Market and Business Analysis of Tissue Engineered Blood Vessels

A Major Qualifying Project Report
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Abstract

Cardiovascular disease is the number one leading cause of death in the United States. A myocardial infarction is the medical term for what is commonly known as a heart attack. Myocardial infarctions are caused by cardiovascular disease and more specifically, by the blocking of a main artery in the heart. A team of students and professors at Worcester Polytechnic Institute designed a device and method for producing tissue engineered blood vessels (TEBVs), which are proposed to be a new and effective treatment for coronary artery bypass surgery. The purpose of this study was to decide whether TEBVs were a worthwhile commercial venture by performing a number of analyses. Currently, the method to produce the TEBVs is still being altered and the grafts are still in the early development stages. It was determined, however, through the analyses that TEBVs are a worthwhile venture to invest in due to the high demand in the cardiovascular disease treatment market.

Executive Summary

Cardiovascular disease claims the lives of over 80 million people each year.[1] Globally, there are over 800,000 coronary artery bypass graft (CABG) procedures annually.[2] Due to the high occurrence of such procedures each year, the need for new treatments and procedures continues to rise. The current treatments include:

- Autografts
- Allografts
- Synthetic Grafts

There are a number of problems with the aforementioned treatments. These issues have brought about the need for alternative source of materials for cardiovascular disease. Section 4.1 reviews the current treatments and also introduces a new alternative treatment known as tissue engineered blood vessels (TEBVs).

A Worcester Polytechnic Institute project team from 2010 was posed with the challenge of designing a method for the tubular self-assembly of cells to create a TEBV. Currently, there are a few organizations/companies producing TEBVs; however, the time it takes to produce one TEBV is one of the main constraints in the production process. This constraint was also a constraint for the WPI project team and without a front-end processing period and post-maturation period, the project team was able to build a vessel within a three day period. The aforementioned periods are part of a four phase TEBV production process that is highlighted in section 4.3.3. It is believed that TEBVs would provide a treatment alternative for CABG procedures.

This report was produced in part by the management department and the biomedical department at WPI. It was designed to analyze the business factors related to TEBVs and whether TEBVs are a worthwhile venture in which to invest. The investigation focused on the cardiac market but more importantly, the target markets in which the TEBVs would be marketed. This investigation was performed under the assumption that WPI will first sell a "plug and play kit" to generate enough revenue to gain FDA certification for the TEBVs for in-vivo applications. This report provides an analysis of:

- Cardiovascular disease
- Current treatments
- Alternative graft source such as TEBVs
- WPI TEBVs and process
- A business model
- A cost analysis on the "plug and play kit" design idea
- A cost analysis on the TEBVs
- A SWOT Analysis
- A Market Analysis

Through the aforementioned analyses, it was determined that the TEBVs produced at WPI have a promising future. It is important that WPI and the inventors of this technology begin collecting test data on the TEBVs to provide the FDA with the necessary data to gain approval for clinical applications. The proposed business model, as seen in Chapter 3, states that the inventors should first sell the kits to begin generating revenue. With the generated revenue, the inventors can then fund the testing necessary to gain FDA approval for clinical applications. The

author believes that once the TEBVs are FDA approved, TEBVs will become the industry standard for the CABG procedure.

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1. Introduction/Problem Statement

Cardiovascular diseases are among the leading causes of death in adults world-wide. In 2006, there were 80 million people in the United States who were reported to have some type of cardiovascular disease.[1] Cardiovascular diseases are caused by a number of factors such as the buildup of fatty material in arteries, smoking, and triglycerides.[1] When fat and cholesterol build up in the arteries, the build-ups begin to block blood flow, ultimately resulting in cardiovascular disease and heart attacks.

Myocardial infarction, also more commonly referred to as a heart attack, is one of the effects of cardiovascular diseases. Heart attacks claim the lives of over one million people annually.[1] According to the American Heart Association (AHA), there are over a million coronary heart attacks in the United States per year. In many cases, when a patient is admitted to a hospital, the surgeon will use a stent to clear the blocked arteries of the patient in order to allow blood to flow to the heart; a stent is essentially an artificial tube implanted in the body to temporarily reduce the constriction of fluid flow. This technique, however, has proven to fail when restenosis occurs and there is a need for alternative methods to curing cardiovascular diseases. Restenosis is a condition that affects about 30% of patients who have undergone the aforementioned procedure and is essentially when the artery becomes blocked again within a few months post surgery.

Another method for treating cardiovascular disease is through the procedure of CABG. In this procedure, surgeons will generally harvest the saphenous vein which is a large vein found in the patient's leg. The harvested saphenous vein is then implanted in place of the clogged artery allowing blood to once again flow to the heart. There are also problems with this procedure however. Lasting pain and scars from the surgery as well as a poor 10 year failure rate have

caused surgeons to use this method in only the most severe cases of cardiovascular disease.[3] During this procedure, surgeons bypass the blocked coronary artery. CABG surgery can be performed using a number of graft source materials including:

- Autografts
- Allografts
- Synthetic Grafts
- Tissue Engineered Blood Vessels (TEBVs)

This technique has failed up to 50% within the first ten years for a number of reasons including the formation of neointima.[3] This condition is considered a new and thickened layer within the artery formed on a prosthesis.

There are also other methods currently in use to help treat clogged arteries. Other than using the saphenous vein, doctors' use artificially created blood vessels that share many properties with real living tissue. There are, however, disadvantages to using the synthetic materials. For example, synthetic arteries have a high tendency to clot again within a few years following implantation and may actually clog at a higher rate than natural arteries.[4] There is a clear need for a substitute to the current graft materials.

Blood vessel tissue engineering is a recent art in which scientists use living cell cultures to create living blood vessels for a variety of applications. Although there are a number of advantages associated with using tissue engineered blood vessels, there are also a number of disadvantages that challenge the viability of the technology. Currently, it takes a long time to produce engineered tissues from cell biopsies.[5] This constraint has led to the need for a more timely method to produce cell-based tissue engineered blood vessels.

A Major Qualifying Project (MQP) team from Worcester Polytechnic Institute was able to develop a method and technology for the tubular self-assembly of cells to create a tissue engineered blood vessel (TEBV).[6] With this technology, the project team was able to successfully engineer a group of living cells into a living blood vessel that could be used for a number of real world applications. One of the group's main concerns was to produce the engineered blood vessels in a significantly shorter period of time than the current clinical trials. Cytograft, a producer of TEBVs, has a TEBV production process that takes nearly 24 weeks to complete.[5] By shortening the time to produce a TEBV, the WPI technology would then be a more attractive product and thus gain a competitive advantage against other companies within the market.

There are many applications in which these engineered blood vessels can be used. One idea developed by the biomedical department at WPI was to design a kit that would allow scientists, doctors, and other stakeholders to produce the TEBVs within their own laboratory for the desired application. The idea of the kit was introduced by Professor Marsha Rolle of the WPI Biomedical Engineering department. Essentially, the kit would allow scientists with little experience of the technology to create living tissue within their own laboratory. The kit would include the required means to produce the TEBVs along with an instruction manual explaining, in detail, the required processes to produce the TEBVs.

Although this technology is new and useful, there are many factors to consider when understanding the biomedical industry. This paper focuses on the benefits of pursuing a company in which the main revenue will be generated through the sale of TEBVs and a manufactured kit to produce TEBVs. A block diagram (Figure 1) shows the life cycle of the product produced at WPI from the sale of a kit to the sale of TEBVs. The author proposes that WPI first sell the kit

that will be marketed as a research tool. The revenue generated from selling the kits will be used to research and study the long-term patency and efficacy of the TEBVs thus providing ample research to obtain insurance reimbursement codes and FDA approval for in-vivo use.

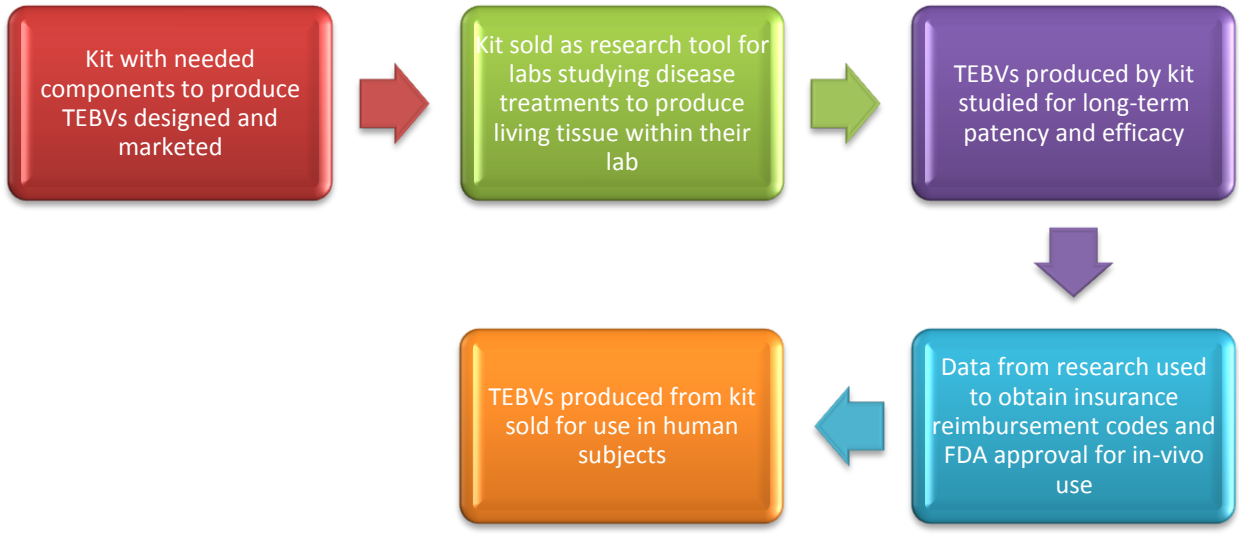

Figure 1: Block Diagram of the Life Cycle of the WPI Product.

To understand the factors that will ultimately affect the sale of TEBVs, the following analyses were completed:

- An analysis of the industry
- An analysis of the competition
- An analysis of risk factors
- An analysis of FDA regulations
- An analysis of the barriers to entry
- An analysis of the stakeholder's involved

- A market segmentation analysis

Following the analysis of these factors, the author garnered an in depth understanding of the product as well as its marketability. This report and analysis provides a number of recommendations as well as a target investment value that will be necessary for entry. The goal of this report was to provide investors with an in-depth understanding of the product and its ability to succeed in a competitive market place.

2. Methods/Procedures

To successfully determine the marketability of TEBVs, an in-depth analysis of both the kit and TEBVs ability to compete in the market was conducted. It was important to assess the costs associated with producing TEBVs as well as the costs associated with the kit. It was also important to understand the market position of the TEBVs. To further understand these concepts, the author completed a comprehensive literature review. The author also conducted interviews with professionals to garner a more in-depth practical view on TEBVs and their marketability (Figure 2).

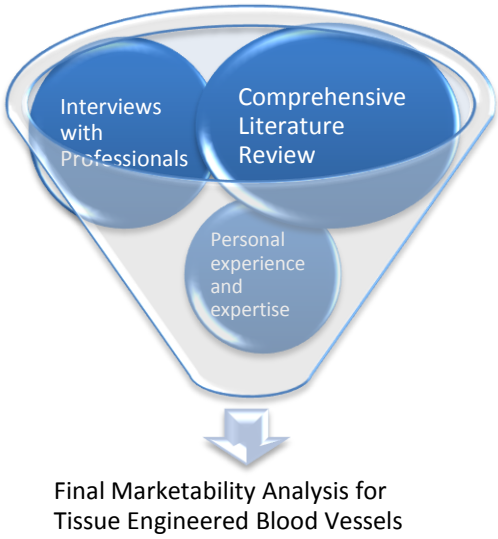

Figure 2: Report Methodology- Inputs and Final Output

An in-depth review of scholarly articles, medical journals, legal documents (including patents), regulatory documents released by the FDA, and market statistics and sources was essential to understand the separate issues regarding the technology.

During the research stage of this report, interviews were conducted with professionals within separate fields relative to the nature of the topic, e.g.: biomedical engineers for the technology, and a mechanical engineer from a manufacturing plant. The information obtained from these analyses was used when making final recommendations for the viability and marketability of TEBVs. Additionally, the author conducted both a S.W.O.T. analysis (strengths, weaknesses, opportunities, and threats) of the technology and a cost-benefit analysis.

3. Results

Based on the assumption that FDA approval for the use of TEBVs in clinical applications will be obtained, it is expected that the TEBVs will have significant market potential in the treatment for cardiovascular disease. This is partially based on the fact that each year, there are over 800,000 coronary artery bypass grafts performed.[2] Due to the high frequency of procedures, it is likely that the demand for a product of this nature is very high.

Through the analyses throughout this report, it is seen that the TEBVs produced at WPI are similar but not the same as any other technology in the market. There are companies and laboratories producing and testing TEBVs; however, one main constraint of TEBVs is the time it takes to produce one unit. At this point, the WPI process has a favorable time to produce which will prove to be important when marketing the TEBVs. Although it is not possible to calculate a payback period for TEBVs, it can be assumed that with the high demand (over 800,000 CABG procedures annually) for treatments for cardiovascular disease, the payback period will be within the first year. As stated in the break-even analysis in section 4.3.6, WPI or a company based from the WPI technology will only need to produce and sell 17 TEBVs to break-even with an initial investment of $100,000. This can also be seen in Appendix 8.4.

It is recommended that WPI use the technology and TEBVs to create a start-up company following the review of the medical supplies and devices industry, the pharmaceuticals manufactured industry, and the benefits of starting a company versus licensing the technology. There is promising potential for growth and expansion in both target industries. As stated in section 4.4.5, the percentage of compensation WPI would receive through a licensing partnership is very low compared to the potential earnings of a start-up company.

Proposed WPI TEBV Business Model

The proposed WPI TEBV business model is a two phase process. The two steps are used to ensure that the needed funds are obtained for FDA certification of the TEBVs for clinical applications. Phase one of the process includes the sale of the TEBV-producing kits, as proposed in section 4.3.2. The idea behind this phase of the business model is that the proposed company will produce and sell the kits for use in medical research. Phase 2 of the business model is the sale of TEBVs. A schematic of the business model can be seen below (Figure 3).

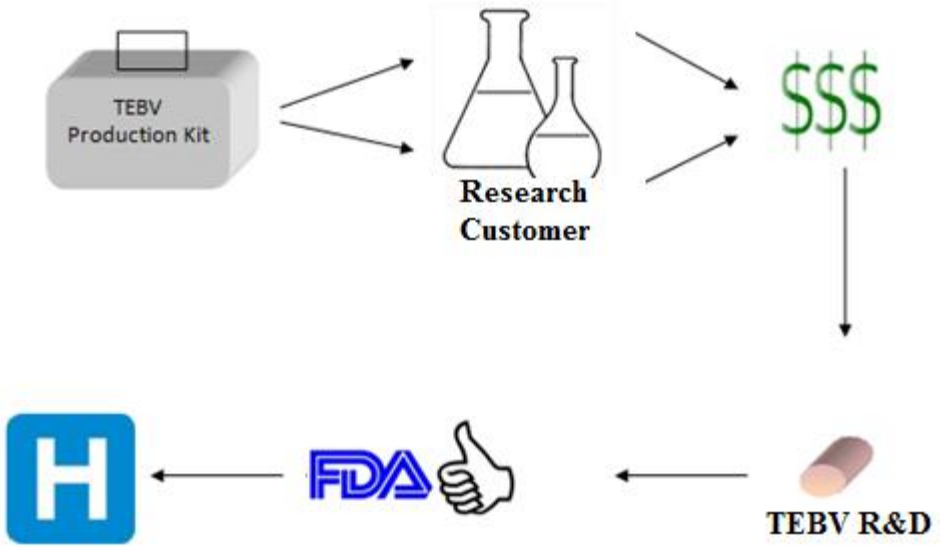

Figure 3: Proposed Business Plan Flow Chart

Figure 3 depicts the process flow of each phase of the proposed business plan. During phase one of the proposed business model, the business will sell the kits to medical research firms and/or universities. By doing so, it is expected that the business will generate the needed revenue to perform clinical research on the TEBVs produced from larger scale versions of the kit. The clinical research performed on the TEBVs will then be used to gain FDA approval for clinical use of the TEBVs. It is mentioned in L'Heureux's study that there is a need for 4-6 years of data to prove a product is cost effective.[5] Once the TEBVs are approved for clinical use, the final phase of the business plan will be to sell the product to hospitals/surgeons.

To generate the interest and demand in the product, the company will first need to successfully market the product. This can be done through a number of mediums including scholarly articles, medical journal reports/articles, and medical supply and device catalogs. The use of a lease program during the initial stages of the start-up company can also be an effective means to delivering the product to the more customers.

Lease Program

As a start-up company, there are going to be many challenges associated with successfully marketing the new product. The basic idea of this process is that the company would first need to produce between 10 and 20 units. Upon completing the manufacturing process, the company would then advertise to the target market through the means of industry catalogs and biomedical expos. The main advertising campaign in the early stages of the company would be to lease the products to users for a free 30-60 day trial giving the user ample time to collect sample data. Once completing the lease, the user would then have both the data and experience to determine whether the device is necessary to their research. There would then be two options available to the lessee:

1) To purchase the current leased product.
2) To return the item and purchase a new product.

The company would also need to have the lessee sign a contract stating that they would not allow other laboratories to sell the product and also would protect WPI from any misuse or potential injury caused by the product. If WPI is able to generate enough revenue through the sale of the kit to receive FDA approval for the TEBVs, the author feels that it would be a worthwhile venture for investors to pursue.

4. Discussion

4.1 Coronary Heart Disease and Treatments

4.1.1 Coronary Heart Disease

Coronary heart disease is one of the leading causes of heart failure because the coronary artery fails to provide the heart with the required nutrients to continue functioning normally. As time passes with this lack of nutrients, the contractile portions of heart muscle begin to die causing what is known as a myocardial infarction, or a heart attack. The simulated drawing below (Figure 4) shows how a clogged left coronary artery causes a portion of the heart to die due to lack of nutrients and blood flow.

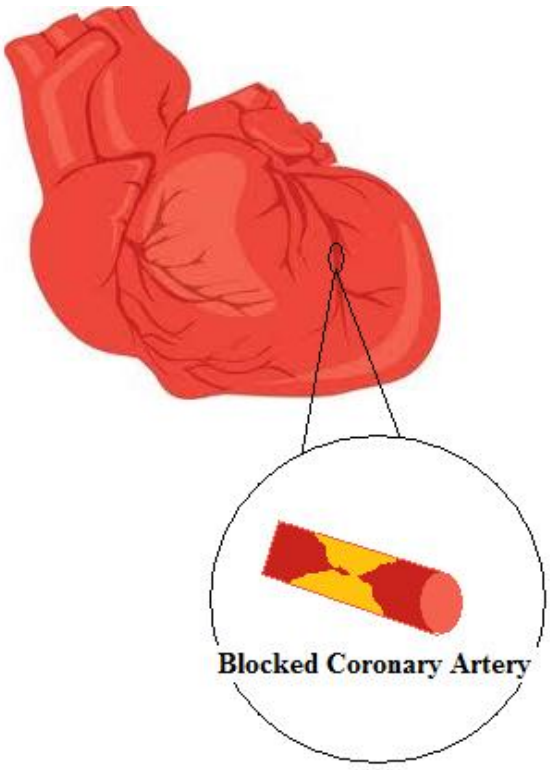

Figure 4: Coronary Heart Disease- Blockage of the Left Coronary Artery

As stated in the introduction, most heart attacks are treated using a stent.[7] With this method, a stent is inserted into the clogged artery and then used to push the clotted material against the walls of the artery, thus allowing blood flow to return to normal levels. There are disadvantages to using a stent, however, such as the failure rate. In 21% of cases in an experiment reported by the New England Journal of Medicine, when a stent is used, the artery becomes blocked again just hours after surgery.[8] There are other alternatives to using stents to treat cardiovascular disease.

Grafts are another common treatment used to combat cardiovascular disease. The dictionary definition of a medical graft is, "a piece of skin, bone, or other living tissue transplanted or to be transplanted from one body, or place on a body, to another, where it grows and becomes a permanent part." Grafts are commonly used in the treatment of cardiovascular disease; more specifically, coronary artery bypass grafts are used to treat blocked arteries.

4.1.2 Autografts

Coronary artery bypass grafts (CABGs) are used in treating coronary heart disease. In severe cases of coronary heart disease, surgeons will use the saphenous vein, located in the leg, as a graft for use in the heart. The saphenous vein is inserted in place of the clogged artery, allowing blood flow to return to normal levels. There are disadvantages to CABG surgery, however, such as continued internal bleeding after 24 hours post surgery, heart rhythm disturbances, and a relatively high 10 year failure rate. According to a report by Medicine Net, an online database including information and data regarding medical procedures, 44% of CABGs fail within 10 years post surgery due to clotting that occurs within the grafted saphenous vein.[7] Due to the high failure rate, there is a clear clinical need for a new method for treating cardiovascular disease.

Autografts are a potential option for surgeons when treating cardiovascular disease. An autograft is a procedure in which surgeons use a vein or artery from the patient as a bypass of the clotted artery causing cardiovascular disease. There are two different sites that surgeons generally harvest grafts from to bypass the clotted artery. The first is the saphenous vein located in the leg of the patient. The second artery used by surgeons is the internal mammary artery, located in the thoracic cavity of the chest.[7] There are advantages to both grafts; however, there are a number of disadvantages associated with both procedures that bring about the need for an alternative method for cardiovascular disease treatment.

Internal mammary artery grafts (IMAs) are also used in treating coronary heart disease. Surgeons will extract the internal mammary artery from the thoracic cavity in the chest. It is noted, however, that approximately 40% of patients do not have vessels available for harvest due to factors such as age and disease.[9]

4.1.3 Allografts

Allografts are another potential option for surgeons when treating cardiovascular disease. Allografts are similar to autografts in that they use real living tissue; however, an allograft is a tissue or organ transplant, usually from a cadaver donor, to a patient (host). Allografts have a number of complications that make them a less viable option for treatment versus the other known treatments. Due to the different gene type of the donor, the host is susceptible to graft versus host disease.[10]

"Graft versus host" disease is a condition in which the host's body rejects the implanted organ or tissue. Leukocytes, also known as white blood cells, recognize the graft due to foreign antigens surrounding the surface of the organ/tissue. The leukocytes then attack and destroy the organ or tissue causing the graft to fail. This then presents a need for another organ transplant.

There are methods to combat this condition through the use of drugs; however, the drugs used cause the body to stop recognizing antigens thus making the patient highly susceptible to other diseases and air borne illnesses. This is due to the lowered immune response because the body is attacking the graft. These drugs are dangerous because the patient loses the ability to fight and overcome illnesses leading to potentially fatal complications.[10]

4.1.4 Synthetic Grafts

Synthetic grafts are an alternative to auto- and allografts. Synthetic grafts are commonly fabricated using polymer materials such as Teflon and the synthetic fiber Dacron. Unlike allografts with graft host disease, synthetic grafts are not rejected by the human body; There is however, a foreign body response. With Dacron grafts and other similar materials, it is unlikely that a detrimental foreign body response will be experienced.[11] Although synthetic grafts eliminate the risk of "graft versus host" disease, there are a number of other potential complications that make them less viable than other alternatives.

Synthetic blood vessels have a higher tendency to clot than natural vessels within a three year period post-surgery.[9] Reasons for this include the fact that synthetic blood vessels lack the same endothelial layer as natural blood vessels. Because of this, materials floating within the blood stream cause thrombosis to synthetic vessels at a higher rate than in natural vessels. This problem is often seen in smaller diameter grafts. Larger synthetic arterial grafts generally work and have acceptable patency rates; however, smaller grafts with diameters less than 6mm have lasting patency rates below 50%.[11]

4.2 Tissue Engineered Blood Vessels

The concept of engineering tissues, and, more specifically, blood vessels, has been a scientific art on the rise. Through the research conducted for this report, the author believes that TEBVs will one day be the benchmark for cardiovascular disease treatment. Currently, there are a number of methods being used to produce TEBVs; however, one key constraint in most methods is time. This time constraint is caused by another one of the critical constraints in producing TEBVs. The time needed to ensure that the mechanical properties of the TEBV are suitable for use in humans extends the overall production time. The two main methods for the creation of TEBVs are reviewed in this section including both scaffold-based TEBVs and completely cell-based TEBVs.

4.2.1 Scaffold-Based Tissue Engineered Blood Vessels

Scaffold-based TEBVs are currently the most commonly made living vessels. Autologous skin cells, obtained from skin biopsies, are seeded onto a tubular shaped scaffold which is used as a device for structural support. One advantage to scaffold-based TEBVs is their ability to form tissues in vitro in a very short time frame yet maintain all of the required mechanical properties of a native tissue. Another advantage to scaffold-based TEBVs is that they inhibit thrombosis if endothelial cells are present, meaning that they do not clot at a higher rate than native tissue such as the synthetic grafts previously described[12] Finally, by using the scaffold, scientists can seed smooth muscle cells on one side of the scaffold and also seed endothelial cells on the other side. By doing so, the vessel created shares many similar qualities to an individual's native tissue.

There are also a few disadvantages to scaffold based TEBVs. A disadvantage to note is the time it takes to produce a TEBV from a scaffold. Currently, studies show that scaffold based

TEBVs tend to take up to 2-3 weeks for the vessels to completely mature and be ready for implantation.[6] Cell-based TEBVs take longer to produce due to the time needed for the cells to produce the necessary structural properties. Although scaffold based TEBVs have advantages that make them more viable than the aforementioned alternatives, there remains the need for a more effective method to produce patent vessels.

4.2.2 Cell-Based Tissue Engineered Blood Vessels

Completely cell-based TEBVs have many advantages, making them the focal point of many studies regarding tissue engineering. These cell-based tissues have high value in that they are the closest alternative to native tissue. One main advantage to cell-based TEBVs is the absence of any foreign or synthetic material. Synthetic materials allow for raised rates of infection, immune response, inflammation, and graft rejection.[6] Another advantage to note is that TEBVs have an extremely low thrombosis rate, meaning that they do not clog easily.

Completely cell-based TEBVs arrange themselves into a tubular structure and are then implanted in vivo without the use of any scaffold. One of the most popular current methods to produce cell-based TEBVs is through a process called "sheet based" tissue engineering. The general concept of this process is that the cells are laid in a sheet like structure and are allowed to culture for 6-8 weeks. The sheet is then cut and rolled around a cylinder and allowed to mature in culture for another 12 weeks. There are a few disadvantages with this method. First, the method produces TEBVs that are not necessarily homogenous, meaning that the sheets are not equally thick in all areas leaving some sections of the TEBVs weaker than others.[13] These weak areas can cause problems to the host in that the vessel may burst or tear in the weakened areas. The other glaring disadvantage with this method is the time to produce. Solving this time constraint

and lowering the time to produce a TEBV was one of the main objectives for the project group at Worcester Polytechnic Institute.[6]

4.2.3 Worcester Polytechnic Institute Tissue Engineered Blood Vessels

A Major Qualifying Project (MQP) team from Worcester Polytechnic Institute was able to develop a method and technology for the tubular self-assembly of cells to create a tissue engineered blood vessel. With this technology, the project team was able to successfully engineer a group of cells into a living blood vessel that could be used in treating cardiovascular disease. One of the main objectives of the WPI project was to have this process take seven days or less. The process also needed to be reproducible, require minimal manipulation, and be easy for the user to remove the living tissue. It is interesting to note that the TEBV production process requires minimal manipulation, resulting in less chance of contamination from the workers as well as a lowered chance for human error.[6] The group was able to meet these objectives. The group placed living cells within a polycarbonate tube, spun it for fifteen minutes at a designated speed, allowing the cells to distribute evenly around the inner wall of the tube. The tube was then placed in an incubator for three days allowing the cells to form a cohesive tissue construct.

The method and device designed at WPI takes advantage of the centrifuge, a device used to separate cells from media in a cell suspension. The group used a polycarbonate cylinder filled with cells and media. This cylinder was then spun using a small motor for fifteen minutes. During the fifteen minute cycle, the cells within the polycarbonate cylinder were “pelleted” to the inner diameter of the cylinder. The cells then aggregated together and created a tubular tissue construct which was removed from the tube and placed in a bioreactor for three days. The three day incubation period allowed the cells to grow with continuous nutrients through the form of

cell media. In Figure 5, one can see a schematic showing conceptually how the cells pellet against the inner diameter thus causing the cells to form a cylindrical tubular shape.

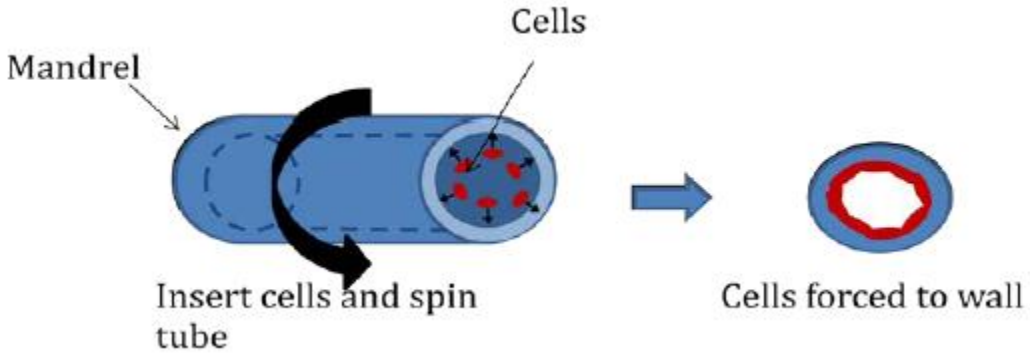

Figure 5: MQP Group Centrifugal Force Design.[6]

4.2.4 Main Applications

Clinical applications are the most likely end result for the WPI TEBVs. There are Food and Drug Administration (FDA) regulations governing the use and sale of medical devices and products which will initially limit the products applications, which are reviewed in section 4.3.3. Because of these regulations and the high costs associated with approving a product, the author decided that research is the most viable application for a start-up company revolving around the WPI TEBVs.

The device designed at WPI could potentially provide many advantages to the drug research field. Drug producing companies in the pharmaceutical industry could use the device to produce sturdy living vessels for testing new cardiovascular disease treatments. Research laboratories at universities and hospitals could use the vessels to better understand the effects of different diseases on human blood vessels.

4.2.5 Secondary Applications

As stated above, strict FDA regulations and the high costs associated with approving a product make it difficult to start a company with a product that is used in vivo, or in other words, on human subjects. Although a start-up company may not be able to afford the costs associated with certifying a device with the FDA, it is important to note that the long term business plan for the WPI device is aimed toward clinical applications of the TEBVs. The company would first focus on selling TEBV producing kits to generate enough revenue to eventually approve the TEBVs through the FDA. This would open an entirely new market to sell the product for clinical applications.

4.2.6 Initial Design Materials

The materials used in designing and manufacturing the current model of the device at WPI are relatively simple. The project team from 2009 fabricated a three part system utilizing a cell suspension tube, a small 3 volt hobby motor, and a custom bioreactor for cell incubation. The cell suspension tube was created by using a lathe and a 3/8" diameter piece of polycarbonate plastic. The polycarbonate rod was cut into 3" units creating a tube. (Figure 6).

Figure 6: Polycarbonate Tube Cut to Shape by WPI Project Team.[6]

Polycarbonate Tube

The 3” polycarbonate tube of 3/8” diameter was then drilled with a lathe to produce a ¼” diameter hole through the center of the tube that reaches a depth of ¾”. The other end of the tube was then drilled with a 1mm diameter hole that was ¼” deep for insertion of the motor. The polycarbonate plastic was an appropriate material for the tube due to its high melting point and structural properties. The high melting point is important because it allows the unit to be autoclaved, which is an effective method of sterilization. The final step of assembly for the polycarbonate tube was to fill the open end cap on the top with silicone glue. This was done to seal the top of the tube to ensure the cell suspension would be contained within the tube. The glue set within 24 hours and the tube was ready to use.

Hobby Motor

The motor used to spin the polycarbonate tube is a basic 3-volt hobby motor. The project team clamped the hobby motor into a three point clamp stand (Figure 7), which held the motor in place allowing it to spin the polycarbonate tube. Finally, a battery pack was used to house two AA batteries which were clamped with alligator clamps to power the motor. These components were all used in a Biosafety Cabinet to ensure a sterile work space.

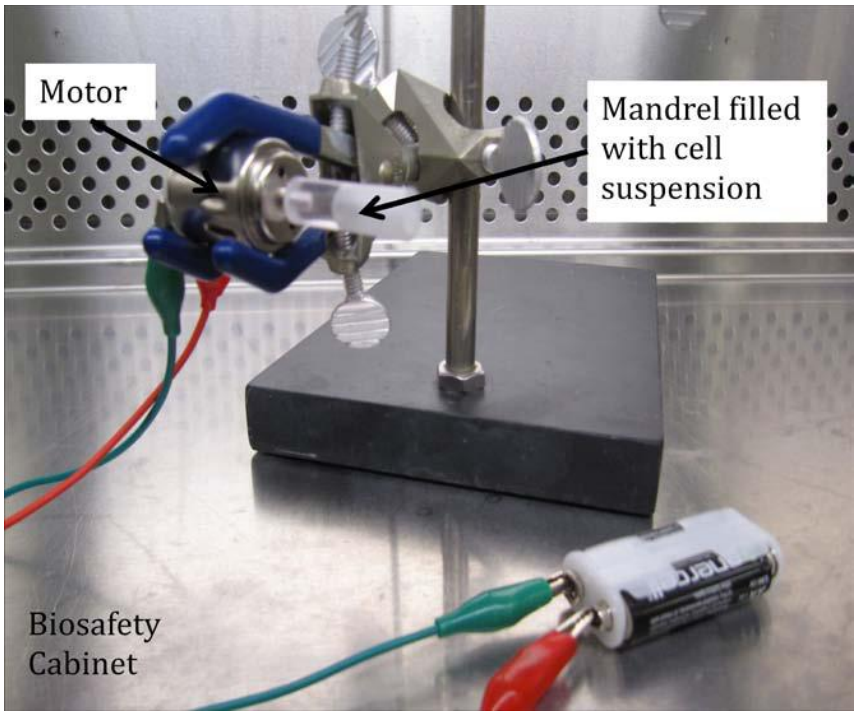

Figure 7: WPI device consisting of the battery pack with two AAs, the alligator clips to power the motor, the 3 volt hobby motor, the three point clamp stand, and the polycarbonate tube attached to the motor.[6]

Incubation Chamber

The final aspect of the WPI device was the incubation chamber. The chamber was fabricated using a 50 mL conical tube, a T-75 gas exchange screw top, a three-way stopcock, and a 5 mL syringe.[6] The project team drilled a hole in the bottom of the conical flask to allow gas to diffuse through the top cap. The incubation chamber can be seen below (Figure 8).

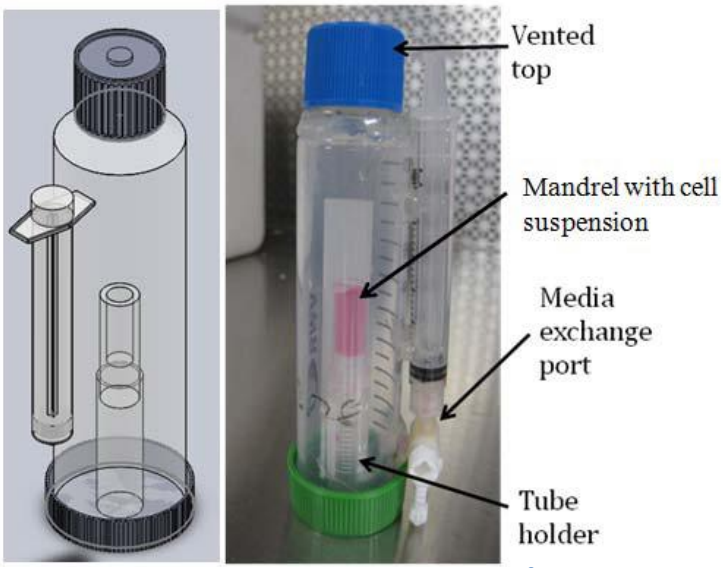

Figure 8: WPI Incubation chamber.[6]

4.2.7 Future Manufacturing Techniques

Due to the raw experimental form of WPI device, there are a number of additions and upgrades that the device will need to have to gain commercial value. Currently, the design, as seen in the previous figures, shows that the device is in its simplest form. There are several aesthetic upgrades as well as functional upgrades that will need to be made in order to successfully produce a product that is market ready. The most important of these upgrades will be the implementation of an encased hobby motor. This will eliminate many of the risks of injury due to the motor. It will also eliminate the need of the alligator clips (Figure 7). Finally, the end product of this process, the TEBVs, will need to be manufactured on a larger scale so that they meet the specifications of a native blood vessel.

3 Volt Hobby Motor

As previously stated, the WPI project team from 2009 used a 3 volt hobby motor to spin the cylindrical tube containing the cell suspension. The 3 volt hobby motor will still be sufficient

for spinning; however, it will need to be encased in a plastic box to ensure safety to the user and add aesthetic value. The group has decided that the batteries and battery pack should be eliminated to reduce cost for the user. By eliminating this component, however, there needs to be an alternate power source to run the motor. The group decided that the most efficient, user-friendly and safe approach to solving this dilemma is to power the motor with an AC plug and wall outlet, similar to those used in household appliances.

Bioreactor

During a personal communication with Professor Marsha Rolle, it was decided that the most applicable and marketable bioreactor at this stage of the research would be a self-contained bioreactor within the polycarbonate spinning cylinders. With this design, the polycarbonate spinning cylinder seen in Figure 6 above would include an in-flow tube and an out-flow tube. To feed the cells, one would simply pump cell media through this closed circuit in which the cells would continually receive media. This would reduce the overall cost of a kit by eliminating the bioreactor since it would be included within the cylinder.

4.2.8 Packaging Techniques

When the WPI TEBV manufacturing process is completed, the product will then need to be packaged for shipping to the customers. The kit will be an enclosed case with a snap-lock closing mechanism to hold all components within the case, as seen in Appendix 8.1. Included within the case will be the 3 volt hobby motor component with AC power, a "starter pack" of polycarbonate cylinders with specified amounts of cylinders such as 25, 50, 75, or 100 pieces, a syringe for cell implementation, a bioreactor for cell culture and incubation, and a user manual. The user manual will be the key component of the kit and will be one of the main selling attractions of the product in that it will enable users to produce TEBVs within their own

laboratories. The TEBVs produced from this kit will need to be transported using a cell incubator in order to keep the cells alive when they travel from "bench to bedside," meaning that the TEBV will be transported from the laboratory directly to the patient.

4.2.9 Secondary Market Opportunities

Clearly, the most profitable part of the company will be the manufactured TEBVs. This, however, will be a future form of revenue as the company will first need to generate revenue through the sale of the kit. The author also realized that there was another market opportunity created through the use of this device. The polycarbonate cell cylinders that are used to sustain the cells while they are being spun will eventually be thrown away following the completion of the TEBV growth. The group will use this disposal of the polycarbonate cylinders to the company's advantage by recommending the sale of additional packages of the cylinders.

4.3 Cost Analysis

4.3.1 Stakeholders Analysis

The stakeholders analysis is used to determine the members, groups, or organizations involved with the successes of a given product. A pyramid diagram can be used to rank the importance of a list of items. This pyramid diagram, in particular, informs the user of the most important groups affected by the TEBVs and kit produced at WPI. In the stakeholder diagram (Figure 8), the stakeholders at the top of the pyramid have the most at stake and are thus the most important. The market benefit of each stakeholder category is discussed in this section.

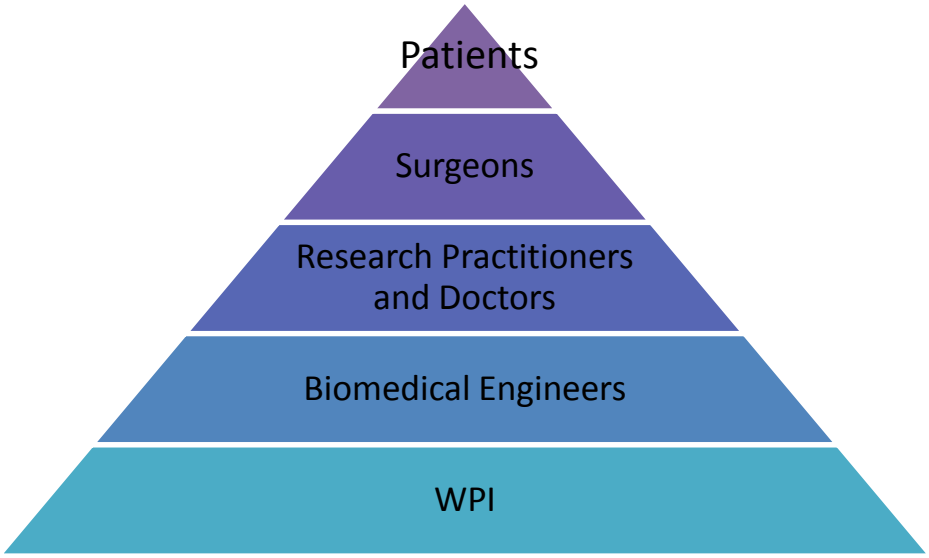

Figure 9: Stakeholders Pyramid

Patients

Patients are the highest ranked stakeholders in the stakeholders pyramid because they are end users of the product. Patients have the most to gain from TEBVs. If the TEBV producing kit introduced by WPI is approved through the FDA (see section 4.3.3) and receives the proper codes for health insurance reimbursement (see section 4.4.9), then clinical applications will become a possibility allowing surgeons to use TEBVs as a treatment for cardiovascular disease. Currently, patients who undergo coronary artery bypass grafts remain in the hospital for around a week; the patients spend up to three days in the intensive care unit.[14] The procedure will become less invasive and thus is expected to be more preferred by patients, by eliminating secondary surgeries to harvest grafts.

Surgeons

According to the Texas Heart Institute at St. Luke's Episcopal Hospital, there were over 450,000 coronary bypass procedures in 2006 alone.[15] Cardiac surgeons perform surgeries related to the heart, including both its vessels and arteries. Following successful approval for clinical use

by the FDA, TEBVs would likely become a safe and effective alternative to the current coronary artery bypass surgical procedure.

In a news release by the American Heart Association, it is stated that up to 40% of patients receiving coronary artery bypass surgery do not have suitable vessels or arteries for graft procedures. As a substitute, these patients receive synthetic grafts. One main problem with these synthetic grafts is that they can cause severe infections and only 20% remain patent within 3 years post surgery.[9] By adding the option of using the TEBVs produced by the WPI device, surgeons will have another graft to use as an alternative to autografts and synthetic grafts.

Research Practitioners and Doctors

Research practitioners are the most likely users of the kit produced by WPI. In a study performed by the Foundation for Biomedical Research, over 17 million animals are used each year in the United States for research purposes. This number has caused a number of political campaigns regarding animal cruelty and rights.[16] Although there are a number of claims stating that the animals feel no pain during testing, there are still debates campaigning against animal testing as a preferred method to test new drugs and disease treatments. In a study done during the year 2000, it was found that there over $45 million was spent in biomedical research testing. It is the hope of the project team that the TEBVs produced from the WPI kit will be a valuable research alternative to animal testing. Should the technology work as expected, a small percentage of the animal research market ($45 million in 2000)[17] can be for biomedical research testing for the project team to infiltrate. It is noted that most cardiovascular research, and more importantly research to test treatment alternatives for CABG procedures, is performed on canines because their respiratory system is similar to that of humans.[18]

Biomedical Engineers

Biomedical engineers will benefit greatly from the expansion of the medical device industry. According to the United States Bureau of Labor Statistics, there are over 3,400 biomedical engineers working within the medical equipment and supplies industry. This is the highest concentration of the nearly 15,000 employed biomedical engineers in any of the biomedical industries.[19] Assuming that the technology will work to its desired functions, the author is confident that the product and technology will help advance the field and research performed by biomedical engineers The result may be more job opportunities for BMEs within the field.

Worcester Polytechnic Institute and Inventors

Worcester Polytechnic Institute and the inventors of the TEBV producing device are the final stakeholders of the product. The institution currently has an invention disclosure on the product and process. This is essential to the WPI TEBV producing method because it is the beginning stages of protection for the technology. There is also another patent application describing the method and technology used to produce TEBVs; however, a full patent has not yet been issued.

4.3.2 Cost Analysis of TEBV Device/Kit

The cost of the TEBV producing kit, created by members of the Worcester Polytechnic Institute biomedical department, will rely heavily on the company's ability to successfully combine outsourcing with in-house production. It is important to understand the costs associated with producing and selling the kits as they are essential in the long-term business plan. The production of the kit includes the use of both machines and materials. To produce the kit, one will need a lathe for cutting the polycarbonate spinning cylinders to shape. Also, a CNC machine

is needed to produce the mold (either prototype or permanent) for the motor unit encasing. This section outlines the different potential scenarios regarding the production costs of the kit. Figure 10 highlights the components contained within the case as well as the parts that need machining.

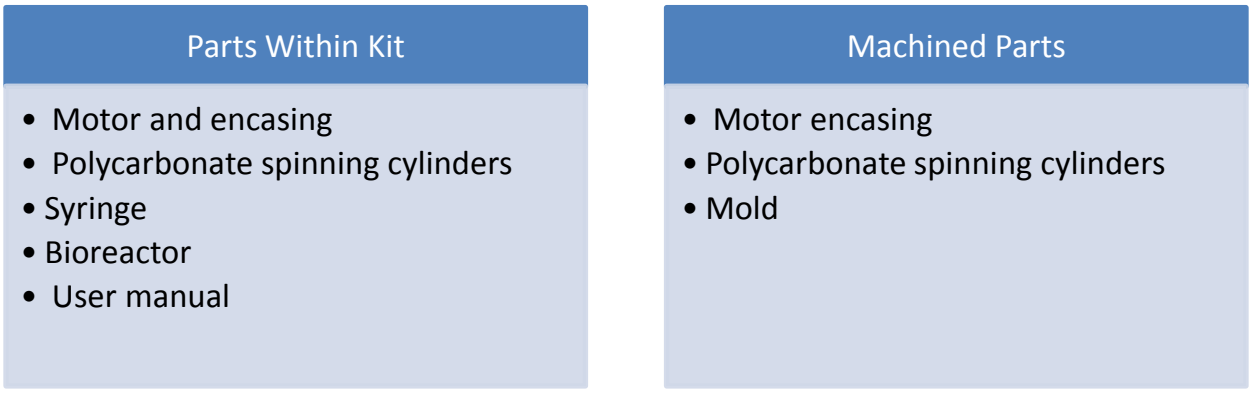

Figure 10: Kit Components and Machined Parts

Completely In-House Production

There are a number of costs associated with manufacturing the kit entirely in-house. Completely in-house production includes purchasing the materials, a lathe, and a CNC machine, along with hiring a mechanical engineer to operate the machinery, manufacturing all components in-house, and assembling the kit. During an interview with Randy Guertin[20], the tool and engineering manager for Applied Plastic Technology in Worcester, Massachusetts, the costs of the required machines was discussed. The following costs associated with completely in-house production are seen in Table 1 below.

Costs (Completely In House)	Number of Units Produced					
	10	30	50	100	250	500
Lathe Cost	$10,000	$10,000	$10,000	$10,000	$10,000	$10,000
CNC Machine Cost (Used)	$25,000.00	$25,000.00	$25,000.00	$25,000.00	$25,000.00	$25,000.00
Prototype Mold (used in CNC machine)	$5,500.00	$5,500.00	$5,500.00	$5,500.00	$5,500.00	$5,500.00
Material Costs for Motor House Unit	$50.00	$150.00	$250.00	$500.00	$1,250.00	$2,500.00
Mechanical Engineer Labor Cost (per hr)	$38.74	$38.74	$38.74	$38.74	$38.74	$38.74
Cost of Polycarbonate Rods (10 units)	$266.00	$798.00	$1,330.00	$2,660.00	$6,650.00	$13,300.00
Total Cost	$40,816	$41,448	$42,080	$43,660	$48,400	$56,300
Total Cost per Unit	$4,081.60	$1,381.60	$841.60	$436.60	$193.60	$112.60

Table 1: Completely In-House Production Cost Analysis. *Median Mechanical Engineer Salary.[21]

The first machine needed in the production of the kit is a basic lathe for the manufacturing of the polycarbonate cylinders. Guertin indicated that the cost of an appropriate lathe would be $10,000. The production team would also need to purchase a CNC machine, which is used in forming the plastic motor housing, a cost of $100,000 new or $25,000 used. Finally, the production team would need to purchase a mold (either prototype or permanent) that would be used within the CNC machine to produce the plastic motor housing. For the purpose of this analysis, a prototype mold ($5,500.00) was used, because the production team would likely want to test the design first with the prototype mold in order to fix any imperfections with the design. Once the design is perfected, it would then be worth purchasing a permanent mold which can withstand long-term production use. The cost associated with the materials for the motor housing units is around $5.00 per unit.[20]

It is equally important to recognize the cost of hiring a mechanical engineer to run the production of the kit. Also, the mechanical engineer brings the expertise of drawing the product on computer design software (such as AutoCAD) and thus would be able to complete many of the required processes. The United States Department of Labor states that the median hourly wage for a mechanical engineer is $38.74 per year. The total cost per kit, if 500 kits are

manufactured completely in-house, is $112.60 per unit. The mechanical engineer was used as the main engineer to run the production of the kit because he/she has both expertise with the machinery and how to complete the required processes.

Completely Outsourced Production

When outsourcing the production of the WPI kit, the costs of manufacturing a mold, the materials, and the labor for assembly must be taken into consideration. To successfully manufacture and assemble the kit, the manufacturing company would first need to design and fabricate a mold to be used for forming the plastic encasing for the hobby motor. There are two types of molds available for purchase through most manufacturing companies. Prototype molds, the less expensive of the two, cost anywhere from $5,000-$6,000 per mold. For the WPI kit, Randy estimated the mold to be around $5,500.

The prototype mold is a perfect option for clients that expect to produce less than 500 units as the mold can only withstand the production of about 500 units.[20] Once the prototype mold is purchased, each unit including the material and machining costs will be $3.00 per unit. Although the goal of the WPI project team is to produce around 25-30 units to first start a lease program, it is expected that long-term goals of the company would include manufacturing more than 500 units.[20]A cost analysis of the prototype mold for production of 10, 30, 50, 100, 250, and 500 units is show below (Table 2). Randy expected to be capable of machining 10 polycarbonate cylinders per hour making labor costs of $2.50 per unit. The material cost for the cylinders is $0.16 per unit. If a prototype mold is used, the total cost per kit, if 500 kits are manufactured, is $45.60 per unit.

Costs (Prototype Molding)	NUMBER OF UNITS PRODUCED					
	10	30	50	100	250	500
Prototype Mold Cost	$5,500	$5,500	$5,500	$5,500	$5,500	$5,500
Unit Cost	$30.00	$90.00	$150.00	$300.00	$750.00	$1,500.00
Assembly Labor Cost ($5 per unit)	$50.00	$150.00	$250.00	$500.00	$1,250.00	$2,500.00
Cost of Polycarbonate Rods (10 units)	$266.00	$798.00	$1,330.00	$2,660.00	$6,650.00	$13,300.00
Total Cost	$5,846	$6,538	$7,230	$8,960	$14,150	$22,800
Total Cost (per Unit)	$584.60	$217.93	$144.60	$89.60	$56.60	$45.60

Table 2: Completely Outsourced Production Cost Analysis for Prototype Mold

The second of the two molds is called a permanent production mold. This mold is fabricated mainly from steel and can withstand long-term production. Permanent production molds cost between $18,000 and $22,000. Again, Randy estimated that the total cost of a permanent mold for the WPI design would be $20,000. It is important to note that by purchasing the permanent mold, the company would then become the owner of that mold and thus could take it to another manufacturing company if that became the most suitable option.

Once the mold is purchased, the individual unit price of the encased motor units including materials and machining costs would be $2.00. Applied Plastic Technology can also assemble the units at an additional labor rate of $25.00 per hour. Mr. Guertin expected that his crew would be capable of assembling five of the encased motor units per hour making the cost of assembly an additional $5.00 per unit.[20] This additional $5.00 per unit is the associated labor cost should the production be completely outsourced. A cost analysis of the permanent mold for production of 10, 30, 50, 100, 250, and 500 units is show below in Table 3. The table also includes the cost of a 10 piece starter pack of polycarbonate cylinders. If the permanent mold is used, the total cost per kit, if 500 kits are manufactured, would be $73.60 per unit.

Costs (Permanent Molding)	NUMBER OF UNITS PRODUCED					
	10	30	50	100	250	500
Permanent Mold Cost	$20,000	$20,000	$20,000	$20,000	$20,000	$20,000
Unit Cost	$20.00	$60.00	$100.00	$200.00	$500.00	$1,000.00
Assembly Labor Cost ($5 per unit)	$50.00	$150.00	$250.00	$500.00	$1,250.00	$2,500.00
Cost of Polycarbonate Rods (100 units)	$266.00	$798.00	$1,330.00	$2,660.00	$6,650.00	$13,300.00
Total Cost	$20,336	$21,008	$21,680	$23,360	$28,400	$36,800
Total Cost per Unit	$2,033.60	$700.27	$433.60	$233.60	$113.60	$73.60

Table 3: Completely Outsourced Production Cost Analysis for Permanent Mold

Mixed Production Scenarios

To help reduce the costs associated with manufacturing, the author has developed a scenario for producing the WPI kit including both in-house and outsourced manufacturing. This scenario includes having the lathing of materials outsourced, component manufacturing outsourced, and assembly of the units in-house. The author decided that it would be beneficial for the company to first purchase a prototype mold. The reason for this is to ensure that the design is tailored to the customers need. By utilizing the lease program outlined in section 4.2.7, the company will be able to receive feedback from the customers/users thus allowing them to make any modifications needed to maximize the function of the products. Once these design changes are made, the company would then be advised to purchase a permanent mold for long-term production. By outsourcing the production aspect of the process, the company could eliminate the need of a mechanical engineer to run the machinery.

Costs (Prototype Molding) Mixed Production	NUMBER OF UNITS PRODUCED					
	10	30	50	100	250	500
Prototype Mold Cost	$5,500	$5,500	$5,500	$5,500	$5,500	$5,500
Unit Cost	$30.00	$90.00	$150.00	$300.00	$750.00	$1,500.00
In-House Assembly Labor Cost ($2.64 per unit)	$26.40	$79.20	$132.00	$264.00	$660.00	$1,320.00
Cost of Polycarbonate Rods (10 units)	$266.00	$798.00	$1,330.00	$2,660.00	$6,650.00	$13,300.00
Total Cost	$5,822	$6,467	$7,112	$8,724	$13,560	$21,620
Total Cost (per Unit)	$582.24	$215.57	$142.24	$87.24	$54.24	$43.24

Table 4: Mixed Production Cost Analysis.

As seen in Table 4, the row highlighted in green shows the in-house assembly costs. All other costs associated with the production are outsourced in this mixed scenario. Of the aforementioned scenarios, the mixed production scenario produces the lowest cost per kit if 500 units are manufactured at $43.24 per kit.

4.3.3 Cost Analysis of Tissue Engineered Blood Vessels from WPI Kit

The following section highlights the costs associated with producing TEBVs for human clinical use. The approval process of the USFDA is also examined.

United States Food and Drug Administration Certification

The United States Food and Drug Administration (FDA) is responsible for regulating and certifying all food and drug products for sale in the market place. The Center for Biologics Evaluation and Research (CBER) is a subdivision of the FDA responsible for regulating and certifying new biological treatments introduced to the market. To obtain approval through the FDA and the CBER, the company must first contact the FDA with specific information regarding the proposed application of the product as well as the positive effects as well as negative effects the product will cause. Once having notified the FDA with the aforementioned

information, the TBEVs must be tested on animals and in laboratories by research scientists to provide clinical performance data to the FDA.[23,24]

Once clinical data is obtained, the company would then file for an application for exemption through the FDA known as an investigational new drug (IND) application. This exemption allows the company to then test on human subjects. This study must be approved by the FDAs board of scientific and medical advisors. This board also consists of consumers within the proposed market. After performing thorough testing on the product, the company will supply the FDA with data proving the long-term patency regarding in-vivo use. Once the company can prove that the product is safe and provides valuable applications and results when used in humans, the FDA will certify the product thus making it market ready. According to the FDA website, a new drug application (NDA) typically takes 10 months to acquire. [23,24]

Cost Analysis of Tissue Engineered Blood Vessels

The kit produced at WPI serves many applications including both research and the potential one day to produce a TEBV that can be used for clinical applications. There are many costs that must be considered regarding the production and culturing of cell-based grafts for clinical use. For the purpose of this study, the author proposed a four phase production method to breakdown the cost analysis of a TEBV. These costs can be correlated to the proposed four phases of production needed to create one TEBV. Phase 1 of the process is the phase in which an initial skin biopsy is obtained. This skin biopsy is used for harvesting the necessary living cells needed to produce a TEBV. Phase 2, the "front-end processing phase," is where the cells from the skin biopsy are obtained and cultured for a 3 week period to prepare them for the spinning phase. Phase 3 is the spinning phase in which the cultured cells are placed into the WPI device. The spinning phase is the phase in which the cells are spun within the polycarbonate cylinder.

Finally, Phase 4 is the stage in which the TEBV is cultured and matured for clinical application (Figure 11).

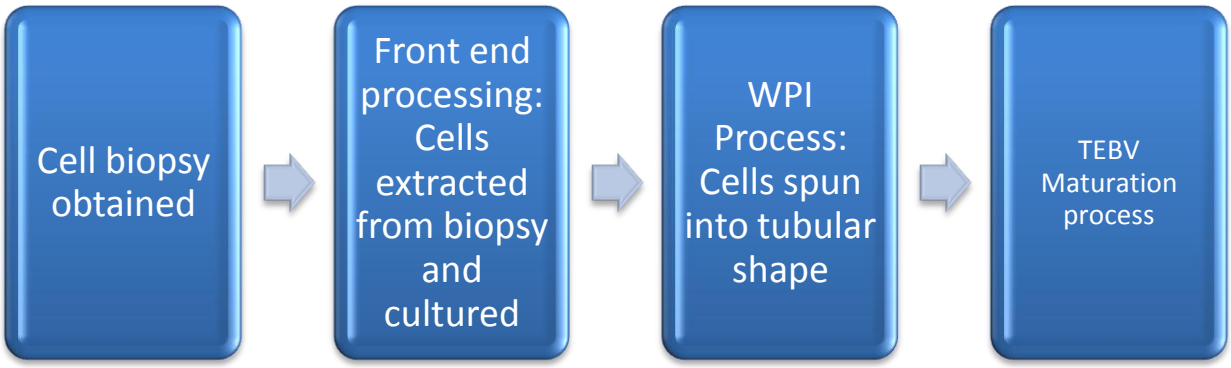

Figure 11: TEBV Production 4 Stage Process

The cost of the skin biopsy taken to provide dermal fibroblasts used in producing the tissue engineered blood vessels must be considered. Also, the cost to ship a skin biopsy is taken into consideration. Next, the cost of the employees needed to produce the vessel through the latter three phases is examined. For the purpose of this analysis, it was assumed that the employees needed to produce the vessels would include two biomedical engineers and a medical/clinical laboratory technician. The biomedical engineers would be capable of performing any tasks related to the TEBVs and cell cultures. The laboratory technician would work directly with the biomedical engineers in ensuring that each TEBV produced is suitable for clinical applications. The technicians would also carry out any needed tasks requested by the biomedical engineers. In the following paragraph, the hourly wage rates of the aforementioned

professionals are discussed. Finally, the cost of materials such as cell media used to feed the cells/TEBVs is examined.

Using data from the U.S. Department of Labor regarding the average salary of a biomedical engineer, it was determined that the mean hourly wage is $39.69.[25] Using similar data, it was determined that the mean hourly wage for a medical/clinical laboratory technician is $18.20.[26]

Phase 1

Phase 1 of the TEBV production process is where the skin biopsy is obtained. The skin biopsy is essential in the process in that dermal fibroblasts are extracted and used to produce the TEBV. The overall time for this process is the shortest of the four phases. The skin biopsies must be shipped to the facility where they will be grown into sheets and cultured. According to Todd McAllister et al., it was stated that the mean transport time for the cell cultures was 26.7 hours.[27] This is important because it is expensive to transport living cell cultures (Table 6).

The cost of 21,692 individual skin biopsies in the state of Florida during the 2009 calendar year was examined. The study conveyed the number of skin biopsies for each hospital in the state as well as the low and high cost of each procedure. The average low cost (associated with punch biopsies), average high cost (associated with surgical biopsies), and the average cost of skin biopsies is shown below (Table 5). [28]

Biopsy Cost		
Low	High	Average
$2,247	$8,876	**$5,562**

Table 5: Average low, high, and overall average cost of a skin biopsy in Florida hospitals during the 2009 calendar year.[28]

The average cost to transport living tissues was found through FedEx overnight next morning delivery shipping is $48.55 for a 3 pound package and $50.65 for a 5 pound package. The average of these two shipping costs is $49.60. An additional cost of $25 is added due to the transportation of "hazardous material." This makes the total shipping cost $74.60 for a skin biopsy. The total cost of the biopsy ($5,562) plus the total shipping cost ($74.60) are added for a total $5636.60 for phase 1 of the TEBV production.

Materials:	Costs:
Cell Biopsy	$5,562
Transportation (overnight)	$74.60
Total Cost:	$5,636.60

Table 6: Phase 1 Cost Analysis

Phase 2

Phase 2 of the process is considered the "front-end processing phase." During this phase, the dermal fibroblasts extracted from the skin biopsies are cultured in order to prepare them for use in the WPI device (kit) noted in Phase 3. There are both labor and material costs associated with this phase. Both biomedical engineers and the technician will be involved in the final three phases of TEBV production. These workers are needed to feed the cells media and to monitor the growth of the cultured fibroblasts. In a 2006 Nature Medicine journal article, Nicolas L'Heureux of Cytograft stated that this phase takes around six weeks to complete. It is also stated that during this time, the cells are fed media that changes three times weekly. Conversely, Phase 2 of the process at WPI has been reduced to just three weeks. There are two segments to the three week phase. The first is a two week front-end processing segment in which the two million dermal

fibroblasts are extracted from the skin biopsy. The second segment is a one week phase in which the cells are doubled until the target of 100 million cells needed to produce a TEBV is reached.

During Phase 2, the goal is to grow 100 million cells from an initial two million cell culture. The initial two million cells will be split amongst three flasks. It was decided through a personal communication with biomedical engineering professor Marsha Rolle that the doubling time for the dermal fibroblasts should be approximately 24 hours. Also, every two days, the flasks used to house the cell cultures must be split into three new flasks to allow room for the cells to grow. An example of this doubling process can be seen below in Figure 12. Also, Table 7 conveys the number of days, number of cells, and number of flasks it takes to reach the target of 100 million cells.

Day	# of Cells (millions)	# of Flasks
1	2	3
2	4	3
3	8	9
4	16	9
5	32	27
6	64	27
7	128	Harvest

Table 7: Cell Doubling Data

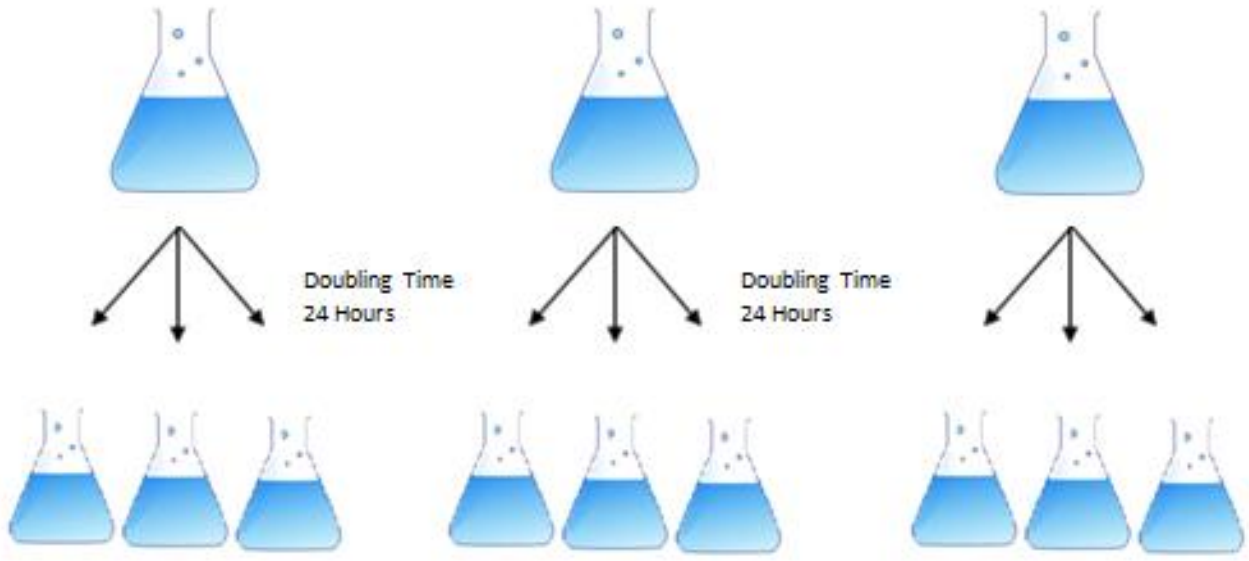

Figure 12: Cell Doubling Flask and Time Example

During a personal communication on January 10, 2011 with Craig Jones, a biomedical engineering student who worked on the 2009/2010 WPI MQP related to this analysis, the time associated with preparing and administering cell media was determined. Jones stated that it takes about 15 minutes to prepare the media and administer it to the cells per dish.[29] Hence, during the 3 week phase and 87 media cycles (six cycles in weeks one and two/81 cycles over 27 flasks in week 3), it is determined that the total labor time for this phase is 1,305 minutes (21.75 hours).

During the three week Phase 2, the cell media is changed weekly to help the cells grow and mature. This frequent changing of the media, however, increases the cost to produce one vessel. The cell media used in the Cytograft process will be used as the model when examining the costs associated with the WPI process. Cytograft currently uses a media composed of Dulbecco's modified eagles medium (DMEM). This media is supplemented with Ham's F12 (20%) which contains streptomycin and penicillin, and FetalClone bovine serum (20%). The total volume of each media exchange is 45mL. By purchasing the cell media ingredients through the online company Sigma Aldrich, the author has concluded that a 10 liter bottle of Dulbecco's

modified eagles medium costs $32.30. Similarly, a 500mL bottle of Ham's F12 costs $23.50, and a 500mL bottle of FetalClone bovine serum costs $128.82. A cost analysis of the required amount of media as well as the total cost for three weeks of media exchanges (3 weeks x 3 exchanges per week (per flask)) plus the included labor for phase 2 is examined in Table 8.

Cost Factor	
Labor:	**Cost**
Biomedical Engineer (2) ($39.69/hr)	$1,726.52
Laboratory Technician ($18.20/hr)	$386.75
Materials:	
Media (87 exchanges= $2.89 * 87)	$251.43
Total Cost of Phase 2	**$2,364.70**

Table 8: Phase 2 Cost Analysis

Phase 3

Phase 3 of the WPI TEBV production process is the stage in which the WPI device used for spinning the cells is implemented. This phase is where the WPI process differs from that of Cytograft's and is likely to be the phase in which WPI can reduce the total production time. Phase 3 takes roughly three days to complete. Currently, as previously stated, Cytograft uses three exchanges of media weekly. Due to the media cycle discussed in L'Heureux's papers, it is assumed that this stage will only need one exchange of media since it will be completed in only three days; however, based on the original cell count versus the new cell count, media will need to be continually administered throughout the three days thus using one media cycle per day.

The total cost of this phase includes the labor rate for the two biomedical engineers and the technician. The biomedical engineer will be used to control the entire process. The technician will be used to assist the biomedical engineer in any processes that need to be completed.

Finally, the engineers and technician will test each vessel produced during this phase for quality control purposes.

It is important to note that although this phase takes three days to complete, engineers will likely be working on this phase of vessel production for a total of only one hour and forty-five minutes (3 media cycles for 15 minutes each and another hour for inserting the cells and removing them from the tube). This is because the cells will be placed into the device, spun for 15 minutes, and then allowed to incubate for the remainder of the three days. The cost analysis of this phase also includes the cost of one exchange of media. A cost analysis for phase 3 can be seen in Table 9.

Labor:	**Cost**
Biomedical Engineer (2) ($39.69/hr)	$128.42
Laboratory Technician ($18.20/hr)	$31.85
Materials:	**Cost**
Media (3 exchanges)	$8.67
Total cost of Phase 3 Production	**$168.94**

Table 9: Phase 3 Cost Analysis

Phase 4

Phase 4 of the WPI TEBV production process is similar to the fourth phase of Cytograft's TEBV production process. During phase 4, the TEBV is removed from the spinning device and allowed to mature over a minimum of 10 weeks. Over the 10 week period, there will be a total of 30 media cycles. With each media cycle taking 15 minutes to administer, the total labor time for this phase will be 450 minutes (7.5 hours).

The total labor time used in calculating the cost of phase 4 will be 10 hours through the assumption that there may be alternative labor needed during this phase. This labor could include frequent quality control checks by the biomedical engineers and laboratory technician and basic tasks performed by the laboratory technician to maintain tissue maturation. As Table 10 conveys, the two staff members of this phase include the biomedical engineer and the laboratory technician.

Cost Factor	
Labor:	**Cost**
Biomedical Engineer (2) ($39.69/hr)	$793.80
Laboratory Technician ($18.20/hr)	$180.20
Materials:	
Media (1 exchange= $2.89 * 30)	$86.70
Total Cost of Phase 4	**$1,060.70**

Table 10: Phase 4 Cost Analysis

Total Costs

The total cost of one tissue engineered blood vessel is calculated by adding the costs associated with each of the four phases of production. Table 11 examines the summation of costs for the four phases. The author assumes that this cost can be considered accurate in that the estimated time values used in calculating labor costs are accurate and based on both Cytograft's and WPI's current production methods. The cost of media was examined by using the online biomedical supplies distributor Sigma Aldrich.

Phase	Cost
Phase 1	$5,636.60
Phase 2	$2,364.70
Phase 3	$168.94
Phase 4	$1,060.70
Total Cost to produce one TEBV:	**$9,230.94**

Table 11: Total Cost to Produce One TEBV- Phase Summation

4.3.5 Economic Factors of TEBVs

The TEBVs produced using the process at WPI will likely have limited direct competition in the market as outline in section 4.4.2. Due to the current limit of competition within the industry and the assumption that WPI's TEBVs become the industry choice for CABG, WPI will have an easy market to control. This will be especially true if the product is able to surpass the competing products in both design and function. The product is also likely to succeed due to its ability to have alternative applications for clinical use. For example, the TEBVs could be used to replace damaged or destroyed vessels or arteries in other parts of the human body other than being used strictly for coronary artery bypass surgery.

The supply and demand are important factors to consider when bringing a new product to market. The elasticity of the product is also an important factor to consider. Patients, the end-users of the product, are likely to find the cost of this product relatively inelastic. This means that the product is necessary for the patient and therefore the patient is likely to choose this product regardless of the price, even though most of the cost is borne by a third-party insurance company.

In Figure 13 below, the supply and demand curves are examined for the TEBVs produced by WPI. The following figure shows an example of how the supply and demand will change should the product experience sales success in the market. The supply and demand curves and their movements are based on the standard supply and demand model of a successful product. It should be noted that the demand curve moves to the right due to the benefit that the TEBVs bring to the market place. As the products demand raises over time, the company started by WPI inventors will likely streamline the production process to adequately supply the market with TEBVs by increasing the efficiency of the manufacturing process. This increase in efficiency is likely to cause the supply curve to move right as more units will be produced through the more streamlined production method.

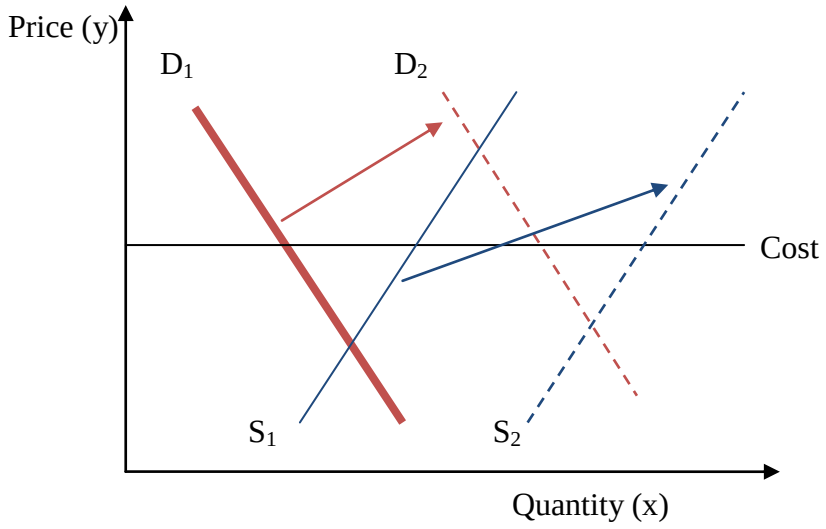

Figure 13: Supply and Demand Curves for WPI's TEBVs

4.3.6 Break-even Analysis

A break-even analysis is used to determine how many units must be sold in order for a company to break-even and thus begin generating a positive net income, without regard to time.

WPI Kit Break-Even Analysis

The following section outlines the break-even analysis for the TEBV producing kit manufactured by WPI. For the purpose of this analysis, the cost of $215.57 per kit (Table 4), will be approximated at $220.00 per kit. This number was chosen because it was mentioned that the project team would first attempt to produce 30 kits for sale. First Research, a database provided by WPI in which industry statistics are examined for each industry in the U.S. market, states that the average margin for products in the medical supplies and devices industry is between 40%-60%.[30] For the purpose of this analysis, we will assume that the WPI kit will have a margin on the lower end of this spectrum. This was done to ensure that the break-even analysis cover the bare minimum of necessary sales to break-even. This was done to ensure that the production team would know the maximum number of units that needed to be sold in order to break-even. The margin was set at 45% so that the selling price of each kit would be $320. In Table 12, shown below, the break-even point for the WPI device is examined. Appendix 8.3 examines a chart of this data.

BREAK-EVEN ANALYSIS FOR WPI KIT				
Number of Units Produced and Sold	Fixed Cost (mold)	Total Cost ($45 per unit)	Total Revenue	Net Profit
0	$5,500.00	$5,500.00	$0.00	-$5,500.00
1	$5,500.00	$5,545.00	$320.00	-$5,225.00
2	$5,500.00	$5,590.00	$640.00	-$4,950.00
3	$5,500.00	$5,635.00	$960.00	-$4,675.00
4	$5,500.00	$5,680.00	$1,280.00	-$4,400.00
5	$5,500.00	$5,725.00	$1,600.00	-$4,125.00
6	$5,500.00	$5,770.00	$1,920.00	-$3,850.00
7	$5,500.00	$5,815.00	$2,240.00	-$3,575.00
8	$5,500.00	$5,860.00	$2,560.00	-$3,300.00
9	$5,500.00	$5,905.00	$2,880.00	-$3,025.00
10	$5,500.00	$5,950.00	$3,200.00	-$2,750.00
11	$5,500.00	$5,995.00	$3,520.00	-$2,475.00
12	$5,500.00	$6,040.00	$3,840.00	-$2,200.00
13	$5,500.00	$6,085.00	$4,160.00	-$1,925.00
14	$5,500.00	$6,130.00	$4,480.00	-$1,650.00
15	$5,500.00	$6,175.00	$4,800.00	-$1,375.00
16	$5,500.00	$6,220.00	$5,120.00	-$1,100.00
17	$5,500.00	$6,265.00	$5,440.00	-$825.00
18	$5,500.00	$6,310.00	$5,760.00	-$550.00
19	$5,500.00	$6,355.00	$6,080.00	-$275.00
20	$5,500.00	$6,400.00	$6,400.00	$0.00

Table 12: Break-Even Analysis for WPI Kit

In Table 12, there are four major categories regarding the manufacturing of the WPI kit. The fixed cost of $5,500.00 is for the prototype mold that will be used to produce the first 30 kits. The calculations in Table 12 were done by using the formula TVC= FC+VUC*n/n. This formula is for the total variable cost and considers the fixed costs, variable unit costs, and the number of units produced. As seen in the table, the WPI kit would have a relatively short payback period of only 20 units. This means that once the company has purchased the prototype mold and sold 20 of the kits, the company would then begin generating a net profit from the

units. A break-even analysis does not include the cost of labor; it merely takes into account the fixed costs and unit costs associated with a product as well as the selling price.

WPI Tissue Engineered Blood Vessels Break-Even Analysis

This section examines the break-even analysis for the production of WPI's tissue engineered blood vessels. As previously stated, First Research database lists that the average margin for products sold in the medical supplies and devices industry is between 40%-60%. When calculating the margin on the WPI kit, it was assumed that it would be on the lower spectrum of this range due to the mechanical nature of the product. When deciding the percent margin for the WPI TEBVs, due to the nature of the product and the fact that no product currently exists in the market with the same applications, the author assumed that the product would receive the higher end of the margin range at 60%.

As seen in Table 13 below, the examined values are the initial investment of $100,000, the total cost per TEBV plus the initial investment, the total revenue, and the net profit. The author set the initial investment at $100,000 to test the payback period for potential investors. This is a standard investment by angel investors to start-up firms. Angel investors are people who supply firms with capital. The total TEBV cost was calculated by adding the initial investment to the cost of one TEBV. The cost of the TEBV was multiplied by the number of units produced. The total revenue for the TEBVs was calculated by multiplying the total cost of the TEBV by the 60% margin and then by adding the margin to the cost to produce one TEBV. As seen in Table 13 regarding the cost analysis of TEBVs, it costs about $10,000 to produce one TEBV. The revenue associated with one TEBV was calculated to be $16,000. Finally, the net profit was calculated by subtracting the total costs from the total revenue. It was found through this analysis that with an initial investment of $100,000, the break-even point for the sale of

WPIs TEBVs is at 17 units. Table 13 below examines the break-even analysis for WPIs TEBVs with an initial investment of $100,000. It can be seen that with an initial investment of $100,000, investors can expect a positive return on investment (ROI) at 17 units sold with a total net profit of $2,000. Appendix 8.4 examines a chart of this data.

BREAK-EVEN ANALYSIS FOR WPI TEBVs				
Number of Units Produced	Fixed Cost (Investment)	Total Cost (Labor+ Materials)	Total Revenue	Net Profit
0	$100,000.00	$100,000.00	$0.00	$ (100,000.00)
1	$100,000.00	$110,000.00	$16,000.00	$ (94,000.00)
2	$100,000.00	$120,000.00	$32,000.00	$ (88,000.00)
3	$100,000.00	$130,000.00	$48,000.00	$ (82,000.00)
4	$100,000.00	$140,000.00	$64,000.00	$ (76,000.00)
5	$100,000.00	$150,000.00	$80,000.00	$ (70,000.00)
6	$100,000.00	$160,000.00	$96,000.00	$ (64,000.00)
7	$100,000.00	$170,000.00	$112,000.00	$ (58,000.00)
8	$100,000.00	$180,000.00	$128,000.00	$ (52,000.00)
9	$100,000.00	$190,000.00	$144,000.00	$ (46,000.00)
10	$100,000.00	$200,000.00	$160,000.00	$ (40,000.00)
11	$100,000.00	$210,000.00	$176,000.00	$ (34,000.00)
12	$100,000.00	$220,000.00	$192,000.00	$ (28,000.00)
13	$100,000.00	$230,000.00	$208,000.00	$ (22,000.00)
14	$100,000.00	$240,000.00	$224,000.00	$ (16,000.00)
15	$100,000.00	$250,000.00	$240,000.00	$ (10,000.00)
16	$100,000.00	$260,000.00	$256,000.00	$ (4,000.00)
17	$100,000.00	$270,000.00	$272,000.00	$ 2,000.00
18	$100,000.00	$280,000.00	$288,000.00	$ 8,000.00
19	$100,000.00	$290,000.00	$304,000.00	$ 14,000.00
20	$100,000.00	$300,000.00	$320,000.00	$ 20,000.00

Table 13: Break-Even Analysis for WPI TEBVs.

4.3.7 SWOT Analysis (Strengths, Weakness, Opportunities, Threats)

A SWOT analysis is used to determine the strengths, weaknesses, opportunities, and threats of any given product. It is useful in that it helps a company better understand that benefits of their product versus the negative aspects. The strengths are the features that make the product valuable to the end-user. The weaknesses are the limitations that may be a detriment to the overall function of the product. The opportunities section covers the business opportunities that a business may experience if they were to sell the proposed product. Finally, the threats section is used to better understand the threats to the products success, such as competitors within the target market. A SWOT analysis was performed for the TEBVs produced through the means of the WPI technology and method. (Figure 14).

Strengths	Weaknesses (Early in experimental stage)

• Made from living cell cultures thus having similar mechanical properties as native tissues
• Treats cardiovascular disease and may help prevent future occurrences
• Can take cell culture from patients to generate autologous tissue
• New and unique; Entering market with growth potential
• Will improve the overall quality of a patient's life
	• Currently, WPI is unable to control the process
	  ○ Many unknown variables
	• Vessels not always uniform in structure
	  ○ Vessel may not be uniformly strong

Opportunities	**Threats**
• Need for alternative method to current treatment of cardiovascular disease. • Competitors process not as time efficient as WPI's process • Biomedical market is growing exponentially • Future applications outside cardiovascular disease treatment are possible.	• FDA regulations continue to change and become more stringent • Insurance reimbursement and coding • Current lack in funding • Many unknowns; potential for future problems in production process • Reverse engineering of WPI device/kit and method

Figure 14: SWOT Analysis for Tissue Engineered Blood Vessels Produced by WPI Technology and Method.

4.4 Market Position

4.4.1Market Segmentation

Market segmentation is an analysis in which a business focuses on each of the potential buyers for a given product. It is important to understand these potential buyers and what factors may influence their decisions. The biomedical industry has a number of potential buyers due to the fact that TEBVs have many applications. The three most obvious potential buyers are pharmaceutical companies, doctors/hospitals, and research and university laboratories.

Pharmaceutical companies are promising potential buyers due to the current expansion of the pharmaceutical industry towards the biomedical and biotechnology industries. The pharmaceutical companies would most likely use this technology to perform tests on living cardiovascular tissues to test the safety and efficacy of the manufactured drug. The pharmaceutical industry is one of the largest industries in the market with four of its companies in the top 20 by market capitalization.

Doctors and hospitals would be the most important market segment to capture because it would help save lives; however, it would be the most difficult to capture. This segment would be responsible for the in vivo use of the TEBVs. Doctors would use the TEBVs during surgery to help cure patients of clogged arteries, cardiovascular diseases, etc. Although this market segment would be the most beneficial to the general population, it would be the most difficult to capture due to the stringent regulations set forth by the FDA.

Finally, the most realistic market segment is comprised of research laboratories and universities. The author feels that this segment is the most realistic in the short-term because the laboratories would not be using the TEBVs on living subjects. The laboratories would use the TEBVs for testing of all sorts including drug testing, disease testing, etc. The idea of creating a

kit for plug and play use would have appeal and value to these laboratories for a few reasons. First, the kit would eliminate extra training for scientists as they would receive a kit with specific directions on how to produce the TEBVs within their own labs. Also, the kit would eliminate the extra staff that the laboratory would need to hire to produce the TEBVs eliminating cost and allowing the labs to maximize profit.

Through the analysis of these market segments, the author has provided an in-depth analysis of the advantages and disadvantages of each segment. Also, an analysis of the stakeholders involved as well as a cost benefit analysis of the segments was performed to better understand each of the four segments. Finally, an analysis of the regulations and standards that would have to be met to sell to each of the four segments was crucial to understanding the costs associated with producing and selling the TEBV kits.

4.4.2 Competition

One key component to analyzing a product's target market is the current competition. A target market is the market in which the proposed company plans to sell the product. The Memorial Sloan-Kettering Cancer Center located in New York, New York holds a patent on an apparatus for growing cells under variable hydrostatic pressures (US Patent 7,435,587).[31] In the patent, what is described to be a device that is enclosed and has at least one side set-up for "cell growth." The device also has a means for administering and regulating the flow of cell media in order to feed the cells at a constant and/or continuous rate. The patent was filed on December 20, 2004 and is currently owned by the Cancer Center. It is stated on the center's website that the device and method has been tested with a cell study; however, efforts are still being made to fabricate and test the unit's functionality. The Cancer Center is a research facility and thus the technology is not actually being produced for sale; however, it is interesting to note that the

Cancer Center has a section on their website for "Technologies Available for Licensing," where this apparatus can be found. It is dually noted that the device and its respective patent are not currently licensed to any individual or corporation. Due to its inactive status, this device would not be considered a competitor as it is not currently in production for sale at this time. It is important to note, however, that the patent could be licensed.

Cytograft, a company located in Novato, California, designed and patented (US Patent 7,744,526)[32] a device for manufacturing TEBVs. The device created by Cytograft performs a very similar function to the device created at WPI. The outcome of both devices is a tissue engineered blood vessel; however, Cytograft uses a rolling device to roll a sheet of cell tissue into a blood vessel where as the device created at WPI uses a machine to spin the cells thus allowing them to form the tube structure on their own. This phenomenon is not fully understood yet, but WPI is able to reduce the time to produce to about 13 weeks (as seen in section 4.3.3). The time to produce is much more efficient then Cytograft, which presently takes 24 weeks from the initial client meeting until the day the vessel is implanted into the patient. Although the Cytograft process takes a longer time, their product is currently in clinical trials giving them a clear advantage of market entry time. By having their product already in clinical trials, Cytograft will theoretically be able to enter the market prior to WPI and thus establish a client base long before WPI. Cytograft's ability to produce a living tissue engineered blood vessel makes them a direct competitor to WPI's TEBVs.

Organogenesis, INC., a company located in Canton, Massachusetts, designed and patented (US Patent 7,521,231)[33] a method for preparing engineered tissues. The process defined in this patent is similar to that of Cytograft's in that the company cultures cells and eventually fuses the cells into a sheet. Although Organogenesis, INC. does not currently produce TEBVs,

the patented technology is the first step in the process towards developing a method to produce TEBVs. Currently, the most similar product manufactured by Organogenesis, INC. is a product called Apligraft. Apligraft is a dual layered cell construct used in treating and curing venous leg ulcers. This was the first cell based product to receive FDA approval in 1998.

Finally, an article published in a recent issue of Science Translational Medicine, Laura Niklason and a group of engineers from the Yale Medical Group discovered a method for producing "readily available tissue-engineered vascular grafts." With this method, the engineers were able to produce a vascular graft using human allogenic or canine smooth muscle cells.[34] The cutting edge aspect of these vascular grafts is that they do not consist of cellular material. During the process, all cellular material is eliminated by using detergents; making the grafts nonimmunogenic.[34] This means that the grafts are unable to provoke an immune system response. During pre-clinical testing, the human grafts were tested in baboons and passed a number of tests including dilation tests, burst pressure tests, and suture pull tests. Canine grafts were put through similar functionality/patency tests in canine subjects and conveyed similar results.

The interesting aspect of this new method to producing tissue-engineered vascular grafts is the ability to produce them independent of cellular material. By producing grafts independent of cellular material, and greatly reducing the occurrence of immune rejection of the graft, this new technology must be considered as competition to the TEBVs produced at WPI. Although these grafts have potential benefits and are currently in clinical trials, the process still takes between three and six months.

4.4.3 Industry Analysis

There are a number of industries to consider when entering the market with a new biomedical device. The device and method invented at Worcester Polytechnic Institute (WPI) can fall into two separate industries, the manufactured pharmaceuticals and the medical supplies and devices industries. The method and device can be considered as part of the manufactured pharmaceuticals industry, which includes the sale of pharmaceutical drugs; however, the industry is beginning to expand by the addition of biomedical/biological products. The manufactured pharmaceutical market is driven by each company's desire to cure and treat illness and disease.[5] The proposed use of the WPI's TEBVs in this industry would be as test subjects for new drugs. The vessels would also be used in testing alternative treatments in relation to cardiovascular disease. It is interesting to note that the demand of the pharmaceutical industry is driven by the aforementioned factors because it leaves the industry open for expansion.

The second industry that would be relevant to the product designed at WPI is the medical supplies and devices industry. This industry is the most applicable in the event that WPIs device, the kit, is capable of producing a stable tissue engineered blood vessel for use in humans to treat cardiovascular disease. Once the vessels are tested to prove long-term patency, they would receive through the FDA. With this approval a company built through WPI to produce the TEBVs would be eligible to enter this market. Potentially, surgeons and doctors would purchase the TEBVs for use in treating cardiovascular disease in their patients. The demand is driven by different factors in the medical supplies and device industry. The medical supplies and device industry's demand is driven by demographics.[30] In regards to this demand, WPI has favorable population demographics as it is located in Worcester, MA, which is located in the vicinity of many highly regarded medical facilities. According to the *U.S. News and World Report*,

Massachusetts General Hospital (within a distance of 50 miles) is ranked within the top five hospitals in the world in 13/15 potential categories.

When analyzing the market, it is important to take an in depth look at each of the prospective entry industries. The pharmaceutical industry would be the most applicable for the device (kit), as well as the initial vessels designed and manufactured at WPI. The pharmaceutical industry is comprised of such companies as Johnson & Johnson, Pfizer, and Merck. First research states that, The US manufactured pharmaceuticals industry generates nearly $200 billion annually amongst 1,500 companies.[35] It is also noted that the industry is dominated by the upper 3% of the companies, which generate $160 billion of the annual $200 billion.

Over the past few years, the pharmaceutical market has expanded with the introduction of the biotechnology industry. Because the industry is dominated by larger companies, the smaller companies within the industry have a lot of competition. The difference between the large and small companies, however, is the demand is driven by different factors. It was noted that the demand is driven by the desire to cure illness in the larger companies. Inversely, the smaller companies demand is driven by their ability to produce specific products that can target one or two ailments.[36] The smaller companies lack the ability to compete with larger and more established companies within the same market niche. In order to remain competitive, smaller companies need to target a specific niche that no larger company is targeting. The technology designed at WPI is specific and original enough to give the company a competitive edge in the expanding pharmaceutical market.

The latter of the two industries discussed is the medical supplies and device industry. This industry is the more practical choice for WPI should they design a kit for “plug and play” use by laboratories and doctors. The medical supplies and device industry is comprised of over

11,000 companies. Yet it generates about $125 billion less in revenue per year than the pharmaceutical industry. This is largely due to the fact that the pharmaceutical industry has a larger client base than the medical supplies and devices industry. Although the revenue stream is less than that of the pharmaceutical industry, it is important to note that in the 2010 calendar year, the medical supplies and devices industry had a growth rate of 9%, whereas, the pharmaceutical market had a growth rate of 6%.[30,35]

The medical supplies and devices industry is composed of companies such as Medtronic, Boston Scientific, and Johnson & Johnson. First Research is an online database supplied by WPI consisting market and industry analyses. First Research is published by Hoovers, which is a business research company. The website allows individuals to research a number of different aspects of each industry and the companies in which they include. In the analysis performed by First Research, in relation to the medical supplies and devices industry, the database claims that the technology invented at WPI is clearly specialized although it has many applications.[30]

Following the analysis of the individual industries, the author concluded that the more appropriate industry for WPI to market plug and play kit would be the medical supplies and devices industry. The TEBVs can be marketed in manufactured pharmaceuticals industry. Although, initially, the company will focus on marketing the kit, the author believes that a company formed through WPI will be capable of competing in multiple industries. For example, Johnson & Johnson competes in both of the prospective markets that were analyzed in this report.[30]

4.4.4 Marketing WPI TEBVs and Technology

The TEBV producing kit will likely be marketed to research facilities looking for a means to produce living tissue constructs that can be used for testing new drugs and disease treatments. It is essential that WPI can provide data to the research facilities proving that they will be a beneficial research tool in developing new drugs and treatments. There are two major identifiable benefits for researchers using the WPI kit, namely the ability to produce living tissues through a "do-it yourself" medium.

The first major benefit is the kit's ability to produce a living tissue construct that can be used for a multitude of applications. The second major benefit of the kit is its ability to "do-it yourself." It is the author's recommendation to WPI that the product be marketed for its "do-it yourself" ability as this will be appealing to research facilities. By marketing this aspect of the product heavily, researchers will see the benefit of the product in that they will need no prior knowledge of the technology in order to produce living tissue constructs within their facilities. This stage of marketing is essential to the prospective company's future. It will likely be the building block for future expansion of the company by generating the necessary revenue to be capable of producing and selling living TEBVs for use in humans to treat cardiovascular disease.

When marketing the TEBVs produced by WPI, the end-users of this product are the patients. It is important, however, to recognize that surgeons and doctors performing the procedures to treat cardiovascular disease are the consumers of the TEBVs and the actual decision-makers for the products. Surgeons and doctors will need to be convinced that the TEBVs produced at WPI are both safe and provide a valuable benefit to the patient that no other alternative treatment can provide. It is dually important that the treatment be approved by the FDA and coded by insurance companies.

Ultimately, doctors choose which treatments they will use within their practice. It will be critical that the company is able to prove to doctors that the TEBVs provide a clinical and medical benefit to the patient and will also provide an economical benefit to the doctors. The doctors must understand that they will have a successful product for their patients. If WPI's TEBVs do not perform better than the competition, then the medical benefits will need to outweigh the cost difference among alternatives. If the vessels are able to perform like native vessels, the author feels that it will be easy to convince surgeons of the TEBVs benefits.

4.4.5 Benefits of Licensing Technology versus Starting a Company

One question that arises when performing a cost analysis on the TEBVs produced by WPI is whether it would be more beneficial to license the technology to a larger firm. Licensing intellectual property to a larger company is a common procedure for smaller companies/potential companies to generate revenue in a market that they likely could not infiltrate on their own. There are three different types of licensing that can be considered:

- Lump sum licensing- A larger company purchases the rights of a smaller company's intellectual property with a single payment.
- Royalty based system- A larger company would pay a smaller company based on the volume of products sold.
- Cross-licensing- Where the two companies license products to each other in a trade type manner.

The most applicable licensing scenario for the WPI TEBVs would be a sale volume based licensing agreement in which the larger firm would make payments to the WPI company based on the number of units the larger firm sells. According to William H. Black, many licenses are

set at a rate of 2-3% royalties.[37] This means, for example, if a company were to license the WPI TEBVs and thus sell them for $5,000 per unit, then the royalties paid to WPI for the licensing agreement per unit would be $150. By engaging in this form of licensing, engineers from the WPI based company would then be able to focus more on enhancing the current technology rather than worrying about the burdens of starting a new company based on a single product. To generate interest from larger firms about potentially licensing the TEBV technology, WPI could publish articles in medical journals and magazines informing the industry of the technology and its beneficial effects.

The latter option to licensing the technology would be to generate a business plan and start a small "start-up" company. Although starting a new company is a massive task to undertake, it can have many benefits to the owners. One disadvantage to a start-up company is that it would be difficult to gather all of the assignees and inventors on the patent together to start a private business. If all members were not involved, an agreement for compensation to the members not included in the start-up company would need to be established.

There are two types of start-up companies that would be beneficial for the inventors to consider, namely LLC and LLP. A limited liability company (LLC) gives limited liability to its owners. This type of company is similar to a partnership in that the owners are allowed to utilize "pass through taxation." In essence, this means that owners individually claim a share of the total companies profit taxes on their own individual tax returns.

The second of the potential start-up company scenarios is an LLP, commonly known as a limited liability partnership. Similar to the LLC, the LLP gives limited liability to its owners. Also, the partners are not responsible for each other's misconduct should something go

drastically wrong. Finally, the LLP is covered under a different level of tax liability then that of a corporation.

After reviewing the potential scenarios, the author believes that the inventors of the TEBVs at WPI should consider producing a business plan and entering the industry as a start-up company. Through the analysis in the previous sections, the author believes that the TEBVs will provide a substantial benefit to the patients that receive the treatment. Also, the benefits of licensing are low due to the low royalty percentage. If the TEBVs perform like native blood vessels during, in-vivo testing, they could become the standard in the treatment of cardiovascular disease thus making the start-up company an extremely profitable venture.

4.4.9 Health Insurance Reimbursement Coverage

Health insurance in the United States is defined as any program that assists in the payment of medical bills for qualifying patients. Health insurance can come from a multitude of mediums including but not limited to: private insurance firms, social insurance provided by the government, or welfare programs run by the government. In a report published in 2008 by the United States Census Bureau, approximately 85% of Americans are covered by health insurance.[38]

Assuming that the TEBVs produced by the method and product produced at WPI are approved for in vivo use by the FDA, there will need to be adequate health insurance reimbursement for patients receiving treatment. According to a study by Nicolas L'Heureux, co-founder of Cytograft Tissue Engineering, the high costs associated with advanced therapeutic procedures make health insurance reimbursement a necessity.[5] It is noted in this study that the FDA requires stringent safety and efficacy data to grant approval for clinical applications. It is duly noted that Medicare programs funded by the U.S. government demand that the product in

question shows cost effectiveness over time to prove that it is worth reimbursement. It is mentioned in L'Heureux's study that there is a need for 4-6 years of data to prove a product is cost effective.[5]

L'Heureux's study compares three similar tissue engineered products which currently receive health insurance reimbursement, namely Carticel produced by Genzyme, Apligraft produced by Novartis, and Dermagraft produced by Advanced BioHealing.[5] In Table 14, the reimbursement levels are shown. It is interesting to note that the cost of Carticel is around $25,000.[39] At this cost, the insurance reimbursement is about 70% of the total cost. It can be assumed that due to the similarity of the products (Table 14) relative to the product designed at WPI, WPI's TEBVs are likely to receive a similar reimbursement.

Company & Product	Reimbursement Level (in U.S. dollars)
Carticel, produced by Genzyme	$17,600
Apligraft, produced by Novartis	$1,200 per 44cm^2
Dermagraft, produced by Advanced BioHealing	$535 per 37.5cm^2

Table 14: Comparison of Reimbursement Levels for Three Tissue Engineered Products.[5]

HCPCS Coding: Level I & Level II

In order for a product to be "market ready," it must qualify for health insurance reimbursement. Once approved by the FDA through the steps outlined in section 4.4.3, a new medical product or device must be coded for medical billing through the Centers for Medicare and Medicaid Services (CMS). This is done through the healthcare common procedure coding system, more simply known as the HCPCS. There are two subunits of the HCPCS known as level I and level II.

Level I, which is the current procedural terminology (CPT), is used to denote medical services and/or procedures that are performed by health care professionals. These codes are revised by the American Medical Association (AMA).[40]

Level II HCPCS is a coding system used to represent medical products, procedures, and supplies. It is important to note that the items covered in level II HCPCS are not covered by level I HCPCS. There are several types of HCPCS level II codes which include:

- Permanent National Codes
- Dental Codes
- Miscellaneous Codes
- Temporary National Codes

Permanent HCPCS level II codes are used by all private and public health insurance companies. The codes are regulated and monitored by the "CMS HCPCS Workgroup." The Workgroup is comprised of members from each of the involved parties. Included in this group are private insurance agencies, insurance pricing, data analysis, coding, and Medicaid. The involved parties meet to discuss the needs of each other and whether the program is meeting those needs. The Workgroup is also in charge of adding new codes, revising existing codes, and deleting codes that are not being used.[40] The TEBVs produced from the WPI device will be considered medical products and will fall subject to these level II codes.

Once the procedure is coded, health insurance providers will consider products or services for insurance reimbursement. Each insurance provider will have its own level of coverage for any given products or services. The specifications taken into consideration when a product is reviewed for reimbursement by public and private insurers include the effectiveness of

the device and whether the effectiveness of the device is worth the cost.[40] In other words, the benefits versus the costs are analyzed. In direct relation to the effectiveness of the device versus the cost, L'Heureux states that the current method of treating vascular disease, through the harvest and implementation of the saphenous vein, has incidences of thrombosis up to 15% in the first 12 months post surgery. By eliminating this procedure, which causes complications through secondary harvest operations, health insurers can yield cost savings of more than $5,000 per patient.[5] It is likely that the TEBVs produced by the WPI device will be coded by level II HCPCS and thus be eligible for health insurance reimbursement.

5 Conclusions and Recommendations

Worcester Polytechnic Institutes TEBVs have a promising future in both the medical supplies and devices industry and the manufactured pharmaceuticals industry. As stated in the results, over 800,000 patients globally receive coronary artery bypass grafts.[2] With a potential market of this size, it is expected that TEBVs will have a high demand in the market place. Although the technology is currently still in the pre-clinical stage, the analyses in this report show that the TEBVs can be very successful in the cardiac market. It was determined in the cost analysis that the approximated cost to produce one TEBV with the WPI process is around $10,000. Economies of scale are the production cost breaks a company experiences due to expansion. In other words, this concept means that as a company expands, the unit price of the products produced decreases. It is expected that with a more streamlined process, WPI will be able to reduce this cost to produce. As seen in Figure 15 below, the concept of economies of scale is reviewed.

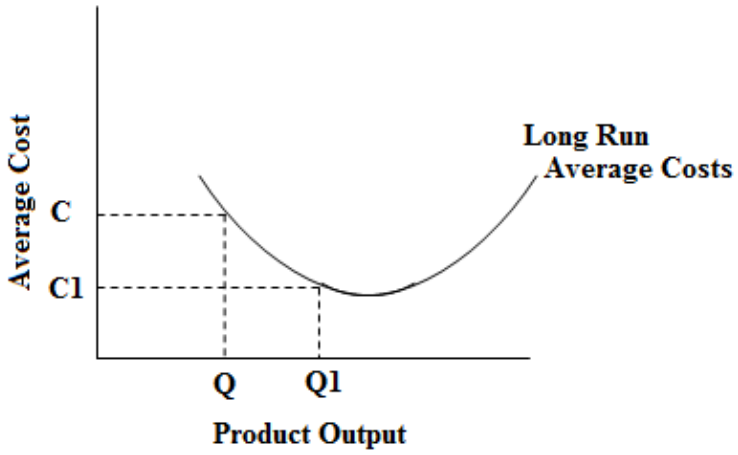

Figure 15: Economies of Scale

Figure 15 clearly shows that as the output increases from "Q" to "Q1," the cost decreases from "C" to "C1." This illustrates that over time, as a company produces more products, the process will become more streamlined thus lowering overall cost.

One way that would reduce the cost to produce one TEBV is reducing the overall cost of the skin biopsy. As noted, a skin biopsy is around $5,000, which is half of the overall production cost. This could be done by having a professional work within the firm to extract the skin biopsies from the patients. Not only would this eliminate the shipping cost, but it would also reduce the company's outsourcing costs.

Another factor that will need to be considered in the future is the testing. It is unknown, at this point, how many TEBVs will need to be tested for each patient in order to consider the TEBV safe for clinical use. For example, WPI may need to produce four TEBVs for "patient x" so that three can be used for testing. If one of these three fails, then WPI will have to start the process over to produce four new vessels to test. This discrepancy in the technical specifications of individual TEBVs may prove to be costly. Tests such as burst pressure, suture pull, and stretch/tear tests are all standard tests that the WPI TEBVs may be subject to.

In conclusion, with 800,000+ CABG procedures yearly, there are a number of patients who can potentially benefit from WPI's TEBVs. Payback period is defined as the time it takes for the return on investment to pay out to the investors. It is impossible to calculate the time it will take to sell the required number of TEBVs to break-even; however, if the TEBVs are produced for the projected cost of $10,000, it is expected that with an initial investment of $100,000, the company will only need to sell 17 units to break-even on the initial investment. Based on the data collected and analyzed in this report, even if this estimate is off by a factor of

ten, the author recommends that the TEBVs produced at WPI's Gateway Laboratories are a worthwhile venture to pursue further.

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7 Glossary

Allograft- A graft of tissue obtained from a donor of the same species.

Autograft- A graft of tissue obtained from a patient and used in the same patient's body.

Centrifuge- A piece of equipment driven by an electric motor that puts an object in rotation around a fixed axis which applies force to the perpendicular axis.

Competitive Advantage- A strategic advantage that one business has over another business within its competitive industry.

Coronary Artery Bypass Graft (CABG)- A surgical procedure in which surgeons bypass the coronary artery due to coronary artery disease.

Endothelial Cells- Cells that are part of the endothelium in the human body; Endothelium is the thin layer of cells lining the interior surface of blood vessels.

Fibroblasts- Type of cell that synthesizes the extracellular matrix and collagen.

Graft- Material, especially living tissue or an organ, surgically attached to or inserted into a bodily part to replace a damaged part or compensate for a defect.

Graft vs Host Disease- A common complication in which functional immune cells within the body attack a graft due to its "foreign" nature.

Market Capitalization- A measurement of size of a business enterprise equal to the share price times the number of shares outstanding of a publically traded company.

Payback Period- Period of time required for the return on investment to repay the sum of the original investment.

Plug and Play Kit- Refers to the ease of use of the device. This means that the device is usable by any individual capable of reading the user manual.

Restenosis- The re-narrowing of a blood vessel/artery that has been previously treated.

Return on Investment (ROI)- Ratio of money gained or lost on an investment relative to the amount of money invested.

Stent- An artificial tube inserted into a natural passage or conduit in the body to prevent or counteract a cardiovascular disease induced constriction of blood flow.

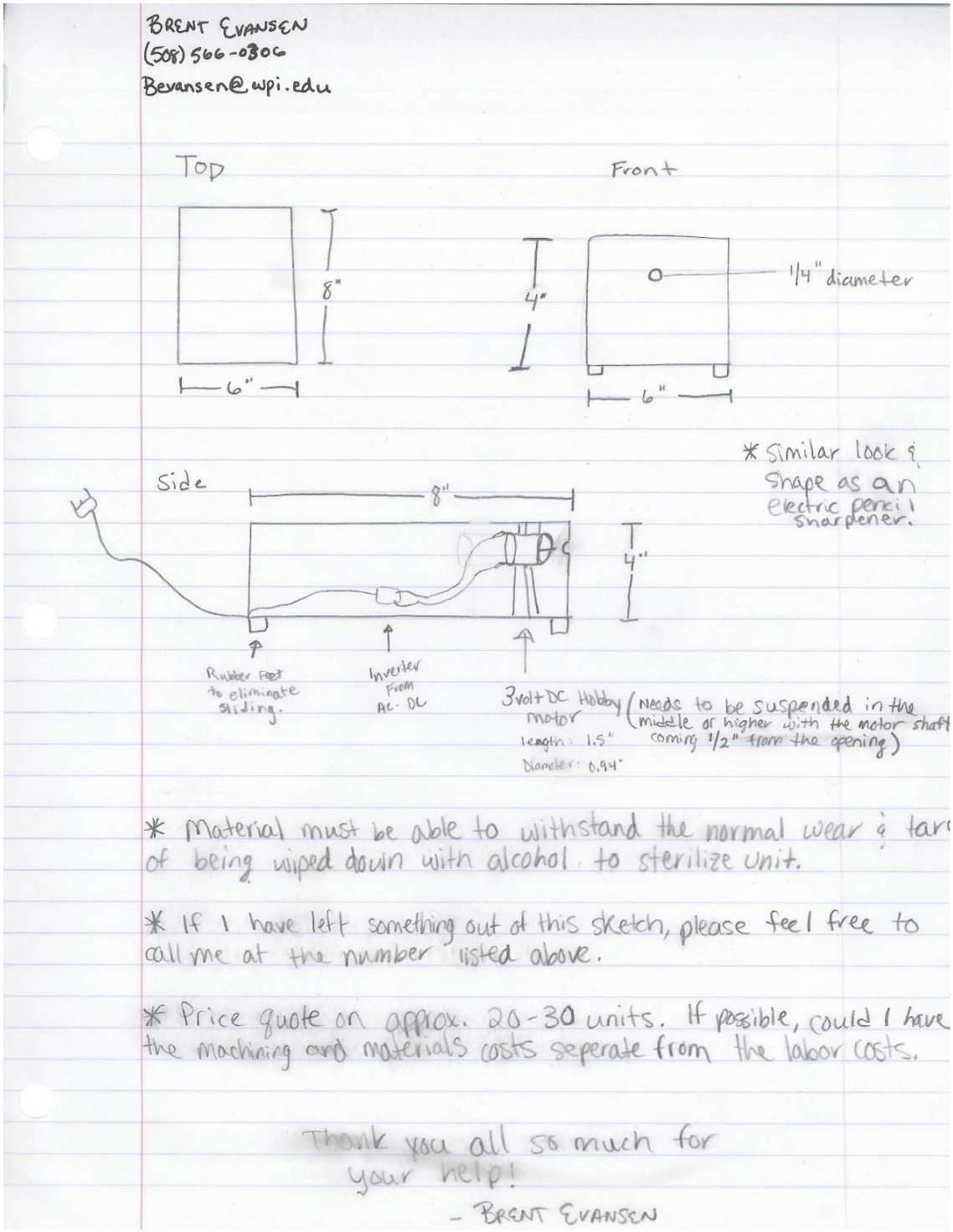
Thrombosis- The formation of a blood clot within a blood vessel constricting flow of the circulatory system.

Tissue Engineered Blood Vessel (TEBV)-A living biological blood vessel that shares the same or similar properties to that of native living tissues. TEBVs are designed by engineers.

Triglycerides- One of the three fatty acids in which contributes to the blockage of arteries causing cardiovascular disease.

8 Appendices

8.1 Rough Design of Motor Encasing Unit Sent to Manufacturing Companies



8.2 Biomedical Engineering Department Problem Statement

Market and Business Analysis of a Cellular Assembly Device for Tissue Engineered Blood Vessel Fabrication

MQP: Brent Evansen, AY 2010-2011
Advisors: H. Vassallo, M. Rolle

Technical Background

Tissue engineering has emerged as a promising approach to creating blood vessel equivalents that can be used surgically to replace diseased or damaged blood vessels. Tissue engineered blood vessels (TEBV) may also be valuable as unique 3D *in vitro* models of human vascular structure and function and powerful new tools to advance vascular disease research.

Current methods for producing TEBV have primarily focused on utilizing a synthetic or natural scaffold material that can be seeded with cells to create a living vascular tissue equivalent. Alternatively, TEBV generated entirely from living cells (without exogenous scaffold materials) may have unique advantages, including a lower incidence of infection, a lack of foreign scaffold materials, more favorable mechanical properties (more compliant, less stiff) and greater contractile responsiveness. However, there are many challenges associated with creating "scaffold-free" cell-based TEBV, including the need for 1) a device or technique that reproducibly assembles cells into a tube shape, 2) the large volume of cells needed initially to create tubular tissues, and 3) the long culture time required for cells to synthesize structural proteins (extracellular matrix) and mature into a strong, transplantable tissue.

To address these needs, a WPI BME MQP Team (Burford, Jones, Soderbom, Sullivan; Advisor: Rolle[1]) designed a device that uses centrifugal force to rapidly assemble a large number of individual cells suspended in cell culture medium into a cohesive, tube-shaped, 3D tissue within a few days. To date, the technical focus of the project has been on creating, validating, and refining the device and evaluating the effects of different manufacturing and operational parameters of the device on the structure and function of the resulting tissue tubes. An invention disclosure describing the device and method of cellular assembly to form tube-shaped tissues was filed with the WPI Office of Technology Transfer in September 2010.

The ultimate technical goal of this project is to create a device that is inexpensive and easy to use which rapidly and reliably converts a suspension of cells into a robust, tube-shaped tissue.

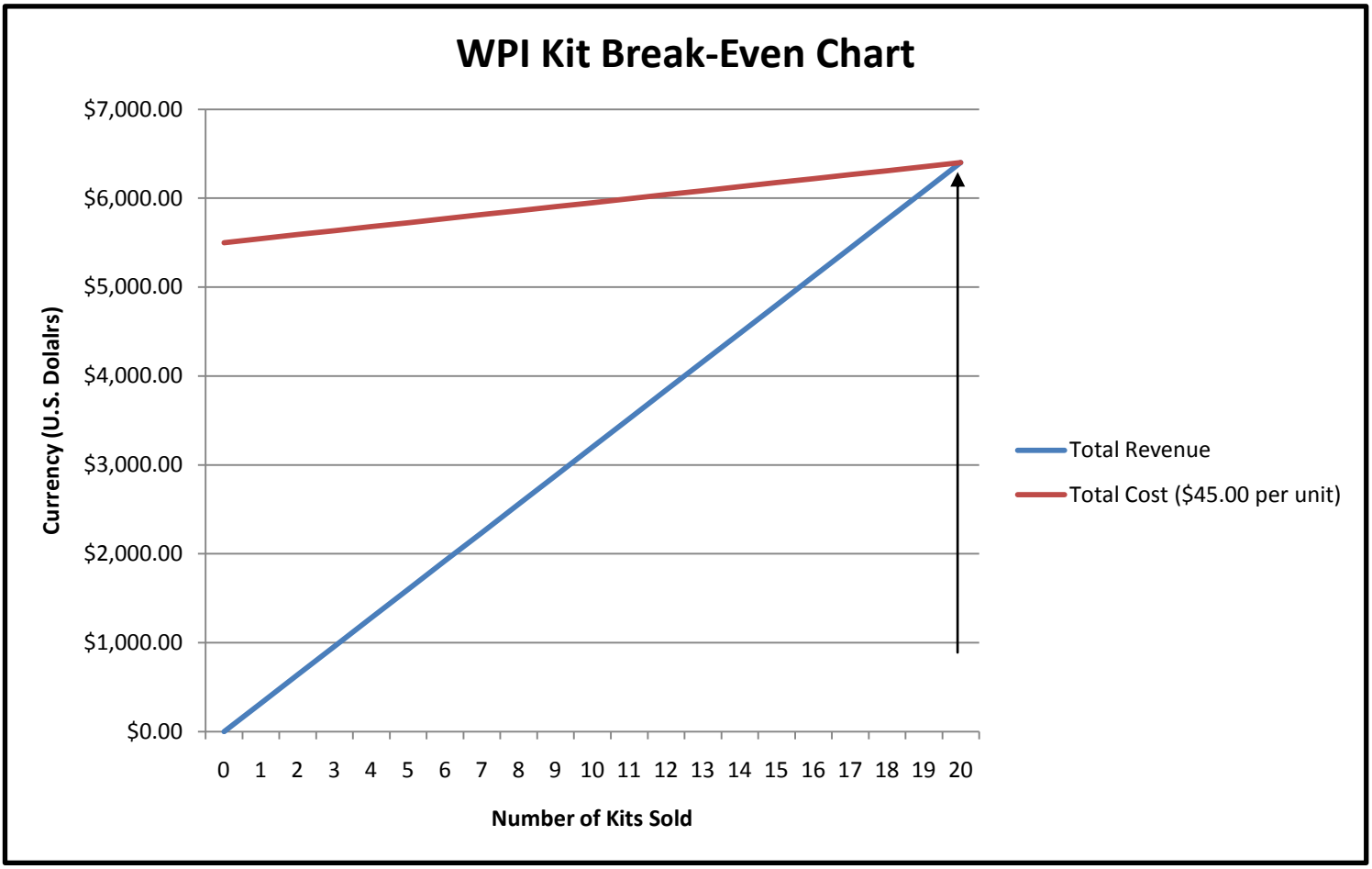
Marketing Problem Statement

Assuming that the above technical goal can be met, we would like to refine the device such that it could be packaged and sold as an inexpensive device or "kit" to enable its user (scientists, surgeons, etc.) to inject or infuse a suspension of cells of their interest

into the device and create a living, cell-based, tube-shaped tissue for research or therapeutic purposes.

To attract funding to start a company to manufacture these devices, we need to generate a business plan detailing the need for the product, the size and scope of the potential market for our product, the costs to produce (manufacture, sterilize, package, etc.) the product, identification and analysis of the competition, and any other challenges and opportunities unique to the manufacturing and marketing of our device. Ideally, this analysis will lead to a report and presentation that could be “pitched” to venture capitalists to attract funding to start our company.

8.3 WPI Kit Break-Even Chart



8.4 WPI TEBV Break-Even Chart