DEVELOPMENT AND COMMERCIALIZATION OF
PERITONEUM LINED STENT FOR THE TREATMENT OF
PERIPHERAL ARTERY DISEASE

by

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Abstract

By

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Cardiovascular disease is the leading cause of death in the United States and atherosclerosis is its major grounds. Based on statistics for aging population alone, a conservative prediction is, there will be approximately 190,000 peripheral vascular procedures performed in 2020 (American heart association). A major component of peripheral arterial disease (PAD) is obstruction of blood flow to the lower extremities from atherosclerosis. Of the arteries in the lower extremity, the superficial femoral artery (SFA) is the most commonly affected by PAD. There is no ideal endovascular solution to treating lower extremity occlusive disease, as they have not yet proven to be efficacious in the SFA and in some cases, have performed worse than bare metal stents. The thesis will focus on Peritec Bioscience’s novel peritoneum lined stent (PLS) development and its commercialization plan. The PLS has shown excellent performance in animal and early human clinical studies. The PLS is attached to a self expandable stent which must be crimped and attached to the catheter at the time of surgery for deployment in the SFA.
1. **Introduction**

1.1 **Internship at Peritec Biosciences**

As a part of the Master’s program requirement, I got an opportunity to intern at Peritec biosciences, a Cleveland Clinic Spin off Company. I assisted the company in writing Federal grants and involved myself in Tissue Lined Stent development. During my internship, I got the opportunity to write several grants for institutions such as National institutes of Health, Third Frontier etc. As a grant writer I assisted Dr. Sarac Timur (Founder and President, Peritec Biosciences Ltd.) in preparing budgets, commercialization plan and grant submissions to NIH. The responsibilities that I mainly undertook during the course of my internship are briefly described below:

- Assisted in writing grants for Peritec to institutes such as NIH, Third Frontier and other Federal Govt. Agencies.
- Conducted due diligence to assess market potential and feasibility for Peritec designed Tissue Lined Stents.
- Actively involved n performing quality testing for the stents and supervising seamstress in the development of Tissue Lined stent.
- Gained experience in maintaining controlled documents and protocols adhering to FDA guidelines and GLP practices. This is providing me with additional managerial experience.
1.2. Overview of Peritec Biosciences

Peritec Biosciences, Ltd. is a spin-off of the Cleveland Clinic Foundation that develops innovative vascular and cardiovascular surgical products to improve surgical outcomes through product longevity and cost effectiveness. The company’s technology involves the incorporation of a superior biological tissue, the peritoneum, into two implantable products - peripheral vascular stents and vascular patches. PeriTec has already obtained 510(k) approval for the peritoneal/fascia vascular patch. This is a precursor to attacking a larger peripheral market. The company is currently developing the peritoneal lined stent graft to treat peripheral artery disease in the superficial femoral artery (SFA). The billion dollar market that this platform technology is increasing quickly due to various lifestyle habits in the Western countries.

Current surgical products using synthetic material such as Dacron and ePTFE or biological tissue (pericardium) offer less than optimal results. The company’s technology offers important advantages. PeriTec’s proprietary peritoneum material is the tissue lining the abdominal wall of all mammals. It is strong, yet flexible, and is only 100 microns thick. It possesses the same cellular structure as that of the inner lining of blood vessels. These characteristics allow for size customization, less likelihood of obstruction, and a greater product life expectancy. In addition to these attributes, the peritoneum material is in abundant supply and competitively priced in relation to other biologic tissues.
The peritoneum-lined stent will require an Investigational Device Exemption (“IDE”) and human clinical trials leading to a PreMarket Approval (“PMA”) with the FDA.

1.3. Scope of Thesis

The main purpose of this thesis is to analyze and evaluate the current situation of Peritec Biosciences Ltd. with respect to the development and commercialization of Peritoneum Lined Stent.

a. Understanding the product development process

b. Evaluate the future success of the Peritoneum Lined Stent

Final recommendations will be provided to help the Company move quickly in its developmental and commercialization process. The recommendations are given on basing the current situation of the company. These recommendations will be given only after thorough analysis and understanding of the scientific technology and a commercialization plan that covers the understanding of the Peripheral Artery Disease market, competition and financial aspects.

The flow of the thesis is as follows.

Firstly, the technological details behind the development of Peritec’s Tissue Lined Stent will be detailed. This will enable us to understand the scientific background behind this venture.
Then the Commercialization plan will discuss the current market scenario, Competition, intellectual property, sources of funding etc. All of this detailed information will enable the development of a marketing plan. Based on my understanding and experience gained at Peritec Biosciences Ltd, the marketing plan will be developed appropriately that will help the company move forward in its development and commercialization process.
2. Technology Description

2.2. Scientific Background

2.2.1. Peripheral Arterial Disease and The Superficial Femoral Artery:

Peripheral arterial disease (PAD) is a type of cardiovascular disease that occurs when the arteries carrying blood to organs or extremities of the body are blocked. This disease limits the flow of oxygen-rich blood to various parts of the body. When peripheral arteries narrow due to plaque, the flow of oxygen-rich blood is restricted in the leg, arm, or other parts of the body and this can lead to cell death due to lack of oxygen and nutrition. People with PAD have greater risk of getting a heart attack and stroke. About 1/3\textsuperscript{rd} of patients suffering from PAD die of heart attack or stroke. Severe PVD might cause severe infection and lead to loss of limb.\textsuperscript{1}

Fig 1: Atherosclerosis in the lower limb\textsuperscript{22}
The Superficial Femoral Artery is the most common site of stenotic atherosclerotic lesions of all peripheral arteries. Recently data determined that approximately 8 million men and women age 40 and older have PAD\textsuperscript{24}. The risk factors for PAD are similar to those for coronary heart disease, although diabetes and cigarette smoking are particularly strong risk factors for PAD. \textsuperscript{2}

Some of the risk factors are

- Smoking - tobacco
- Age
- Personal history of vascular disease, stroke, obesity, heart attack.
- Diabetes mellitus
- Dyslipidemia - elevation of total cholesterol
- Hypertension

### 2.2.2. **Superficial Femoral Artery**

The superficial femoral artery begins behind the inguinal ligament and passes down the front and medial side of the thigh. It ends at the junction of the middle and lower third of the thigh. There it passes through an opening in the Adductor Magnus and becomes Popliteal Artery.

The superficial femoral artery (SFA), the longest artery of the lower extremity, is a direct continuation of the common femoral artery beyond the deep femoral branch. The thigh and lower leg are dependent on the SFA for blood and nutrient supply. The SFA is the most common site of stenotic atherosclerotic lesions of all peripheral arteries. In fact, 50\% of all atherosclerotic occlusive disease outside the heart involves the SFA.\textsuperscript{3}
Currently, there is a ground swell of clinicians including cardiologists, vascular surgeons, interventional radiologists, and now cardiovascular surgeons, who utilize minimally invasive techniques to treat arterial occlusive conditions due to atherosclerosis.  

**Atherosclerosis** is the condition in which an artery wall thickens as the result of a build-up of fatty materials such as cholesterol. **Thrombosis** is the formation of a clot in the arteries that prevents the flow of blood through the circulatory system.

![Figure 2: Response to Vascular Injury](image)

Restenosis refers to the narrowing of blood vessels which were previously treated, leading to restriction in blood flow. This prevents the flow of blood through the arteries.

### 2.1.3. Minimally Invasive Treatment Options of Atherosclerosis of the SFA:

The options for minimally invasive treatment of SFA occlusive disease include: Percutaneous Transluminal Angioplasty (PTA), stenting, and atherectomy (lasers/rotor routers).
Percutaneous Transluminal Angioplasty is performed to treat narrowing of arteries by passing a wire along the femoral artery that is affected. The end of the catheter contains a balloon. The balloon is inflated at the site of the injury to expand the wall and improve blood flow. It effectively compresses the atherosclerotic plaque and reopens the narrowed vascular lumen. However, PTA and stent placement are plagued by restenosis and thrombosis. Thrombosis is the formation of a clot in the arteries that prevents the flow of blood through the circulatory system.

Restenosis refers to the narrowing of blood vessels leading to restriction in blood flow. This prevents the flow of blood through the arteries. Restenosis occurs when vascular smooth muscle cells undergo cell proliferation and migration with subsequent synthesis of extracellular matrix and collagen resulting in neointima formation. Neointimal formation is the major cause of restenosis and can cause in-stent stenosis within months.

![Fig 3. Normal artery on the left and restenosis after PTA on the right](image)

2.1.4. **Stenting:** The process of using a metal scaffold to prop open arterial blockages is called stenting.

A stent is an artificial tube inserted into a natural conduit in the body to prevent flow restriction. There are various types of stents that are used to treat SFA blockages.
The majority of stents initially used to treat lower extremity SFA blockages are bare metal nitinol stents. However, these stents have restenosis rates which range from 35% to 50% in the first year following treatment. The restenosis rate of stents placed in long lesions (>6cm) in the SFA has been as high as 78% after 12 months. The reason for SFA stent restenosis is multifactorial and complex. PTA and stenting causes endothelium to denude which consequently exposes underlying components such as collagen, Von Willebrand factor, fibronectin, and laminin. Exposure of these components leads to platelet adherence, aggregation and activation, along with release of inflammatory mediators. The end result is formation of a dense scar tissue, called neointimal hyperplasia, which leads to thrombosis.

Another minimally invasive device used to treat blocked SFAs is atherectomy, which removes plaque and blockage from an artery in the body and simultaneously widens the arteries that are narrowed due to arterial disease. These include lasers and mechanical atherectomy devices. Unfortunately, similar to PTA and stents, the durability of atherectomy devices is suboptimal, with one year restenosis rates up to seventy percent. The last resort is bypass surgery, which is maximally invasive, and involves rerouting the plumbing. Bypass is a procedure where one’s own vein or a prosthetic conduit is used to divert blood around the blockage. While long-term restenosis is significantly less, bypass procedures involve lengthy hospital stays that average 7 days, significantly greater than minimally invasive stent procedures (< 24 hours). This is followed by several weeks spent in rehabilitation, adding to a lot of expense.
There has been a significant development in the area of Stents. Different types of stents have been developed post Bare mental stents.

1.) Drug coating the stents similar to heart stents 2.) Lining the stent with prosthetics etc.

Drug coated stents have significantly improved the efficacy of stents placed in the coronary arteries of the heart, but they did not prove efficient in the superficial femoral artery. Drug eluting stents are coated with biodegradable polymers that allow drugs to elute off within in the injured area. Till the drug lasts, the effect is positive. Once the drug wears of the stent, the problem of thrombosis, restenosis occurs again. The most promising drug eluting stents to prevent restenosis are ones that have been coated with rapamycin, sirolimus, paclitaxel, and everolimus. They act primarily by preventing smooth muscle cell proliferation. However, these have not fared as well in the SFA. Drug eluting stents have not been proven effective in lower extremity clinical trials.

In the SCIRROCO I and II trials, drug eluting stents fared no better than bare metal alone. Multiple negative findings from the use of drug-eluting stents have been reported, including acute thrombosis, inflammation induced by the polymer, toxic effects of the drugs, and a delay or incomplete re-endothelialization.

**Fig 4:** A. Large SFA plaque
3. **Peritec’s Technology**

3.1. **Tissue and Nitinol Hybrid Technology**

Hybrid technologies using drugs and nitinol stents or prosthetic linings and stents have not proven to be efficacious. However, Peritec’s Tissue Lined Stent technology looks promising with enormous potential in this market. It is a well known fact that animal tissues have higher compatibility rate in medical applications. Peritec’s proprietary technology is based on a tissue lining the inner walls of a bare nitinol stent. The tissue used here is Peritoneum.

The **peritoneum** is the serous membrane that lines the inner walls of abdominal cavity in the higher vertebrates. It is composed of mesothelium and is supported by the connective tissue. Peritoneum is fibroelastic tissue covered by a single cell layer known as mesothelium, which lines the abdominal cavity and organs of all vertebrate animals. It is abundant and easily harvested from cows and other animals. The peritoneum is composed of a single cell layer of mesothelium and basement membrane. It is a smooth, natural surface that functions as a confluent layer similar to endothelium. Bovine peritoneal tissue consists of a single cell layer of mesothelium which is similar to artery endothelium. Mesothelium lines the surface of dense connective tissue. The lower portion of this dense connective tissue has elastic tissue coursing through which makes the tissue very durable. Normal arteries contain elastic tissue, which helps the tissue recoil back in a pulsating environment.

The use of tissue peritoneum as a potentially viable material in the treatment of SFA atherosclerosis has emerged. Peritoneum has been used to reconstruct the inferior vena cava in pigs with excellent results\textsuperscript{17}. Dr. Sarac et.al used peritoneum with fascia to repair
an infected aortic stump in several patients. There has been no evidence of stump rupture or aneurysmal enlargement after six years\textsuperscript{18}. This indicates the peritoneum is a durable material that can effectively be used in blood vessels. Peritoneum is abundant and easily harvested from cows and other animals. Peritoneal tissue was first used in the 1970s by a Polish researcher to cover the inner lining of synthetic graft material \textsuperscript{19}. In these experiments, Teflon grafts were lined with canine peritoneal tissue and used to replace a portion of the abdominal aorta in dogs. These grafts showed superior durability, patency, and histological features to Teflon grafts alone. The theory for success was that the tissue provided physiological benefits while the prosthetic afforded structural integrity. Peritec’s proprietary peritoneum carries similar characteristics as that of the cellular structure of the inner lining of blood vessels. These characteristics allow for size customization, less likelihood of obstruction, and a greater product life expectancy. In addition to these attributes, bovine peritoneum material is abundant in supply and competitively priced in relation to other biologic tissues.

![Fig 5: First self expanding tissue lined stent](image)

Nitinol is a shape memory alloy which is formed by alloying nickel and titanium. It has superelastic properties which are similar to that of a bone. This property makes nitinol
advantageous for clinical application. Nitinol is commonly used in the biomedical industry to make stents, heart valve tools, bone anchors, and implants etc. The combination of Tissue with Nitinol forms the Peritec’s Peritoneum Lined Stent (PLS).

3.1.1 Preliminary Studies:

Animal Studies – Peritec received 510k approval from the FDA to use peritoneum with fascia as an arterial patch, which is commonly used to patch arteries after endarterectomy procedures. This occurred after successful completion of mechanical tests as well as in vivo animal studies using a canine femoral artery model. The peritoneal/fascial patch performed better in 3 out of the 7 mechanical tests when compared to a commercially available bovine pericardial patch (Vascu-Guard®, Synovis Inc.) and was equivalent in the other tests. More importantly, the peritoneum with fascia patch performed superior to Vascu-Guard® in failure force and suture pullout force. This demonstrated that peritoneum is a viable tissue that can withstand the vascular forces in vivo. However, it also lends support to the concept that it will be a good stent lining to assist in maintaining patency.

Peritec took this work several steps further. First, bovine peritoneum lined balloon expandable tissue stents were constructed and evaluated them in a restenosis animal model. All dogs were implanted with a bovine peritoneal lined stent (PLS) in the common iliac artery on one side and a commercially available dacron lined stent ((DLS)Wall Graft®, Boston Scientific) on the contralateral side. Vessels were harvested at either one month or six months. All stents were patent at one month, and at six months three DLS thrombosed compared to only one PLS. At six months intravascular
ultrasound (IVUS) of the lumen area demonstrated both proximal and distal regions of the DLS was significantly less than the PLS at one month. **This indicates that the PLS performed superiorly compared to the control stent.**

**Human Trials:** A pilot safety study was initiated in November 2006 to evaluate the safety of the tissue lined nitinol stent in patients with superficial femoral artery occlusive disease. The study completed October 2008; twenty eight stents were placed in twenty one patients. There were no procedural adverse events, and to date 26 of 28 stents were patent out to one year, with seventeen patients out to as far as two years (Figure 6)

![Figure 6: Kaplan Meier Curve of Stent Patency](chart)

While the primary assisted and secondary patency is above 95%, the primary patency remains at 65%. All stenosis occurred at the proximal end, and are attributed to stent tissue designs altering flow. However after re-balloon almost all stents remain patent. Due to the success of the first study a second pilot study was initiated to treat dialysis access and outflow stenosis. To date five patients have been implanted and all the stents remain patent (Figure 7). **This first in man study continues to be supported by the**
equity raised by the Company. No grants from NIH will be used to support this study.

A.                                                                                  B.

![Image of Patient #1 with SFA PLS stent (arrows) now patent 3 years](image1.png) ![Image of First dialysis access outflow patient treated with a PLS now patent one year out](image2.png)

**Figure 7:** A: Patient #1 with SFA PLS stent (arrows) now patent 3 years B. First dialysis access outflow patient treated with a PLS now patent one year out.

### 3.2. Development of the tissue lined stent

#### 3.2.1 Creating computer aided designs of the desired stent model

Preliminary computer aided design (CAD) models of a nitinol based peritoneal tissue lined stent will be made using commercially available softwares. This entails the geometry of the stent with specific dimensions. The unique feature of the PLS is that, the stent’s ends are flared. This provides with greater radial/crush force at the ends compared to the middle of the stent.
A.

Fig 8: Geometric pattern of stent struts for nitinol stent

3.3. Identify Potential Risks associated with the device.

Risk analysis or hazard analysis will be performed to evaluate potential problems with the designed stents, with specific attention to meet Good Manufacturing Practices (GMP) standards. Performing a risk analysis will help identify stent problems prior to distribution and eliminate costs. Regulatory submissions checklists (PMA and 510k) used by the FDA require the company to submit a risk analysis. The basic component level will be identified, effects will be assessed, and potential solutions will be identified.
Table 1: Risk Index Categories

<table>
<thead>
<tr>
<th>Probability of Occurrence</th>
<th>Severity I (death, serious injury)</th>
<th>Severity II (significant damage)</th>
<th>Inconvenience</th>
<th>Negligible</th>
</tr>
</thead>
<tbody>
<tr>
<td>Frequent</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Probable</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Occasional</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Remote</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Improbable</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

After the risk levels are categorized, the acceptance criteria are determined based on the range into which the risk level falls. Table 2 will guide us in determining the acceptance criteria for each level of risk.

Table 2: Risk Index Acceptance Criteria

<table>
<thead>
<tr>
<th>Hazard risk index</th>
<th>Acceptance criteria</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 to 5</td>
<td>Unacceptable</td>
</tr>
<tr>
<td>6 to 9</td>
<td>Undesirable: written and review decision required</td>
</tr>
<tr>
<td>10 to 16</td>
<td>Acceptable: Quality assurance review required</td>
</tr>
<tr>
<td>17 to 20</td>
<td>Acceptable: Quality assurance review not required</td>
</tr>
</tbody>
</table>

Based on the risk index obtained, plans will be made to mitigate risks associated with device failure modes. Specific attention will be paid to the most common risk occurrences, such as stent strain, which can lead to the dreaded stent fracture.
3.4. Construct Prototypes

Prototypes will be constructed based on the CAD models. This suture attachment pattern will be taken into account to assure the integrity of the tissue for future pulsatile flow. The suture attachment pattern will vary along the development of the stent. The prototypes are built in a sterile biosafety cabinet.

Figure 9: A. Stent construction in process B. Construction in a biosafety cabinet

3.5. Tissue Harvest

Peritoneum tissue arrives from the slaughterhouses in cold storage containers. Once the tissue is received, the goal is to remove the fat from the tissue. This is done by a process called Picking, where the fat is removed layer by layer. After Picking, the tissue is washed using Phosphate Buffered Saline (PBS) and Sterilized agent Isoproponol. This helps in clearing the tissue of the residual fat and kills the micro-organisms. Once the tissue is completely washed, it is sewn over plates and stored in 0.25% Gultaraldehyde in a fume hood.
3.6. Stent Inspection

Throughout the development of the process, stent inspections are done at regular intervals to ensure stent’s integrity. Factors taken into account during the construction are:

1. Suture Pattern
2. Tissue alignment with the nitinol stent
3. Seam check to ensure there are no holes in the tissue
4. Final quality inspection of the stent.

The final stents are stored in 0.625% Gulteraldehyde.

3.7. Role of Gulteraldehyde as a storage solution:

Glutaraldehyde is an organic compound with the formula CH₂(CH₂CHO)₂. It is a colorless oily liquid. Gulteraldehyde is used to disinfect medical equipments and
specifically it inactivates viral prions. A gultaraldehyde solution ranging from 0.1% to 1.0% concentration can be used as solution of disinfection and a preservative for long term storage. It denatures cells by cross-linking the proteins. Due to these properties, Peritec uses Gultaraldehyde to store its Tissue and Stents. 21

3.8. Mechanical testing of the prototypes

Stent fatigue testing will be performed to ensure new designs and processes have not altered the stent’s integrity. Below are descriptions of the stent graft pulsatile fatigue testing (SGT), and axial/torsion testing. Both tests are performed on our own equipment shown below.

3.8.1. Pulsatile Fatigue SGT (Fig 11):

This bench top test is intended to provide empirical evidence for the continued structural integrity of the devices when subjected to mechanical flow fatigue replicating in vivo conditions. The test is designed to simulate the device radial fatigue due to expansion and contraction of the vessel surrounding it. Physiological strain of a healthy vessel is modeled using latex arteries implanted with the device. The test is accelerated to obtain results in a shorter time period than physiological rates would allow. The test is conducted under simulated physiological conditions on the EnduraTec 9000 SGT fatigue tester. This operates on the principle of fluid displacement, where electrodynamic linear motors on each side of the tester apply a sinusoidal motion which forces fluid into and out of simulated arteries causing them to expand and contract. A laser micrometer measures the radial strain by measuring the outside diameter of the arteries at 1200 scans
per second. The testing objective is to meet the FDA 1545 “Non-Clinical Tests and Recommended Labeling for Intravascular Stents and Associated Delivery Systems” requirements for *in vitro* mechanical fatigue testing. The test will demonstrate the integrity of the device under mechanical fatigue for a minimum of 10 years post-implantation. A device failure is defined as any broken or cracked strut or disruption of tissue visible at 30x magnification during or at the end of the test, or tissue displacement. Time periods will be altered for the PDO stent, because the bioabsorbable material is subject to degradation.

**Monitoring:**

- Set and apply the pressure limits, displacement limits, and pressure under peak to prevent damage to the tester due to fluctuations.
- Determine the daily monitoring positions, five positions on each stent. Right measurement 3mm from the end of the stent. Record the positions on the Daily Data Sheet.
- Schedule endoscopic inspections at 50, 100, 200, and 400 million cycles. Optionally 1-2 samples may be added at 100 million cycle inspection.
- Daily Monitoring
  - Observe and record the %OD and ODmm for each pre-determined position. Calculate the %OD average. If necessary adjust the displacement levels to maintain the target %OD. $\text{Strain}\% = \frac{\Delta OD}{OD_{\text{min}}} \times 100$, as defined per ASTM F2477-06: Standard Test Methods for *in vitro* Pulsatile Durability Testing of Vascular Stents (2007).
• Analyze the trend in data

• Inspect the device through endoscope

Test Completion: Inspect the devices while still on the instrument. Carefully place a 30x/10x endoscope within the artery and while looking through the optic coupler thread the scope through the center of the device. Use the 90° angle mirror for closer inspections if the condition and the ID of the device permit.

![Image of Pulsatile Fatigue Tester](image)

**Figure 11: Pulsatile Fatigue Tester**

3.8.2. Axial/Torsional Testing (Fig 12):

This bench top test is intended to provide empirical evidence for the continued structural integrity of the devices when subjected to mechanical torsional and axial fatigue replicating *in vivo* conditions. The test is designed to simulate the device fatigue due physiological strain at the *in vivo* deployment site, and is accelerated to obtain results in a shorter time period than physiological rates would allow. The ElectroForce® 3300 operates with high-bandwidth, low-distortion motors, and is rated 2250N (500 lbs)/28.2 Nm (250 in-lbs); it performs precision material tests including tension/compression, axial-torsion, multi-axis loading, fatigue and dynamic materials characterization.
The testing objective is to meet the appropriate standard requirements for \textit{in vitro} mechanical fatigue testing for the current test. The test will demonstrate the integrity of the device under torsional and axial mechanical fatigue for a minimum of 10 years post-implantation. Devices will be reviewed for any broken or cracked strut or tissue tear visible grossly or at magnification at the end of the test.

![Figure 12: 12 Slot Axial Fatigue Tester](image)

Monitoring:

- Set and apply the appropriate limits to prevent damage to the tester due to fluctuations.
- Set up data acquisition to electronically capture displacement max/min, rotation max/min, torque max/min, and cycle count approximately every four hours.
- Manually record displacement max/min, rotation max/min, torque max/min, cycle count and temperature. Document the information on the Daily Data Sheet.
- Daily Monitoring
- Record pre-determined parameters on the Daily Data Sheet
- Observe devices for migration.
- Observe devices for failure.

Test Completion: Inspect the devices while still on the instrument. Carefully place a 30x/10x endoscope within the artery and while looking through the optic coupler thread the scope through the center of the device. Use the 90° angle mirror for closer inspections if the condition and the ID of the device permit.

### 3.9 Peritec Delivery System and Stent Deployment

The stent is placed in 0.625% glutaraldehyde and stored at 4°C until implantation. Peritec has pioneered the use of a tube of peritoneum inside the Nitinol stent. Initially, the PLS is housed in liquid which is a disinfectant and keeps the peritoneal tissue wet. Note that it is in the stored and transported in the deployed state. If kept in a crimped state like other stent systems, it is difficult to rinse properly. Once the stent graft has been rinsed, it is crimped and placed in a sheath. This sheath is part of the cartridge that attaches to the catheter. At this point, the system is ready for use like any other stent system. The peritoneum acts as a scaffold for re-endothelization (the healing of the inner surfaces of vessels or grafts by endothelial cells). It is believed that the peritoneum looks to the blood and the body as less foreign than Nitinol. The PLS can be delivered using minimally invasive techniques instead of a full, open surgical procedure. The advantages typically include less pain, faster recovery and smaller incisions in the body thus offering an innovative effective alternative to other stent candidates including bare metal.
Currently, bare metal stents are deployed by crimping onto the catheter during the manufacturing of the delivery device and implant. The delivery catheter with the stent mounted and sheathed are then collectively sterilized as one unit and transported to the user.

Specifically, the stent, in its relaxed or deployed state, is placed on the guidewire lumen which is part of the delivery catheter. It is then crimped using a funnel-like device or iris/pneumatic system, for example, and subsequently sheathed by another layer of the delivery catheter. This layer retains the stent in its crimped state until the time of stent deployment; at which time this layer is retracted, deploying the stent.

The unique composition (biological tissue) and attachment (Tissue) of the PLS requires a special manual crimping system. The PLS is kept moist and the whole system must remain at or slightly below room temperature during the process to preserve the biological integrity. The crimping process must also involve little or no sliding of the PLS which would disrupt the tissue lining on the ends of the stent, negatively affecting the physical integrity of the tissue. Current stent crimping techniques (available from commercial suppliers such as Machine Solutions) which are applied to Nitinol or other flexible metal stents are performed predominantly on bare metal stents and utilize either low temperatures (e.g. $-40^\circ\text{C}$) or forces, pneumatic or mechanical methodologies, to reduce the diameter of the self-expanding stent. These are not acceptable for crimping the PLS because they would damage the tissue lining. The stent-graft needs to be kept in glutaraldehyde in the deployed state. The Peritec Biosciences system that will be utilized
in the surgical suite requires trained personnel to crimp and complete the catheter loading process.

4. **Commercialization Plan**

4.1. **Value of the project, Expected Outcomes, Impact**

A common and frustrating outcome of vascular surgical procedures is restenosis (reclogging) of stents and bypass grafts. Scarring from surgery and the physical processes (e.g. inflammation) that cause vascular disease contributes to the formation of new blood clots and the closure of blood vessels. Other approaches to peripheral stenting have not shown significant clinical benefit. Even in the coronary applications, the use of drug eluting stents has dropped precipitously as the hazards associated with the current standard of drug elution have become widely disseminated. **The clinical need for new, superior arterial substitutes that are resistant to clot formation and restenosis is enormous for the many U.S. patients with peripheral vascular and coronary heart disease.**

There are a plethora of devices that are vying for the market. Developing robust technologically advanced products are critical to successful therapy and to capture the market. In the peripheral stent market, new technologies such as drug eluting stents and bioabsorbable stents have not demonstrated significant improvement. PeriTec’s tissue lined stent nitinol stent offer features that will serve best in the market for several years down the line. Standard metallic stents also lead to occlusion after a period of time.
The SFA market, amongst many other peripheral technologies, is an underserved market. According to a new report by iData Research, the U.S. peripheral vascular device market is worth $2.8 billion with expected growth to over $5.3 billion by 2016. The increase in detection and treatment of peripheral arterial disease (PAD) is the main driver of this market. The main products are the peripheral stents and stent-grafts.

The market for peripheral stents, used for treating PAD is rising exponentially. There is a double-digit growth since 2005. This is expected to grow much faster than the coronary stent market through 2016. Public awareness about the threat of PAD is creating a greater market space. Along with new technologies such as drug eluting stents, biologic covered stents etc, awareness has been a major driver in the growth of peripherals stent market. \(^{24}\) Nitinol stents clearly showed improved patency rates compared with those of balloon angioplasty. \(^{25}\)

This gives rise to a significant market opportunity for people to develop new products with effective solutions. With increasing high rates of morbidity and disability there is significance need in the market to develop novel stents to treat Peripheral Arterial Diseases.

**In 2006 Peritec Biosciences introduced a novel self-expanding stent design, the peritoneum (biological tissue) lined stent (PLS) to provide a solution to the problems with the current treatment of atherosclerosis in the SFA.** The peritoneal lined stent offers less complications resulting in fewer secondary procedures, thus providing improved quality of life and lower costs for overall treatment of SFA atherosclerosis. The
technology could also be used to elute drugs into the vessel wall if needed by imbuing the tissue with the proper dosing.

Peritec aims to develop valuable treatment modalities for the complications of rapidly growing cardiovascular disease associated with the increase in an aging population, diabetes and obesity. More effective and longer lasting treatments mean savings in human suffering, medical costs, and loss of productivity. During the next few years, the sales from PeriTec will contribute significant numbers of manufacturing, sales, research, and administrative jobs, with corresponding substantial additions to tax revenue. More importantly, PeriTec will help catalyze the growth of today’s small but expanding life sciences industry in the Midwest region (an especially distressed economic area). The associated benefits go beyond the new jobs and growing tax revenues. Growing innovative technology companies create an atmosphere that improves the community in many ways beyond its jobs. Educational standards rise through formal and informal mentorship and the spirit of entrepreneurship is elevated.

PeriTec has gone through a meticulous 3 step process to prove the efficacy of it’s PLS. The first step was to prove the safety of the material as a biocompatible vascular candidate. This resulted in a peer-reviewed publication in the Journal of Vascular Surgery and the receipt of a 510(k) from the US FDA for the use of peritoneum and fascia as a vascular patch. The second step was to prove the value of the peritoneum stent in an animal model, which was published in the Journal of Endovascular Therapy Error! Bookmark not defined.. The third was to develop and revise an on table crimping system and begin implants. All of these are completed. We are now
concentrating on optimizing the system for commercialization by developing our own scaffold and becoming self-sufficient.

4.2. Missions & Goals - PeriTec is directed by its mission to become the worldwide leader in next generation stent technology. The goal of Peritec Biosciences, Ltd is to;

1. Establish PeriTec tissue lined products as the Standard of Practice for peripheral stenting
2. Develop and introduce at least one significant new indication every two years
3. Establish a market oriented multi-national business presence to address the worldwide needs and opportunities for our technologies and systems
4. Ensure patient and clinician satisfaction by providing the highest levels of quality and performance
5. Provide a stimulating, challenging and cooperative work environment with growth opportunities for all employees
6. Increase the equity value of the company

Although the platform technology has a number of other viable medical applications, being small, the Company must focus its resources on developing the clinical application for treatment of SFA disease following the positive clinical data. Thus the next steps which will allow Peritec to avoid OEM (original equipment manufacturing) stents, which are not designed for tissue, but also will allow become completely self-sufficient by developing our own stent back bone scaffold to accommodate the tissue. One a standard
has been established for treating SFA, Peritec can start using this Product for multiple applications such as for Hemodialysis Access Graft etc.

4.3. Milestones Achieved so far:

**YEAR 1 (2003) – Inception – Agreements and Launch (Equity raised)**

- Secured fully executed license agreement with CCF
- Obtained all related documentation for patent application
- Completed private round of equity financing
- Established legal entity, Board of Directors and management structure
- Secured lab and office location
- Recruited lab personnel – MD/PhD and lab technicians
- Obtained Institutional Review Board (IRB) approval for animal research
- Began animal and bench-top testing for vascular patch (months 3 through 6)


- Continued with animal testing of Patch
- Obtained data that demonstrates technology feasibility and prepare 510(k) application
- Started animal implants using balloon expandable stent


1. Obtained 510(k) and received approval for commercializing vascular patch
2. Finished animal trials of PLS expandable stent
3. Developed initial crimping system
4. Prototyped initial catheter / delivery system


- Launched initial mechanical testing of peritoneal lined nitinol stent
- Tested human ready delivery system
- Started international human clinical trials. Implanted 2 humans as of November 2006.

**YEAR 5 – (2007) refine initial delivery system, Extensive Mechanical Testing, Continue International Human Clinical Trials, And Second Generation Crimping System**

- Redesigned handle
- Redesigned proximal tip
- Implanted 11 humans
- Completed 10 year simulated 10 million cycle axial/torsion test for PLS and the 400 million cycle pulsatile fatigue test for PLS is currently 75% completed

**YEAR 6-2008**

- Under development - second generation crimping system (95% complete)
- Designed and developed runner cartridge system. (complete)
- Completed 10 year simulated 10 million cycle axial/torsion test for PLS and the 400 million cycle pulsatile fatigue
- Implanted 8 humans with SFA
- Implanted 5 humans with dialysis access

**YEAR 7- 2009**

- 21 out of 21 patients with SFA have been in place with no side effects. 19 out of 21 patients are still out safe for 30 months now. 5 of 5 dialysis access are still safe and open.
- Able to crimp and deploy runner cartridge system to deploy any stent.

**4.4. Regulatory Strategy**

As the FDA has already provided a 510(k) for the use of peritoneum with fascia for vascular patches using the identical fixation protocol, The company should lay ground work for getting CE mark approval for the Tissue Lined Stent treating SFA disease.

1. Stent design testing Dec 2010
2. CE Mark Application and Europe site validation Mar 2011
3. Schedule pre-IDE meeting with FDA May 2011
4. CE mark Review Aug 2011
5. Submit IDE to FDA Oct 2011
6. FDA review Oct 2011
It is estimated that PAD afflicts approximately 15 million people in the United States, and the number is expected to increase above 20 million in the next ten years. The growth rate was 12.5% and project compound annual growth rate is estimated to be 18.1% for the years from 2005-2012.\textsuperscript{27,28} PeriTec’s peritoneal-lined stent will have substantial advantages over the bare metal stents and stent grafts currently available or under development. The peritoneal lining is extremely durable and will not wear off like drug coated stents, so its anti-clotting and anti-clogging properties will remain viable in the long-term. In addition, PeriTec has determined based on the costs of the tissue lining, stent, and manufacturing process, that it can provide the system at a selling price of approximately $2,000. PeriTec’s stents will cost less than drug coated stents that cost approximately $3,500/stent, and are extremely expensive to manufacture. According to Frost and Sullivan, these devices require at least two to three stents per each interventional procedure. Although the Peritoneum Lined Stent (PLS) will be slightly more expensive than bare metal stents, the efficacy and decrease in repeated follow up procedures should enhance market acceptance of the price point. This allows PeriTec to be cost competitive and target a 40% market share of a $6 billion market over a 5 – 10 year period.\textsuperscript{27}
4.5.1. **Customer:** The Peritec’s Tissue lined stent’s customer will involve physicians who are treating PAD. Specific customers for the lower extremity stents include a number of specialties including: Vascular and Cardiovascular Surgery, Interventional Radiology, & Cardiology.

4.5.2. **Market Share:** Market share can shift if there is an introduction of novel technologies, which PeriTec promises to deliver. We initially are focusing on the SFA because it is the largest unmet clinical need in stenting. It has a market size of $600,000.00. Historically, SFA solutions have fallen into two major categories: 1) atherectomy devices for surgical removal of the plaque; 2) stents with or without polymeric coatings. The atherectomy devices include technologies such as a spinning blade to core out and remove the plaque. While the FDA has approved a few of these, none has shown long term efficacy. Stents have not proven significantly beneficial over PTA either. Initially, stents for the SFA had significant fracture problem due to the initial poor understanding of the stresses and strains in the SFA. The second generation stents have principally solved the strut fracture problem (with fracture rates from 1%-2%). However, they have not increased the efficacy of the treatment as the neointimal hyperplasia (scar tissue formation) continues to plague this solution. The Company’s initial target market for SFA stenting is large and growing as a result of the increase in vascular disease associated with ageing, dietary habits, and lack of exercise and diabetes. The data in Figure 9 shows the growth of the SFA market in the US from 2001 to 2006. Figure 10 presents the viewpoint of one of the large medical device firms regarding the SFA stent market.
Many new devices are expected to come out during this period adding to growth in revenues. Moreover, recent approval of plaque removal devices such as Spectranetics CliRPath and Foxhollow’s Turbohawk are expanding the applicability of stents. It is projected that the growth rate is higher for femoral-popliteal market than other segments. PeriTec is targeting a 40% share of this market over the next 5-10 years.

**Figure 13: Current Peripheral Stent Manufacturers**

<table>
<thead>
<tr>
<th>Company</th>
<th>2005 (%)</th>
<th>04/05 Trend</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cordis/J&amp;J</td>
<td>24.8</td>
<td>Decreasing</td>
</tr>
<tr>
<td>WL Gore</td>
<td>16.7</td>
<td>Stable</td>
</tr>
<tr>
<td>Guidant</td>
<td>13.3</td>
<td>Stable</td>
</tr>
<tr>
<td>Boston Scientific</td>
<td>12.9</td>
<td>Stable</td>
</tr>
<tr>
<td>Cook, Inc.</td>
<td>12.0</td>
<td>Increasing</td>
</tr>
<tr>
<td>Medtronic</td>
<td>8.8</td>
<td>Decreasing</td>
</tr>
<tr>
<td>ev3 Inc.</td>
<td>3.6</td>
<td>Increasing</td>
</tr>
<tr>
<td>C. R. Bard, Inc.</td>
<td>2.6</td>
<td>Stable</td>
</tr>
<tr>
<td>Abbott Laboratories</td>
<td>1.3</td>
<td>Stable</td>
</tr>
<tr>
<td>AngioDynamics, Inc.</td>
<td>0.4</td>
<td>Stable</td>
</tr>
<tr>
<td>Edwards Lifesciences LLC</td>
<td>0.4</td>
<td>Stable</td>
</tr>
<tr>
<td>Endologix</td>
<td>0.3</td>
<td>Increasing</td>
</tr>
<tr>
<td>Other</td>
<td>2.9</td>
<td>Decreasing</td>
</tr>
<tr>
<td>TOTAL</td>
<td>100.0</td>
<td></td>
</tr>
</tbody>
</table>

*Note: All figures are rounded; the base year is 2005. Source: Frost & Sullivan*
4.5.3. Future Markets

While it is easy to envision the PLS gaining share from either bare metal or drug eluting stents, the tissue technology underlying the Company is a platform technology. Other Target Markets include dialysis access grafts, TIPS, Saphenous Vein Grafts, and the coronary market. Owing to the size and scope of the entrenched companies in the coronary space, PeriTec has put the coronary market beyond the near term horizon.

4.5.4. Competition

The market leaders in the femoral-popliteal stent market are majorly concentrated in the renal, iliac, and biliary stent markets. Cordis has a 40 percent market share, while Boston scientific has an overall 20 percent market share. The 20 percent market share is held by other manufacturers. The market is decreasing for the off-label usage of the devices.
Gore and Baird have had their devices approved by FDA and their market share is going to increase.

**Figure 15: Peripheral Vascular Stent and Stent Grafts Market Share**

In the near term, the competitive environment can be broken into two segments: 1.- Competitive Biological Materials; 2- Other Solutions for the SFA. A few similar cardiovascular and vascular technologies are currently being investigated or marketed in the product categories that PeriTec has targeted. Cook Group Incorporated’s early research work has shown that the inner lining of the intestine is a possible alternative
biological tissue; however, it tends to cause clotting quickly and is highly susceptible to infection. This intestinal lining approach has failed in human testing. Synovis Technologies is using bovine pericardium for carotid artery patches, and Edwards Lifesciences Corporation has developed xenogeneic bioengineered bovine bioprosthetic heart valves. Given the cellular composition of the peritoneum, PeriTec’s product offers multiple benefits, including compatibility, longevity, and reduced stenosis, in turn leading to fewer post-surgical complications and lower costs for arterial revascularization. No other tissue lined stents are sold in the United States.

4.6. OTHER SOLUTIONS FOR THE SFA

Atherectomy and laser methodologies for extracting plaque from the SFA have been around for quite a while. They are clearly able to remove the arterial plaque. However, these are unsatisfactory due to the rapid occurrence of restenosis of over 50% at one year with amputation rates of 25%. The only approved stent graft with an SFA indication has 50% patency at one year vs. 45% for PTA (Gore Viabahn PMA results). This stent is an ePTFE covered nitinol stent. It does have the benefit of a covered stent, however, the ePTFE is an inflammatory material and thus, the results have been of marginal value over stand-alone PTA. Recently, Bard Peripheral Vascular company has got approval from the FDA for their bare metal stents, but it is no better than the other bare metal stents.

4.7. Intellectual Property (IP) Protection

To date, three patents awarded to Dr. Sarac have been licensed exclusively to PeriTec Biosciences Ltd. through the Cleveland Clinic Foundation. The first patent issued
encompasses the use of peritoneum as a stent lining and was issued in June, 2003 (patent # 6,579,307). In 2004, the Company engaged Townsend, Townsend & Crew, a renowned West Coast IP law firm, to review the patent landscape and provide comfort to the investors that PeriTec could proceed unimpeded by IP issues. A second patent for construction of the PLS was awarded in November 2006 (patent # 7,137,947). Subsequently, the Company engaged Knobbe, Martens, Olson & Bear in December 2006 perform four pieces of work:

1) Review the TT&C work
2) Do a patent landscape search using internal KMOB resources
3) Hire an independent patent search firm to do a patent landscape search
4) Review the patents cited by the patent examiner when the original patent was being considered

This review has again confirmed the strength of the Company’s original patent. An additional patent for tissue processing and use of peritoneum as a drug delivery carrier was granted (patent # 7,559,953). The other patents filed include the initial crimping system, catheters, handle. In addition all international filings have been completed.

4.8. Finance Plan

The Company has thus far been funded by grants and equity investment by investors, and this will continue to be the case. PeriTec has been awarded an SBIR fast track grant to develop the unique crimping system, which is near complete. Small medical device companies have a long road both in terms of time as well as cash requirements to get their products to market. PeriTec has had a very committed and strong group of
investors. They have laid out their expectations with every round of funding and Peritec has achieved their milestones. As the development continues to be successful, equity financing is expected to be available. The sources will include our current investor base, venture capital firms and/or the large medical device companies (as partners). However, given the current economic climate, an STTR grant will accelerate development and independence.

4.9. Marketing Plan

It is clear from the early stage of the company that detailed domestic market plans are difficult to define. However, Peritec Biosciences has planned an aggressive international market introduction that will overlap to some degree with the completion of the regulatory efforts in the US to achieve FDA approval with a reasonable probability that the European market will be accessed earlier. Peritec should enter the USA market before establishing itself in Europe. This will enable them to create their own market space. Peritec should also set up sales offices in other countries such as India, China etc.

European distribution arrangements

Every attempt will be made to negotiate parallel review – audit, design dossier and tissue review. This is not the norm but has been done before. In an effort to provide additional cash inflow for the stent, the company’s management team plans to submit multiple federal and state grant applications over the next several years. This will allow us to proceed with manufacturing stents on a larger scale.
5. **CONCLUSION**

The immediate plan for Peritec Biosciences is getting CE mark approval for the Peritoneum lined stent for peripheral artery disease. This can be done by Partnering with prospective companies in Europe for distribution. Simultaneous, Peritec should start its clinical trials in USA for FDA approval. For this, Peritec should set up a larger manufacturing unit and hire more seamstresses. In order to do so, Peritec needs funding, potentially from venture capitalists.

Commercialization can come from a variety of sources. In addition to taking tissue lined stent to the market, I believe there are three other sources of near term revenue.

A variety of our intellectual property is useful beyond deploying stents. The next generation crimping system developed can be used for multiple purposes such as for the use of heart valves in the operating room.

Out licensing some of Peritec’s products such as the vascular patch that obtained 510(k) approval

Venture capital funding and Grants need to become a constant source of funding for Peritec to pace faster.

Growth will be managed as PerTec prospers into a sustainable business entity, adding appropriate functions in marketing and sales, manufacturing, customer support and finance to meet the demands of our expanding customer base.
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