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Competitiveness of chitosan-based implants

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Biomaterials have been extensively developed and applied in medical devices. Among these materials, bioabsorbable polymers have attracted special attention for orthopedic applications where a transient existence of an implant can provide better results, when compared with permanent implants. Chitosan, a natural biopolymer, has generated enormous interest due to its various advantages such as biocompatibility, biodegradability and osteoconductive properties. In this paper, an assessment of the potential of a developed innovative production process of 3D solid and dense chitosan-based products for biomedical applications is performed and presented. Therefore, it starts with a brief explanation of the technology, highlighting its main features. Then, several potential applications and their markets were identified and assessed. After choosing a primary application and market, its potential as well as its uncertainties and risks were identified. A business model suggesting how to materialize the value from the application was sketched. After that, a brief description of the market as well as the identification of the main competitors and their distinctive features was made. The supply chain analysis and the go-to-market strategy were the following steps. In the end, a final recommendation based on the assessment of the information was prepared.

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1. Introduction

Over the past decades, there have been significant advances in the development of new biomedical materials. Although current treatments using “passive” materials have proven efficacious, tissue-engineering approaches using materials that actively interact and integrate with their biological environment are being considered as promising future alternatives for both failing tissues and organs [1–3]. The multitude of materials studied to perform this task include synthetic polymers like polycaprolactone, poly(lactic-co-glycolic acid), poly(ethylene glycol), poly(vinyl

alcohol) and polyurethane; and natural polymers, such as alginate, gelatin, collagen, starch and chitosan [4]. Among all, natural derived polymers are of special interest due to their biological and chemical similarities to natural tissues.

In 2012, the global biomaterial market was valued at \$44 billion and is expected to grow at a compound annual growth rate (CAGR) of 15.0% from 2012 to 2017 [5]. This indicates a great opportunity in terms of revenue and market growth. Moreover, more than 22% of the global population in 2050 is expected to be over 60 years [5]. Indeed, the innovation opportunities made possible by changes in the numbers of people – and in their age distribution, education, occupations, and geographic location – are among the most rewarding and least risky of entrepreneurial pursuits [6]. The critical need to maximize outcomes from the

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substantial investments in health and biomedical research that some countries have been making is more reachable now than ever [7].

Motivated by these trends, Altakitin was created. Due to the well-known and frequently reported chitosan's broad spectrum of applications along with unique biological properties including biocompatibility, biodegradability to harmless products, nontoxicity, remarkable affinity to proteins, antibacterial, haemostatic, antitumoral, among other properties [4,8], Altakitin had decided to focus its research on this polymer. Moreover, according to PubMed, that comprises over 22 million citations for biomedical literature from MEDLINE, life science journals and online books, there are over 12,500 publications referring to chitosan and this number has been increasing over time [9], as shown in the graphic of figure 1. Accordingly, taking into account this growing trend of biomedical research related to chitosan and the increasing gap between research and chitosan-based products development and commercialization, Altakitin has been focusing its activity on the production of biomaterials, namely chitosan, and on the development and production of chitosan-based medical devices.

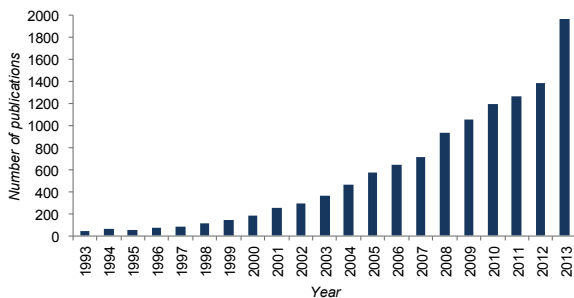


Fig. 1. Number of publications related to chitosan over time [9].

The aim of this article is to assess the potential of an innovative production process of 3D solid and dense chitosan-based products for biomedical applications. Thus, the following section starts with a brief explanation of the technology that was developed, highlighting its main features. For this technology, several potential applications and their markets were identified and assessed. After choosing a primary application and market, its potential as well as its uncertainties and risks were identified. A business model suggesting how to materialize the value from the application was also sketched, followed by a brief description of the market as well as the identification of the main competitors and their distinctive features.

The supply chain analysis and the go-to-market strategy were the following steps. To conclude, a final recommendation based on the assessment of the information gathered during the last 3 years and on a deep analysis was prepared.

2. Technology

Before start thinking about the potential applications of a certain technology, product, or even an idea, it is crucial to identify its main features. Thus, for the new production process of chitosan-based solid and dense products that was developed, it is very important to state from the very beginning its main properties and, compared to the known state-of-the-art, its key distinguishing characteristics. By doing this, the product development team is able to start listing potential applications.

The present technology relates to a novel process, based on a wet gelation process, which was developed for the production of 3D dense chitosan-based specimens to be used in the future generations of bioabsorbable implants, mainly for orthopedic applications [10,11]. The specimens that result from the process are considerably dense and easy to machine. The results suggest that the production process can yield 3D structures that, with proper design, can be good candidates to be used as absorbable implants for different types of applications, within different medical fields such as orthopedics, sports medicine and maxillofacial surgery. As a result, this technology allows the:

- production of 3D dense natural polymer-based specimens, avoiding the problems associated with the stimulation of chronic inflammatory reaction and toxicity by synthetic polymers, on one hand, and taking advantage of the previously mentioned appealing properties of chitosan, on the other hand;
- production of specimens with different sizes, shapes and properties;
- control of specimens' degradation rate and mechanical performance through an intrinsic attribute of their raw material (DD), but also by blending chitosan with other materials.

In conclusion, the developed technology is a production process of chitosan-based implants with potential use in many different medical applications where features as biocompatibility, biodegradability, bioactivity and biomechanical integrity are of crucial importance.

3. Potential Applications

Coming to an understanding of what customers value is usually a more fruitful exercise than merely asking them to submit their own solutions. It is said that the process of innovation begins with identifying the outcomes that customers want to achieve and it ends in the creation of items they will buy [12,13]. Consequently, this stage demands a lot from the product development team and includes a mix of external search, creative problem solving within the team and systematic exploration of the generated solutions. At this stage, a list of potential applications and their assessment is usually made, using the brainstorming tool, by doing a literature review (review papers, research papers, books, patents, among others) and by interviewing some potential customers, users and experts in the field. For each application, it is important to think and assess different application scenarios. This assessment can be made by listing the pros and cons of each scenario.

To understand the potential acceptance of chitosan-based medical devices, as well as the key decision drivers and their decision makers, it is recommended to conduct several interviews. Among these interviews, it is important that some can be conducted to experienced physicians with know-how with bioabsorbable devices in surgery. Moreover, it is also essential to understand from them whether they would use chitosan-based implants if they were readily available in the marketplace. Thus, in addition to understand about surgeons' willingness to use the implants, the aim of this research is to understand where these surgeons envisioned using them (e.g. low-weight-bearing orthopedic applications) and what are the chitosan-based implants' factors of success (e.g. the product itself, chitosan's properties, company's sales force, etc.). From these interviews, the main concerns regarding chitosan-based implants and how they can be overcome should be also addressed.

Table 1 resumes some possible applications, as well as their pros and cons. The list of applications and their assessment were made by doing a literature review, including brochures and websites of the commercially available bioabsorbable implants, and by interviewing some potential customers/ users/ experts in the field. Although implantable chitosan-based medical devices are believed to be very promising for different purposes, including nerve regeneration [14,15] and cartilage repair [16], the potential applications that were assessed are mainly for orthopedic and trauma care.

Table 1. Pros and cons of potential applications of chitosan-based implants

Application	Pros	Cons
Arthroscopy: use of chitosan-based implants (e.g. tacks, anchors, arrows, needles, screws) in shoulder (e.g. Bankart repair, rotator cuff tears repair) and knee (e.g. meniscal repair, anterior cruciate ligament reconstruction)	<p>Biocompatibility, biodegradability and cell affinity</p> <p>No cytotoxic effects</p> <p>Small and easy to shape implants</p> <p>Complications with existing absorbable implants have been reported [17,18]</p>	<p>Big bioabsorbable implants competitors in the market: Smith & Nephew (Suretac); Arthrex (Meniscal DartStick System; Bio-Interference screw); DePuy Mitek (Panalok; Spiralok; RapidLoc); ConMed (Bio-Anchor; Contour Meniscus Arrow; BioScrew)</p> <p>Additional knowledge in this field required (e.g. pull-out strength properties, cyclic loading tests properties)</p>
Bone Fixation: use of chitosan-based implants (e.g. pins, nails, screws) in lower extremities (e.g. osteotomies, foot, ankle and tibial fractures) and in upper extremities (e.g. hand, clavicular, humeral and radial fractures)	<p>Biocompatibility, biodegradability and cell affinity</p> <p>No cytotoxic effects</p> <p>Initial flexural mechanical properties</p> <p>Complications with existing absorbable implants have been reported [18]</p>	<p>Big bioabsorbable implants competitors in the market: DePuy Orthopaedics (OrthoSorb Pin); Bioretac (ActivaPin; ActivaNail; ActivaScrew); Biomet (ReUnite Orthopedic Pin)</p> <p>Difficult to achieve big implants sizes required for some applications</p> <p>Additional knowledge in this field required (e.g. long-term mechanical performance)</p>
Cranio-maxillofacial Reconstruction: use of chitosan-based implants (e.g. plates, screws, mesh panels) in facial surgeries (e.g. pediatric and adult fractures, plastic surgeries)	<p>Biocompatibility, biodegradability and cell affinity</p> <p>No cytotoxic effects</p> <p>Initial flexural mechanical properties</p> <p>No bone growth restriction</p>	<p>Big bioabsorbable implants competitors in the market: Biomet (LactoSorb); Inion (CPS System); DePuy Synthes (Rapid Resorbable Fixation System)</p> <p>Difficult to achieve some implants sizes and geometries required for some applications</p> <p>Additional knowledge in this field required (e.g. how to allow bending of the plates to fit facial curved surfaces during surgeries?)</p>
Spine: use of chitosan-based implants (e.g. plates, screws, cages, meshes) in spine surgeries (e.g. cervical and lumbar fusion, decompression)	<p>Osteoconductive, absorbable and bioactive</p> <p>No cytotoxic effects</p> <p>Compressive mechanical properties</p> <p>Few bioabsorbable implants competitors in the market (e.g. Inion; SBM)</p>	<p>Additional knowledge in this field required (e.g. what is the best chitosan-based cage design for spinal fusion surgeries?)</p>

4. Primary Application

Having in mind that innovation is not looking at need alone, but looking at need and opportunity, among all the potential applications identified and studied, and after careful analysis of all the information gathered during the previous step, the most attractive one should be chosen, in order to focus in one specific market, since the establishment of target specifications for a product is very important from the beginning [19].

4.1. Chitosan-based intervertebral fusion cages

Orthopedic implants market is *per se* extremely attractive. The global market is projected to reach \$46.5 billion by 2017 from an estimated \$21.1 billion in 2007, growing by a CAGR (2007-2017) of 8.2% [20]. The spinal implants market is considered as a very important and lucrative sub segment of orthopedic industry. Spinal devices are observed to be the fastest growing segment with a CAGR of 9.3% [21], being Medtronic (USA), DePuy Spine (USA), Synthes (USA), Stryker (USA), Orthofix International (Netherlands), Biomet Spine (USA), Zimmer (USA), Orthovita (USA), among other companies, the key players in this market [22]. Within this market, lumbar interbody fusions that have been performed in patients with degenerative disk disease and discogenic pain syndromes have been increasing as well [23], making it an attractive market for chitosan-based devices.

The spine, also known as the vertebral column or spinal column, is a column of 26 bones in an adult human body: 24 separate vertebrae interspaced with cartilage, and then additionally the sacrum and coccyx [24]. The vertebrae are named by the first letter of their region (cervical, thoracic, or lumbar) and with a number to indicate their position along the superior-inferior axis. For example, the fifth lumbar vertebra (which is the most inferior one, located beneath the fourth lumbar vertebra) is called the L5 vertebra. Degenerative disc disease occurs when the intervertebral disc between two vertebrae begins to wear out. This intervertebral disc degeneration usually takes place asymptotically in early life in most human beings and is one of the most common causes of chronic pain [25,26]. The process of degeneration causes the disc to lose its ability to act as a shock absorber between the vertebrae. This can lead to pinching and irritation on the nerves, which causes pain into the legs [27]. Thus, fusion of the degenerative and unstable spinal motion segment can

give significant relief from this disabling and often progressive condition [28]. In September of 1996, the FDA approved interbody cages for use in the intervertebral disc space, providing a new technique that allows the spine to be fused with less morbidity (e.g. less post-operative discomfort) than in the past [29]. Nowadays, these devices are commonly used to treat problems such as disc degeneration, disc herniation, spine instability, among other problems [30–33].

The intervertebral fusion implants are designed as “cages” so that bone graft can be placed inside them, allowing the bone to grow from the vertebral body through the cage and into the next vertebral body [29]. Not only the cage design, but also the choice of cage materials plays crucial roles in the long-term results [34]. Nowadays, hollow horizontal cylinders, vertical rings, and open boxes are standard designs and these cages are made of metal (e.g. titanium), polymer (e.g. PEEK), carbon fiber, or allograft bone [29,35]. This surgical technique in which one or more of the vertebrae of the spine are united together so that motion no longer occurs between them, can be performed in different spine regions - cervical, thoracic and lumbar - by using several surgical approaches [23,36–38].

The advantages of interbody fusion include direct removal of the dysfunctional disc and preservation or restoration of the disc height [39]. Thus, these devices allow the restore and maintenance of disk space height and normal sagittal contours by stimulating the vertebrae to grow together into one solid bone. This fusion creates a rigid and immovable column of bone in the problem section of the spine [40].

The ideal interbody graft combines a strong mechanical construct to withstand compressive loads across the disc space while providing an osteogenic, osteoinductive, and osteoconductive matrix [41]. The *gold standard* for this matrix is autogenous cancellous bone. However, due to the poor compressive strength of this bone along with other disadvantages, including donor site pain and occasional poor bone quality, especially in the elderly, led to the development of interbody fusion cages [39]. A wide variety of spacers or cages for interbody support in spinal fusion are in clinical use today. Metallic devices have the advantage of being biocompatible, but lack of radiolucency obscures evaluation of fusion status. Moreover, these devices are associated with excessive rigidity that may increase postoperative complications such as stress shielding, device-related osteopenia, and subsidence [31]. Non-metallic spacers (e.g., PEEK) are

radiolucent, but again do not load share as they persist in the interbody space. Allograft bone is radiolucent and shares load with the developing fusion mass, but consistency, availability and potential disease transmission are still some of the issues associated with the use of allografts. As a result, biodegradable polymer-based fusion cages have gained increasing attention [42,43]. Among the potential advantages, the most distinctive are related with the material degradation over time, being replaced by newly grown tissue, and the material mechanical properties that are closer to those of vertebrae bone, thereby distributing the load more evenly to the ingrown bone and the device.

Taking into account the mechanical properties of the tested chitosan-based specimens (data not shown) and the mechanical properties of bone, one can assert that they are in between cancellous bone - compressive strength: 2-12 MPa and Young's modulus: 50-500 MPa - and cortical bone - compressive strength: 100-230 MPa and Young's modulus: 7-30 GPa [44]. With these in mind, and knowing that the vertebral cortical bone *in vivo* has a thickness often less than 0.4 mm and the apparent Young's modulus computed by a finite element method (FEM) inverse analysis was equal to, on average, 374 MPa (SD = 208) [45], chitosan-based implants for spine, such as absorbable spinal cages, can be an appealing application.

5. Uncertainties and Risks

In this process assessment phase, all different kind of uncertainties and risks regarding the product, the production process, the application and the market have to be evaluated. A common problem with new technologies and products is the capability to be scaled up to reach the required yearly volumes that are needed (or expected). Another common important issue is the cost associated with the production. Therefore, since the price is usually an important feature of almost any product, some considerations should be made in order to offer the technology at an attractive and competitive price.

Concerning the medical devices market, many considerations have to be taken into account, such as the reliability of the process regarding the quality of the product. Furthermore, medical devices and products, or applications, before getting out into the market must be approved by health authorities. Consequently, any medical device placed on the market must comply with the legislation and fulfill the more and more demanding requirements defined by

FDA, to be marketed in the United States; the European Commission directives to be marketed in the entire European Union (EU), in the European Economic Area (EEA) and in Switzerland [46]; among other markets' requirements. This often requires the validation of the manufacturing process according to best practices (in medical, pharmaceutical and food it must be assured the cGMP – current Good Manufacturing Practices). Many times this takes a long time and is a costly process. Thus, there is no certainty that all of the requirements are fulfilled and the technology is approved for use and commercialization, since it involves many different aspects, not only technological about production process, but also about the general evaluation of the facilities where the product is obtained, procedures in place to assure product quality, equipment qualification and qualified people.

Another concern that has to be taken into account is the time to market. Health authorities' requirements are more and more demanding and sometimes, when the product is approved, the time to market can be lost, being other product competitor, or substitute, already in the market. So, the know-how in this health authority's submission is also crucial.

5.1. Chitosan-based intervertebral fusion cages uncertainties and risks

Undeniable promising results as far as 3D chitosan-based products biomechanical properties are concerned were already obtained and preliminary results already reported [10]. However, a more long-term characterization both *in vitro* and *in vivo* is still required. It is known that interbody fusion requires a long healing time of more than one year [31]. New bone formation within or adjacent to the fusion device is typically seen by 3 months after the fusion procedure and usually progresses for 18-24 months [23]. Thus, further experiments need to be conducted in order to guarantee that these chitosan-based structures are appropriate for future generations of spine cages, otherwise fast degradation and loss of structural integrity may cause poor fusion performance.

Another concern is the design of chitosan-based cages. Conventional hollowed cylindrical cages or vertical ring types may not be adequate design candidates for biodegradable cages. The thin-wall geometry originally designed for metallic cages may collapse under physiological loading conditions when simply replacing permanent materials, such as titanium or

PEEK, with significantly less-rigid biodegradable polymers [31]. During daily activity, the lumbar spine is exposed to significant biomechanical forces. Studies indicate that a motion segment may experience axial compressive loads ranging from 400 N during quiet standing to more than 7000 N during heavy lifting [35] and, therefore, when designing future spinal cages, this information should be taken into account.

Like other technologies, products, or devices, there is always the risk of substitutes. Although spinal fusion has remained the gold standard for the treatment of spinal degenerative disorders, it can cause restriction of motion and degeneration of adjacent spinal segments through stress which can further delay recovery and in some cases, even lead to unwanted additional back surgery [22]. This has led surgeons and patients to adopt spinal non-fusion or motion-preserving technologies, which maintain the patient's spinal mobility while alleviating severe back and leg pain, offering clinical benefits over arthrodesis or spinal joint fusion [47].

In conclusion, although chitosan-based cages (or spacers) seem to be promising absorbable implants for spinal fusion applications, the above mentioned risks and uncertainties, related with the process, the product and the market, have to be taken into account.

6. Business Model

The business model is an important tool that helps a concept goes from an idea to the market. That means it is a useful tool to explain how to materialize the value from the technology to a specific application to put in the market. The business model stage usually includes the value propositions of a company, meaning the company's offer. Besides that, it usually has three more clusters of information: (i) customer, with the description of target customer segments, customer relationship and distribution channel; (ii) infrastructure, describing the core capabilities, partner network and value configuration; (iii) finance, with the cost structure and revenue streams description [48].

Figure 2 represents a template of a business model and it is useful to explain the value proposition of the selected application.

The value proposition of the presented application could be a totally absorbable chitosan-based intervertebral cage with better biomechanical properties than any other cage, avoiding the need of using autograft bone and promoting a faster fusion, due to the high level of cells adhesion and proliferation.

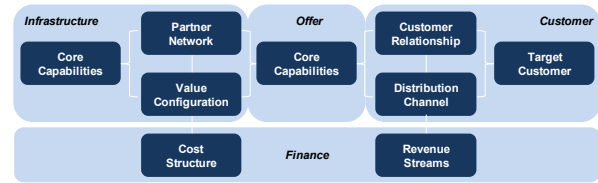


Fig. 2. Business model template [49].

From the technology – the innovative 3D dense chitosan-based structures production process (core capability) – it is possible to obtain the chitosan-based intervertebral cages with the features mentioned before. Then, through the expertise of partner(s), the product could be offered in individual and customized packages, with the appropriate surgical instruments, intended for different spinal fusion surgeries.

The target customers of these medical devices would be orthopedic surgeons specialized in spine surgery, working in hospitals and clinics. These medical care organizations, specially the hospitals, are usually characterized by periodic purchases of large volumes, being cost awareness and looking for the specificity and the quality of the product (e.g. healthcare authorities' certification; surgeons/ patients satisfaction).

In order to build a close and trustful relationship with customers, a certified distributor with a strong sales force could be used. Besides that, the product could be regularly presented and communicated in strategic medical congresses, conferences and seminars (e.g. International Society for the Advancement of Spine Surgery, Congress of Neurological Surgeons, Global Spine Congress, European Spine Congress) to promote and spread its use and to create a strong brand within the medical community. By doing this, it would be easier to introduce new products in the market and/or find new applications for the same chitosan-based implants production process.

7. Primary Market

Although the choice of the primary application can be supported by the global market size and its attractiveness, in this stage is important to identify and decompose the market by country, for instance, and carefully select the primary target market(s), as well as the primary group of users that should be targeted. This process stage can result in a document, known as mission statement, which helps keeping the product development team focused on the project goals. The formulation of this document is important, since it sets from the beginning the product vision. This document usually includes the product description, the key

business goals, the selected primary market(s), as well as the secondary markets, assumptions and constraints, and the identification of the main stakeholders [50].

7.1. Chitosan-based intervertebral fusion cages primary market

As previously mentioned, the global spinal implants market is considered as a very important and lucrative sub segment of orthopedic industry. Taking into account that the innovative technology was developed in partnership with two Portuguese corporations – Ceramed and Altakitin – the primary target market should be Portugal and the remaining countries that require the CE marking, which is a mandatory conforming marking for medical devices sold within Europe, as previously explained. By taking advantage of Ceramed and Altakitin market know-how, customers and other useful contacts, spinal surgeons are the primary group of users that should be targeted. Attending and participating in international meetings and conferences is also highly recommended in order to strengthen these contacts.

Entering the market with chitosan-based bioabsorbable, bioactive and osteoconductive cages for spinal fusion surgeries is a good differentiation strategy to enter in an existing market under an expected dramatic transformation, primarily driven by innovation, globalization and commoditization of products [22]. Thus, within the spinal implants market, there are some niche markets and groups of surgeons specialized in specific surgeries (e.g. intervertebral fusion surgeries) that can start using these innovative chitosan-based cages and help spreading their use.

Finally, since the Asian countries represent the fastest growing markets, due to large population, growing physicians and patient awareness about the new technologies, improving reimbursement coverage, booming medical tourism and increased purchasing power of hospitals [22], these markets cannot be neglected and therefore should make part of the secondary markets list.

8. Competitors

An understanding of competitive products is critical to the successful positioning of a new product and can provide a rich source of ideas for the product and production process design. Knowing the market and its main players, including the existing products, or the potential future products, is crucial [50]. Thus, a comparison of the new product with the main existing

solutions should always be carried out. Taking into account the key features and main characteristics of each product, it is possible to identify the strengths and weaknesses of each of them and see if the new product is able to overcome the identified weaknesses. There are essentially two types of competitors for the technology presented here: (i) those who produce and/or commercialize other spinal fusion devices and (ii) other techniques used as alternative treatment options for low back pain. Although the following subsections will focus on the existing spinal fusion devices, alternative treatment options such as artificial disks have emerged during the last decade and should not be neglected, since it may reduce the need for interbody fusion in the future [51].

8.1. Titanium-based cages for spinal fusion

Originally, interbody fusions were all performed with the patients' own bone from their iliac crest. Besides the bone graft site pain, there was a high nonunion rate associated with these procedures. As a result, the threaded cylindrical titanium cages became popular in the late 1990's, since they helped the success rate of the procedure by providing more firm fixation of the disc space [29]. Moreover, the amount of bone that needed to be harvested from the iliac crest was greatly reduced because only the soft inner cancellous bone was needed for the fusion. Currently, there are also several bone graft substitutes that may even eliminate the need for bone graft harvests [29].

Originally developed to treat race horses with wobbler syndrome (cervical spinal stenosis), the BAK cage (Zimmer Spine) is a cylindrical, hollow, porous, titanium alloy cage that is screwed into position within the disk space [52]. A second-generation cage developed by Charles Ray, the Ray Threaded Fusion Cage (Stryker Spine) is a cylindrical, hollow, titanium, threaded device that contains less metal than the BAK cage [23,53]. The LT-CAGE (Medtronic Sofamor Danek), a third-generation device, is one of the most widely used interbody implant in North America [23,54,55]. Its shape allows increased surface area for bone growth. It is a thin-walled, threaded cage with truncated side walls that facilitate radiographic assessment of new bone formation inside and outside the implant, when compared to the other metallic cages [23]. ST MESH (DePuy Spine), a surgical titanium mesh implant, has an open diamond configuration to maximize the area of bone graft and allow for load sharing [23,56].

One conceptual problem associated with these devices

is their geometric shape. The volume available for bone graft in cylinders is less than that in vertical ring devices, such as the femoral ring allograft. A tapered device as opposed to a cylindrical shape better restores lordosis and sagittal balance [35]. Another concern associated with these metallic-based devices is the production of severe artifacts on magnetic resonance (MR) and computed tomography (CT) imaging [23]. Images from CT scans cannot be used because of the scattering effect of the metal. Despite some new techniques, CT scanning is still insufficient for evaluation of bone density and the level of incorporation of the cancellous bone into the cage [57].

As previously mentioned, there are already several bone graft substitutes that may eliminate the need for autologous bone grafts, commonly used in combination with these cages. This has resulted in the use of different materials such as bioceramics, corals, allografts, and constructs made from carbon fibre or metal. However, the results of fusions performed using these techniques are inconsistent and not convincing [57]. Approved in July 2002 by FDA as the first bone graft substitute equivalent to iliac crest autograft for spinal fusion, for use only with the LT-CAGE, INFUSE Bone Graft combines recombinant human bone morphogenic protein (rhBMP-2) with an absorbable collagen sponge carrier [23]. The rhBMP-2 acts as a signaling molecule to attract mesenchymal stem cells, binding to cell receptors and causing these stem cells to differentiate into osteoblasts and initiate bone formation. However, it has been recently associated with many severe problems, including: difficulty breathing, swallowing or speaking; compression of the airway; respiratory depression; nerve damage; among others [58].

8.2. PEEK-based cages for spinal fusion

PEEK refers to polyetheretherketone, a plastic substance with biomechanical properties similar to those of cortical bone [23,59]. This compound can be machined into any shape and size and is radiolucent on CT and plain radiographs. Depending on the shape, it can be placed through any surgical approach [59]. The main advantages of PEEK-based cages when compared with the metallic devices include their lack of artifacts on CT imaging [23]. On the other hand, they do not provide as good fixation. Generally, posterior pedicle screw supplementation is also necessary [29].

8.3. Carbon fiber-based cages for spinal fusion

The JAGUAR I/F CAGE (DePuy Spine) is one of the available carbon fiber-reinforced polymer implant, which can be machined to meet size and shape requirements. It is predominately radiolucent and produces fewer artifacts on CT and MR images, when compared with metallic implants. This device was designed for the posterior lumbar interbody fusion approach and is always used with supplemental posterior instrumentation. The disadvantage of a rectangular cage placed through a posterior approach is the tendency toward an over-curvature of the thoracic vertebrae [23].

8.4. Allograft bone-based cages for spinal fusion

The main benefit of allograft bone is that there are no surgical risks for the patient associated with harvesting their own bone. Moreover, the absence of imaging artifacts and the placement of a completely biologic device are two more advantages of these devices. However, there are two main drawbacks: (i) lower chance of fusion - since allograft bone does not contain living bone cells, it is not as effective at stimulating fusion as the patient's own bone - and (ii) risk of disease transmission - despite rules and regulations for tissue banks regarding processing and procedures of human tissue, there is still a small potential risk of disease transmission from using cadaver bone [60]. Furthermore, unlike titanium interbody cages, threaded cortical bone dowels are subject to supply shortages and processing problems [35].

8.5. Absorbable polymer-based cages for spinal fusion

Novel uses of bioabsorbable technology are constantly evolving. Bioabsorbable implants are already frequently used in sports medicine surgeries, especially in shoulder and knee ligaments reconstructions [61], and their use is now expanding to the realm of spinal surgery with the aim of help reducing many of the complications associated with the use of non-resorbable implants (e.g. stress shielding, pseudarthrosis), since they have a better match of strength and elasticity to bone [62,63]. In addition, these absorbable implants are radiolucent, offering the ability to assess fusion radiographically and eliminating long-term residual hardware [64,65]. Initial results showed that the reduced stiffness of PLA-based cages can enhance interbody fusion, as compared with titanium cages [66]. Part of the

available clinical and radiographic results have supported the use of interbody devices manufactured from this bioabsorbable polymer for structural interbody support [67,68]. For similar PLA-based implants, however, concerns of early device failure were also raised, with too rapid *in vivo* degradation being the suspected reason [69,70]. Furthermore, other studies showed an increased incidence of nonunion and post-surgical cage migration in patients undergoing lumbar interbody fusion with PLA-based biodegradable cages versus carbon-fiber implants [71] and PEEK-based implants [72].

As spinal interbody implants need to maintain mechanical integrity for a period of at least six months [73], this has serious implications for the clinical application of absorbable polymer-based implants in load bearing situations. Moreover, some authors declare that the disintegration of absorbable polymer-based implants into particles with a very slow hydrolytic degradation rate, as recommended for spinal fusion applications, can induce and maintain a clinically detectable swelling, with the occurrence of foreign body reactions, allowing skepticism regarding the value of these bioabsorbable implants [74,75].

An ideal scenario for interbody fusion is a cage device that has a modulus of elasticity that is the same as or close to that of vertebral bone, that will be absorbed after interbody fusion, maintaining the strength under continuous and alternate loading throughout the period of time required for full spinal bony fusion (a minimum of 6 months) and that will be replaced by cancellous bone, not leaving foreign body material in the spinal segment, but only a bony fusion between the vertebrae [76,77]. Therefore, chitosan-based cages seem to be an appealing alternative to the existing devices that have just been mentioned, as far as biomechanical properties are concerned, although further *in vitro* and *in vivo* long-term experiments are needed.

9. Industry Dynamics

As the name suggests, study the industry dynamics means identifying the forces driving a specific industry evolution. Taking into account the medical devices example, this industry is very dynamic since it is focused on improving the healthcare of the patients but, at the same time, it is also very competitive because manages a large volume of money. It is an industry characterized by having a complex supply chain – raw-material suppliers, big manufacturers, but also small and medium enterprises (SMEs), distributors, hospitals/clinics, patients [5]. A short

representation of the overall and usual supply chain for medical devices is presented in figure 3, being the production process of chitosan-based implants within the responsibilities of the manufacturer.

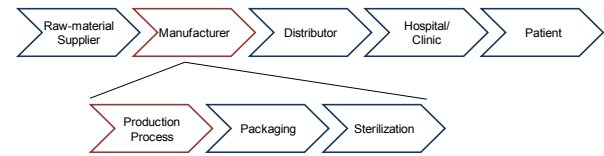


Fig. 3. Chitosan-based implants supply chain.

The goal of the manufacturer is to provide a high valued product to their customers and increase market share, either by existing process improvements, or by offering new products for different applications and getting new businesses. Thus, from the manufacturer perspective, the goal is to have a different product to offer to medical devices companies and distributors, or to have an effective production process by lowering costs and increasing margins. Many companies in the medical devices business incorporate several supply chain blocks and usually, the closer it is from the product utilization the higher is the value. Therefore, it is common that large medical devices companies have their own manufacturer facilities and distribution centers. They also have strong sales force to marketing their products in hospitals and clinics. In order to increase their portfolio, these large companies are constantly looking to different technologies that allow better innovative products that can easily enter in the market and be market leaders [78]. Normally, the Intellectual Property (IP) of the product belongs to the medical devices company, but the production process and its technology IP is owned by the manufacturer, when they are not the same company.

Hospitals and clinics want to have products that can improve the healthcare of patients at a reasonable price. The decision-maker of what product to use for each situation, usually the surgeon, has an enormous impact in all of this supply chain. However, particularly in public hospitals, there are constraints regarding costs, so new medical devices must have a better cost-effective ratio when compared to the available ones. Besides that, the purchasing department and the evaluation of budgeting from hospital executives have an important role in the application decisions. In (private) clinics, the medical devices and their applications tend to be state-of-the-art to attract patients that expect a high level of service, although there is already some pressure from insurance companies. In this case, the buying decision

is more focused on a surgeon-patient agreement and decision.

10. Go-to-Market Strategy

A Go-to-market strategy is a mechanism, or an action plan, that a company can use to propose how to deliver its value proposition to the target market. Therefore, the three main questions to be answered are: (i) what to sell; (ii) how to sell; (iii) who to sell (figure 4). Although these three questions were answered along the previous development stages, it is crucial to define a strategy from the state-of-the-art.



Fig. 4. Go-to-market strategy mechanism [79].

The technology consists of a novel 3D dense chitosan-based structures' production process, developed in partnership with Ceramed and Altakitin, which allows to efficiently producing chitosan-based implants for spinal fusion. In order to bring the intended medical implants to the market, several ways could be adopted, being the one presented here one possible solution.

While defining the strategy, the product development team should not only take into account the available resources, but also overcome some of the existing limitations and identified needs. Therefore, in order to make chitosan-based implants for spinal fusion applications a real product, several risks and barriers have to be overcome, such as:

- Lack of market know-how
- Large initial investment required
- Need for process scale-up
- Need for plant, product, packaging and sterilization validation and certification
- Find adequate and certified distribution channels
- Entrance of new competitors

With this in mind, and in order to bring the invention to the market, a partnership with a medical devices industrial manufacturer with know-how in the field and interested in increasing its product portfolio may be considered. Although both Ceramed and Altakitin have a great experience within the orthopedic medical

devices market, at this stage and to go further with the technology, looking for another partner with know-how in the field that could not only co-develop the technology, but also share the financial investment risks, could be the next step. To do so, crafting a business plan so that it thoroughly and candidly addresses the ingredients of success - people, opportunity, context, and the risk/reward picture - is vitally important [80]. By having the money and the market know-how, the certification process can be done much faster, reducing the time-to-market [81–83].

Surgeons wishing to perform interbody procedures using bioabsorbable cage devices should understand the fundamental differences between the non-absorbable and bioabsorbable cages and should be properly trained in patient selection, surgical technique and correct device handling and placement [62]. Consequently, finding a specialized medical devices distributor with a strong sales force to couch surgeons and sell the products in hospitals and clinics is also very important, not only to gain market share, but also to create a strong brand name and a good reputation in the market. This can be complemented by actively participating in congresses, conferences and by publishing regular papers in the most known spine surgery journals.

In conclusion, after analyzing the market, its stakeholders and its externalities, the presented strategic steps are one possible way to bring new chitosan-based implants for spinal fusion to the market (WHAT) that can be sold through a strong sales force team (HOW) to hospitals and clinics where spine surgeries are regularly performed (WHO).

11. Final Recommendation and Conclusions

After identifying some of the potential applications for the developed innovative technology, as well as a deep analysis of the market and the medical industry for the specific application that was identified and studied, it can be concluded that the potentiality of the technology and the product that can be developed is enormous. However, in order to place it successfully in the market by following the steps presented in the go-to-market strategy section, further information and studies need to be performed.

Firstly, more inquiries to the medical community and particularly to spine surgeons have to be made in order to complete and compile information about market needs, surgical procedures currently being used, advantages and problems associated with the existing devices already in the market.

A detailed cost analysis of the process, from the raw material to the final product, is also highly recommended. Furthermore, the sustainability of the process has to be assessed, as well as its environmental impact. Expanding the IP protection of the technology to other strategic markets must be weighted as well.

Besides strengthening the partnership between the university and the companies involved in the project (Ceramed and Altakitin), a partnership with a bigger medical devices company already established in the market can be advantageous in order to:

- share the required high investments in equipments/ installations to produce the product and know-how in processes scale-up
- reduce the timing for process submission and to increase the possibility to be approved by health authorities
- easily enter in the market, taking advantage of the existing customers and connections
- understand the market dynamics and needs, competition and further explore connections to other companies in the business
- take advantage of the partnerships and of the potentiality of the technology and start thinking and exploring new products and new applications

In conclusion, although the technology seems to have a great potential, the short-term recommendation is to make a deeper research in the field to quantify the main key features of the technology in order to design and perform future studies to validate the premise that chitosan-based implants provide better results than the existing bioabsorbable implants used in spinal fusion surgery.

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