printing method is not very high (Ang et al., 2002). There does not appear to be a known method of producing a chitin and calcium phosphate material which has a highly specific internal porous structure.

The use of the chitin and calcium carbonate combination in bone regrowth materials or bone scaffolds would appear to be novel at the time of this report. The most significant patent application to consider is US2014/0271914 which was filed by Orthovita on the 13 March 2013. The Orthovita patent teaches osteoconductive bone graft material which is made from the combination of calcium phosphate and chitin. It further teaches where the material has a micro-, meso- and macro-porous structure; however the method of manufacturing the pore structure is by freeze-drying.

Additional patents have been filed by Matsumoto dental college, IKO KK, Genus EHF and Kyocera. These patents discuss the use of the chitin and calcium phosphate combination for use in bone regrowth/healing. However, the final material produced by these patents is sufficiently different (i.e. dough-like) and do not discuss a porosity within the material. These patents are of interest only and are not considered to significantly affect the patent strategy.

Current State of Protection

There is currently one application filed for the initial form of the biomaterial which was filed with PCT international (PCT application number PCT/IB2012/057197) with a priority date of the 12 December 2012. This application provides protection for the current method of manufacturing the biomaterial and for the biomaterial itself in film form. The international preliminary report on patentability (IPRP) and international search report (ISR) on this application has been issued and reports that the invention as claimed is novel and has an invention step. This PCT application has subsequently been entered in the United States of America for national phase.

Intellectual Property Strategy

The key aspects of the invention are: the composition of the biomaterial with the porous structure; the method of manufacturing the biomaterial; and the use of the biomaterial as a bone growth scaffold. It is noted that further development of the material and manufacturing process in currently being completed. As such the current patent application discussed above is not considered to provide full protection for the scope of the invention.

In view of the additional advances the next application will need to reflect the developments within the 3D structure, porosity, and strength of the biomaterial. The advantage of these characteristics is that they will allow for enhanced osteoconduction of the biomaterial which is considered to be one of the advantages our product will have over our competitors. In particular, the application will need to protect the new chemical method of manufacturing the material, the composition of the biomaterial, the porosity, and the 3D structure of the material.

The second aspect is regarding the use of the biomaterial; this will reflect the osteoconductive properties of the biomaterial and provide protection for the intended use as a bone growth scaffold. In order to file for the protection of the biomaterial for use as a bone growth scaffold. The team will need to have completed at least the *in vivo* based biological testing as the exemplification will provide support and enablement of the invention within the specification.

At this stage it is considered that the specific details regarding the method of 3D printing the material should remain trade secrets or will be protectable by patents. It is currently unclear what IP will result from the current development process. It is anticipated that much of the 3D printing will be based upon existing machinery and techniques but utilising them for a new material. Therefore, there is little benefit currently perceived in filing an additional patent to protect what may be minor variations to known methods. As such, these variations are considered to be best protected as trade secrets.

In regards to the US2014/0271914, the licensing of this patent will strengthen the patent portfolio of NacreTech add a biomaterial consisting of chitin and hydroxyapatite (calcium phosphate). The use of chitin and hydroxyapatite is a logical next step in the development of the biomaterial and therefore licensing the patent will benefit NacreTech. The license of the patent will also protect us from any infringement suit from Stryker.

Filing Dates and Locations

The date of filing the patent applications is considered vital as the 20 year limitation will be consumed primarily by gaining regulatory approval. However, prolonging the filing date increases the risk of another patent application being filed which anticipates or prevents the acceptance of NacreTech's invention. Therefore, in view of the regulatory considerations and the requirements under support and enablement it is proposed that the best window for filing the patent applications will be shortly before the completion of the *in vivo* based biological testing but before the pre-clinical testing.

In addition, it is proposed that an initial provisional application is filed through the New Zealand patents office. This will then allow for 12 months to complete all *in vivo* biological testing before filing a complete PCT specification at WIPO in view of the Paris convention. The specification will contain all the details regarding the chemical manufacture of the material and the use of the biomaterial as a bone growth scaffold. If it is determined that the application cannot be prosecuted in a single application due to unity, then the applications can be divided out into the two areas for protection. This method of filing is considered to reduce PCT and ISR costs, while ensuring there is sufficient support and enablement for both areas for protection.

The primary filing countries are considered to be the United States of America and the European Union, as these are our largest target markets. This is followed by the countries of manufacture such as India, Mexico and China. Lastly we will be filing in the second tier countries such as Australia, New Zealand, Canada, Japan and South Korea.

Regulatory Considerations

Definition of a Medical Device

A medical device is defined as an article which is intended by the manufacturer to be used for human beings for the purpose of treatment of an injury, disease or modification of the anatomy or physical function, wherein the principal intended action in the human body is not achieved by pharmacological or metabolic means but which may be assisted by such means (as per Medical Device Directive, MDD (93/42/EEC)).

The bioactive bone screw is considered to be a medical device as the intended purpose of the device is to act as a screw for the purpose of treating an injury. The bioactive feature of the screw is not considered to be the principal intended action but assists the intended purpose of the device. Therefore, as the bone screw is a medical device we are required to obtain regulatory approval for the device before the device can be sold.

Explanation of Regulatory Systems

There are two primary systems in order to obtain regulatory approval. The first is the FDA which grants regulatory approval for the United States of America, while the other is CE Mark which grants regulatory approval for the European Union. Each of these systems have slight differences which affect the speed, cost and risk associated with obtaining regulatory approval and will be discussed further below

The FDA has two main routes to market for medical devices. The first is via a Premarket Notification (510k) which is based upon the manufacturer providing satisfactory evidence that a device is substantially equivalent to an existing device with regulatory approval. The second is via a Premarket Approval (PMA) which requires clinical data to support the safety and efficacy of the device.

The CE mark regulations for medical devices is disclosed in the Medical Device Directive, MDD (93/42/EEC). In order to obtain regulatory approval the application needs to meet conformity assessment procedure as set out in the Annexes of the MDD (93/42/EEC), however which annexes a device needs to meet is determined by their classification. The classifications (Is, Im, IIa, IIb and III) define a medical device determine the relative risk of the device dependent upon how long the device is intended to be in continuous use, whether the device is invasive, whether the device is implantable or active, and whether the device contains a substance which is a medicinal substance or has an ancillary function to the device. Hence, the more invasive or the longer a medical device is in the body, the higher the risk and therefore the higher the classification number.

There are several key differences between the FDA and CE Mark systems. The first is the aspects of the clinical data which are examined during application. In particular the CE mark examines primarily on the safety of the medical device while the FDA examines on the safety and efficacy of medical device. Hence, to obtain regulatory approval through the FDA the application needs to show that the device is both safe to a humans but also fulfils the claimed function. The effect of the differences in the examination of the application, is the CE mark system is often faster to grant regulatory approval than the FDA. It is further noted that the FDA will accept foreign clinical data in support of an application, however there are specific formalities as per the IDE in order for the data to be allowable. In particular, clinical studies for CE mark need to fulfil the Helsinki accords, however the FDA requires meeting Sec. 812 of Subchapter H of the Code of Federal Regulations, Food and Drugs.

Key Considerations

To gain regulatory approval a pre-clinical investigation needs to be conducted into the biocompatibility of the biomaterial in the form of a bioactive bone screw. The pre-clinical investigation needs to be conducted in line with ISO 10-993. ISO 10-993 sets out the requirements for testing genotoxicity, carcinogenicity, reproductive toxicity, *in vitro* cytoxicity, sensitization, and biodegradation testing. These tests are required before filing for an IDE exemption from the FDA to perform clinical trials; it is noted that many of the tests detailed in the ISO 10-993 can be carried out during animal trials in the proof of concept stage.

At the time of writing this report no medical device or drug has been granted regulatory approval utilising chitin within the human body. As a result the bioactive bone screw is considered to be a Class III medical device in both regulatory systems. Therefore clinical trials will need to be performed in accordance with both the Helsinki accords and Sec 812 of the FDA act. Performing the clinical trials will increase the cost of development and time to market significantly which is estimated between $10-15 million and six to eight years. The benefit to performing clinical trials is that it increases clinician trust in the product and the brand; existing biomaterial bone screws have been granted regulatory approval based on the 510k process and therefore do not have any substantial clinical data before market approval.

To ensure that the submissions are in accordance with all relevant sections and appendices of the FDA and Medical Device Directive an important consideration will be to find regulatory specialists which are familiar with biomaterials and medical devices. Further areas which the will need to be considered upon completion of additional development is adherence to the goods manufacturing process, sterilisation of the device, and packaging.

Financial Overview

The financial information regarding the separate sections has been listed and summed here to provide an estimate of the total cost to market. The production and cost model of the synthetic nacre material and 3D printer based manufacturing has been included, configured for bone screws, and its result justified with respect to expected cost compared to other products. The values are believed to be conservative at the time of writing but should not be considered accurate; for example much of the later, more expensive, costs would be conducted overseas and is subject to currency exchange rates.

Commercialisation Costs

Following is a summary of a number of costs involved in the bone project up until, and including an estimate of, the clinical trials stage.

Task	Cost(US$)
Material and 3D printer development (seed funding to be sourced by research team)	500,000.00
Proof of Concept testing (Series A)	
µ-CT scanning	2,000.00
Compression strength testing	2,000.00
3-point bending testing	2,000.00
Torsion testing	2,000.00
Fatigue testing*	
***In vitro* degradation testing**	100,000.00
***In vitro* biological testing**	100,000.00
Pre-clinical trials**	200,000.00
Intellectual Property Protection	
Patents***	200,000.00
Total (Series A)	608,000.00
Series B	
FDA approval costs including clinical trials (Makower, Meer, & Denend, 2010)	75,000,000.00
Overall total (Series A + B)	**75,608,000.00**

*Figures not available; determined by duration.
**Initial estimation through consultation with regulatory specialist.
***Takes into consideration attorney fees, filing fees, and maintenance costs over the life of the patents.

TABLE 4 COST OF COMMERCIALISATION SUMMARY

3D Printing Production and Cost Model

Below is a model of the 3D printer screw production, represented by cylinders, and the final cost to manufacture each screw. The final result ($446 per screw), this is considered to be an acceptable cost per screw in view of the proposed health benefits outlined in the value proposition (p. 50). This highlights the importance of achieving significantly improved efficacy over current products and/or reduced total cost of care – synthetic nacre implants, using 3D printing, will be significantly more expensive. However this model is based off only one implant, whereas the adaptive manufacturing system should allow expanding to a range a products (spreading the cost to market) across greater production.

Raw materials				Cost to market		
Cylinder		**Porosity**	**Density (Mg/m³)**	**Stages**		**Total**
Diameter (mm)	4	60%	3	Phase A	$ 608,000.00	**$ 75,608,000.00**
Length (mm)	16		**Density (g/mm³)**	Phase B	$ 75,000,000.00	
			0.003			
pi	3.141592654		**Cost/gram**			
r	2		$2.10			
h	16			Cost-driven price		
				Breakeven (units)		**Total cost/cylinder**
Volume (mm³)	**201.0619298**	**120.6371579**		100000		**446.8325555**
Mass (g)	**0.603185789**	**0.361911474**				**# machines for 4 year breakeven**
Raw materials	**$1.27**	**$0.76**		**Overheads**		**21**
				Operations	Marketing	**with annual units of**
				30%	20%	**25869**
3D printing				Production		
Speed (mm/s)	**Extrusion diameter (mm)**			**Heads per printer**	**3D printer cost**	**Printer Life (months)**
1	0.05			4	$ 10,000.00	6
V/s (mm³/s)	**Total time for cylinder (s)**		**Hours**	**30 days (cylinders)**	**365 days (cylinders)**	**Printer cost/cylinder**
0.001963495	0% Porosity	102400	**28.44**	**101.25**	**1231.88**	**$ 16.46**
	60% Porosity	61440	**17.07**	**168.75**	**2053.13**	**$ 9.88**
Electricity				**Additional costs/screw**		
Current (A)	6	Units/Printer		cGMP Contract Manufacturing		$ 20.00
Voltage (V)	24	30 Days		Post-processing		$ 30.00
Power (W)	144	365 Days				
kW.h/cylinder	4.096					
Cost/kW.h	$ 0.26			Production cost/screw		
Cost/cylinder	**$ 1.06**			**$ 68.79**		

FIGURE 5 3D PRODUCTION AND COST MODEL - *THIS MODEL IS INCOMPLETE AND MAKES SOME ASSUMPTIONS ABOUT THE 3D PRINTING METHOD USED, SUCH AS EXTRUSION DIAMETER, WHICH MAY BE INCORRECT.*

Summary

At this early stage without knowing exactly what is required in terms of regulatory processes and material development and testing the total cost to reach market is an estimate. It is acknowledged that the cost to market of a single application is large therefore a product manufacturing platform strategy will expand the product range and as a result reduce the associated risks.

Value Proposition Summary

Material Advantages

One of the features of the material is the formation of aragonite crystal. The aragonite, a form of calcium carbonate, is known to be stronger than the more common calcite (Roberts, 2009). Existing bone substitutes on the market comprising calcium carbonate such as coral only possess the calcite formation; as such a perceived advantage of the synthetic nacre material is increased strength.

The other composite constitute is the natural polymer chitin/chitosan which while retaining the strength of synthetic polymers breaks down into non-acidic by-products (Azevedo & Reis, 2005). This is a perceived advantage of the existing PLA based materials currently used in the market.

The adaptive manufacturing concept includes a bottom up fabrication process, using 3D printing, which may simplify the production of multiple implant designs and types. This is a perceived advantage over existing methods for producing biomaterial implant products as it eliminates the need for multiple complex manufacturing steps required for different designs.

An additional perceived advantage of the material and manufacturing system is the ability to tailor the synthetic nacre biomaterial properties and product design to individual patient or surgeons requirements. This personalised medicine capability is currently not known to be available in any orthopaedic biomaterial.

Healthcare Economics

Significant benefits are available through the uptake of biodegradable bone screws. The main beneficiaries are expected to be both health care providers such as hospitals and insurance companies as the intention is to reduce the overall cost of treatment. Medical devices for the initial surgery are expected to increase in cost but these are believed to be offset by removing the need for additional surgery to removed said device.

Without the need for a second surgery it is expected that overall there will be additional resources available which can be used elsewhere. Saving in other relevant areas are expected, for example faster recovery timelines will result in reduced bed loads within the hospital. The knock-on effects of this are more effective use of hospital resources such as surgeon time as well as a reduction of waiting lists as the total number of surgeries will have been reduced.

Value to Patients

Patients would benefit from the reduction of metallic devices both during the recovery process and that which remains once healing is complete. The other significant benefit for patients is from removing the need for a second surgery as this will support both their physical needs and reduce the psychological impact. It is expected that the length of time spent in hospital will be reduced, hospital stays can sometimes be harmful or even fatal for patients (Ulrich, Quan, Zimring, Joseph, & Choudhary, 2004). It is expected that healing rates will be increased enabling faster overall recovery because of the gradual transfer of stress to the healing bone, better overall patient outcomes (Hovis, Kaiser, Watson, & Bucholz, 2002).

Future Project Development

Market Research

The material development is expected to take a significant amount of time, once development is complete it is recommended that the market research is repeated and taken to the next level of accuracy. To hasten the process it is recommended that a global report is purchased.

Application Development Team

Once the material is developed to such a stage that it become possible to know what can or cannot be made with the material it is recommended that an application development and design team is created. This team is intended to work with a number of potential users to find the initial specific surgical application for NacreTech to target.

Technical Development

It is necessary for the biomaterial to be developed to include at least the porosity and strength before further testing or development stages is started. Particularly interconnected porosity is required if there is any chance of achieving high quality osteoconduction. If the biomaterial is unable to achieve the porosity and strength targets outlined in the TPP then the target application as an orthopaedic biomaterial would not appear to be viable.

TPP Individual Implant Requirements and Testing

The current target profiles are for the biomaterial in the general load bearing use case and has not been developed for specific use cases as the current strength characteristics of the synthetic nacre material have not been determined. Bone screws is a subset of orthopaedic implants and individual applications will have their own variations. Once the first surgical procedure and its corresponding implant requirements are identified the TPP will need to be modified to reflect the specific requirements of the implant.

Plant Automation and Costs

The process regarding the 3D printing of the biomaterial is still underdevelopment, as a result the financial and scale-up model is only an estimate. Once the process is finalised, this model will need to be re-addressed. In addition, the cGMP manufacturing figure currently includes an estimate of the automation steps for handling, for example packaging and labelling which may not accurately reflect the final value given changes to the manufacturing processes.

Further Intellectual Property

The proposed intellectual property strategy above considers only the intellectual property which has been developed or is currently being developed within Victoria University. However, there are additional areas to which IP will need to be created or licensed in order to commercialise the biomaterial and market a bioactive bone screw. The following areas are detailed below

Internal Pore Structure

The internal pore structure is the precise network of interconnected pores which allow for the osteoconduction but also optimise the strength of the material. Possibly IP could be sourced through the Victoria design school.

Medical Device Design

The design of the device is dependent upon the material strength results from the first stage of biomaterial testing. The strength of the material will provide guidance on specific uses within orthopaedic surgery and therefore which screw design will be needed. Further investigation is required within this area.

3D Printing

As the 3D printing process is still under development, it is possible that licensing agreements may be required.

Regulatory

It is advised that a regulatory expert is acquired early into the proof of concept stage to ensure that the testing meets regulatory standards and to develop the specific plan to gain regulatory acceptance. Regulatory standards have been considered within the proof of concept plan, however only at a high level planning stage.

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