MQP – FRH – FHO2

Developing a Foreign Market Strategy for a Biomedical Device: CircumBlator Treating Atrial Fibrillation

A Major Qualifying Project submitted to the faculty of the

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Abstract

This Major Qualifying Project looks at the potential the CircumBlator, a novel cardiac ablation device, in various markets to develop a go to market strategy for the product. Market and Regulatory research was conducted utilizing sources such as the Atrial Fibrillation Association and the White Book from the European Society of Cardiology. From the research, the United States (US) and the European Union (EU) were seen as ideal markets for initial entry. Guidelines for conducting research and developing decisions were also provided for future teams to conduct similar projects or continue this one.

Executive Summary

Arrhythmia is a condition that plagues its sufferers with either episodes or an unfortunate consistence of irregular heartbeats. The most common form of this condition is known as Atrial Fibrillation and occurs due to a malfunction in the transference of electrical signals in the nerves near the heart. This ailment is found, on average, to affect about one percent of a given populace with the majority of those suffering being over the age of sixty five. Many treatments are conducted to attempt to remedy this condition, including drug and rhythm control. What has been found to be a better solution that rarely leads to complications is known as a rate control treatment, keeping the heart rate within an acceptable range. One of the most common procedures to control the heart rate is cardiac ablation. This procedure essentially scars and deactivates the heart tissue that conducts these malfunctioning electrical signals.

Ablacor Medical Corporation has developed a device to make cardiac ablation a simpler and more permanent solution. The CircumBlator™ is a device that anchors on to the entry for the pulmonary vein. Using an electrode pad and ablation umbrella, the CircumBlator™ will scar the appropriate tissue while closely monitoring its force on the tissue and the temperature of the burn. This project aims to determine an initial market as consideration for this product by researching and analyzing:

- Market data comprised of condition prevalence and treatment information.
- Regulatory research to understand procedural requirements.
- The combination of the both to find a suitable market in both potential acceptance and overall adoption of medical devices.
- The reimbursement process of a selected market's insurance environment.

Using this data, the team aims to create a system of elimination and ordering to find the most ideal markets for consideration. Beginning with a fairly large list of countries and regions, the team researched:

- Atrial Fibrillation prevalence data, such as number of cases, cases per capita, etc.
- The level of adoption of cardiac ablation through number of clinics ablating and number of ablations conducted per year.
- The percent market share the region holds globally in medical devices.
- The annual investment in medical devices.

From this information, the team developed a decision flow and organized the most ideal markets into strategic groups. Then, two countries and one region were picked from these groups based on market strength and potential regulatory excellence. The focus of the regulatory research and analysis at this point was to find a market with the quickest and least costly regulatory process, while still granting benefits. The major benefit found is that many regulatory approvals are accepted internationally, often in lieu of a separate regulatory process. This factor weighed heavily on a decision for an initial market.

Once a market was decided upon, the rest of the efforts involved what entering the market would specifically entail. This research mainly involved looking at the reimbursement process for new and current medical devices to understand what the next steps would be beyond regulatory approval. The final step of the project was a guide that future teams can use to undergo the same process. However, this guideline will provide extra focus for the team's research as well as advice based on the experience of this decision process.

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1 Introduction

This Major Qualifying Project entailed conducting a feasibility analysis on several countries and regions in order to determine a consideration for an initial market. This market is the recommendation for entry for a medical device treating a cardiovascular condition known as Atrial Fibrillation. By applying previous knowledge of market planning and other aspects of business in a group environment, the team aimed to also use knowledge of the biomedical industry and government regulations to produce the most opportune decision. The team then analyzed the methods taken to come to a conclusion and produced a set of guidelines that can be followed to make additional decisions.

Fulfilling the requirements for a management, management engineering, and biomedical engineering focus, this project aided an established business further its goals utilizing knowledge gathered from previous marketing and business classes. The project focused on the success of a biomedical device on a global scale, applying research techniques to uncover regulatory information and reimbursement information used to estimate sales projections. This report was also used as a basis for presentations and a poster design showcasing the team's methodology and results.

The team assisted Ablacor™, a biomedical company aiming to bring an innovative cardiac ablation device to market, by conducting research into the market and regulatory aspects of different countries and regions. After making an initial decision, the team researched the reimbursement process in the select country within the selected region to aid in the estimation of sales projections. To conclude the project, the team supplied a guideline for future teams to complete similar projects, including focal points for each of the stages that the project underwent.

1-1 Mission Statement

The mission of this Major Qualifying Project is to supply Ablacor with a framework with which it can best determine the most suitable foreign markets for entry, and to propose an entry strategy for one country or region categorized as an ideal market.

1-2 Objectives

• To research Atrial Fibrillation and treatment data across selected countries and regions.

• To research the various regulations attributed to implementing a biomedical device in a foreign market.

• To determine, based on the research, the most suitable markets for initial consideration for entry.

• To develop a model to assess the feasibility of entering a foreign market.

2 Background

2-1 Mechanics of Atrial Fibrillation

Atrial Fibrillation (AF) is the most common type of cardiac arrhythmia, or irregular heartbeat. Arrhythmias manifest in a variety of fashions causing the heart to beat too quickly, too slowly, or irregularly and are caused by irregular electrical signals that control heartbeat. In a normal beating heart, these electrical impulses start at the top of the heart and move downwards. The signals originate in the sinoatrial (SA) node which is located in the right atrium. The SA node modifies the pace of impulses depending on the level of activity. Once the signal has left the SA node, it spreads through both atria causing them to contract and pump blood into the ventricles. The electrical signal then moves to the atrioventricular (AV) node, between the atria and the ventricles, which passes the impulse onto the ventricles. The AV node serves as the only connection for impulses between the atria and the ventricles; in addition, it slows electrical signals to allow the ventricles to fill. The resulting impulse from the AV node causes the ventricles to contract and pump blood to the rest of the body.

In patients with AF, the electrical impulses start in the atria or pulmonary veins instead of the SA node. Impulses from across the atria move down the heart in a disorganized manner causing the atria to contract irregularly. As impulses move to the AV node, they arrive rapidly and irregularly. The AV node maintains its ability to control the number of impulses that pass to the ventricles at a given time; however because the impulses arrive so closely together more are able to pass in the same period of time. This causes the ventricles to beat at a higher rate than in normal. Though the ventricles beat faster than normal, their rhythm is slower than the atria due to the AV nodes control of impulses.

Irregular contractions in the atria and ventricles prevent the atria from efficiently pumping blood into the ventricles. The increased contraction of the atria causes only some of the blood to move from the atria into the ventricles. As a result the remaining blood pools in the atria which can lead to blood clots. These clots can travel to the brain and increase the risk of strokes (“What is Atrial Fibrillation?”). The

irregular contraction of the ventricles does not allow for the efficient pumping of blood throughout the body and can lead to heart failure.

2-2 Types of AF

There are three main categories of AF depending on the frequency of incidents and response to treatments, paroxysmal, persistent, and permanent. Paroxysmal AF incidents start suddenly and end without medical intervention. The severity of symptoms can vary from very mild to severe and incident lengths last less than one week (Khoo, Krishnamoorthy, and Lip). Patients with persistent AF have irregular heartbeats that last for longer than one week. Persistent AF symptoms stop on their own or with the aid of common treatment methods. Finally, permanent AF occurs when regular heart rhythms cannot be restored with treatment. Both paroxysmal and persistent AF can evolve into permanent AF ("What is Atrial Fibrillation?").

2-3 Prevalence

Research into AF has increased in recent years; however prevalence data is still largely inconclusive. When looking at data for AF within the US alone, different organizations and scholarly articles present varying numbers. Many of the numbers are general estimates as many people living with AF are unaware of the condition and symptoms until they experience a stroke or heart failure. In addition, there is a low representation of patients with paroxysmal AF as their symptoms vary in severity and length (Chugh et al.).

Though the exact numbers may be unclear, many studies conducted over several years have found that the incidence of AF in the US is approximately one percent of the adult population (Naccarelli et al.). The prevalence of AF greatly increases with age, and has been found to affect between 5% and 9% of individuals over the age of 60 (Chugh et al.). Of all those affected with AF it is estimated that 84% are over the age of 65 (Chugh et al.). The overall prevalence of atrial fibrillation is expected to increase

dramatically over the next decades with estimates as high as 7.56 million in the US alone by 2050 (Naccarelli et al.).

2-4 Treatment Options

There are several treatment options for atrial fibrillation depending on the frequency and the severity of symptoms. If a patient's AF was caused by another condition then the primary course of action is to treat the trigger condition. Outside of treating conditions that trigger AF, there are two main courses of treatment, rhythm treatments and rate treatments. Rhythm treatments aim to set the heart back to normal sinus rhythm, or regular heartbeat, while rate treatments aim to slow the heart rate to within normal limits.

Rhythm control treatments use cardioversion to restore the heart to its regular rhythm. Cardioversion can be accomplished in either of two main methods, through medication or electrically (Gutierrez and Blanchard). When using medicine for cardioversion, it is important to consider all medical conditions that may be affected by the treatment. It is common for doctors to require continuous monitoring in a hospital setting to begin in order to insure that there are no negative results ("Treatments"). Maintaining a normal sinus rhythm with medicine can be difficult due to negative side-effects and the increased risk of ventricular arrhythmias (Gutierrez and Blanchard). In addition to medication, cardioversion can also be done with electrical procedures. Electrical cardioversion uses an electrical shock to temporarily stop the heart and return it to normal rhythm after the procedure. Though rhythm control seems like the better and potentially less invasive option, it is often used as the last course of action in patients after rate treatments have been done. Rhythm control treatments lead to more hospitalizations, and more serious negative side effects (Gutierrez and Blanchard).

Rate control is the primary means of controlling AF as it has fewer adverse effects than rhythm control. Rate control treatments aim to reduce the ventricular heart rate to between 60 and 80 beats per minute ("Treatments"). Generally this is achieved through medication including beta blockers, calcium channels blockers and additional relevant medication depending on the severity of AF.

In addition to rate and rhythm control treatments there are also surgical and catheter procedures that can be used to treat AF. The maze procedure is a surgical procedure done on patients receiving open heart surgery for other heart ailments or who have not responded to other treatments for AF. In this procedure a surgeon makes precise incisions in both atria of the heart (Ad). These incisions create scar tissue that cannot conduct electricity. The scar tissue disrupts the flow of abnormal electrical impulses in the atria that cause AF. There a variations of this procedure and changes to the technique used to create the scar tissue. The maze procedure has a very high success rate, but due the major surgical aspect it is reserved for critical patients.

Catheter ablation is an increasingly common treatment in patients with persistent AF and no other heart conditions. Ablation targets cells that cause the irregular electrical signals in the atria and pulmonary veins. Energy is used to scar the cells causing the irregular impulses which in turn treat the AF. There are a variety of techniques used to target and scar the cells such as radiofrequency energy and cryotherapy. This is becoming an increasingly popular technique and much research is being done on ablation techniques and devices. As of now, very few patients require only one ablation to treat their arrhythmia.

Throughout all of the above treatment processes prevention of blood clots is a key focus. People with AF are at a higher risk of blood clots due to the pooling of blood in the atria. Controlling clotting is especially important as the clots can travel to the brain and lead to strokes. In order to address this concern many AF patients take blood thinners such as Warafin, Dabigatran, and Rivaroxaban (Gutierrez and Blanchard).

2-5 Cardiac Ablation

2-2-1 Techniques

In the early stages of its development, catheter ablation aimed to mimic the incisions made in the Cox Maze surgical procedure for the treatment of Atrial Fibrillation (“Catheter Ablation Techniques”). In the Cox Maze procedure a series of incision and sutures are made in both atria and isolating each pulmonary vein to stop abnormal electrical signals (Fragakis et al.). Due to the intricacy of the Cox Maze

incision patterns, duplication through catheter ablations was very difficult and led to high complication rates.

Research by Michel Haïssaguerre and his team of researchers found that irregular electrical signals responsible for AF mostly originate in or around the pulmonary veins (Jaïs et al.). The results of this research meant that mimicking the Cox Maze method was no longer necessary when performing catheter ablations. In his research he used radiofrequency energy to ablate around the openings of the pulmonary veins. He determined success to be the interruption of irregular or abnormally fast heart rates. Haïssaguerre's research led to the development of pulmonary vein isolation (PVI) techniques.

With Haïssaguerre's discovery of the general source of AF came an increase in different varieties of cardiac ablation and has become the foundation for AF ablation strategies. Researchers throughout the world began to develop varying ways of approaching PVIs (Figure 1). In addition to isolating the pulmonary vein, many electrophysiologists also ablate lines at varying points around the atria and other trigger areas to ensure that all abnormal electrical signals are addressed.

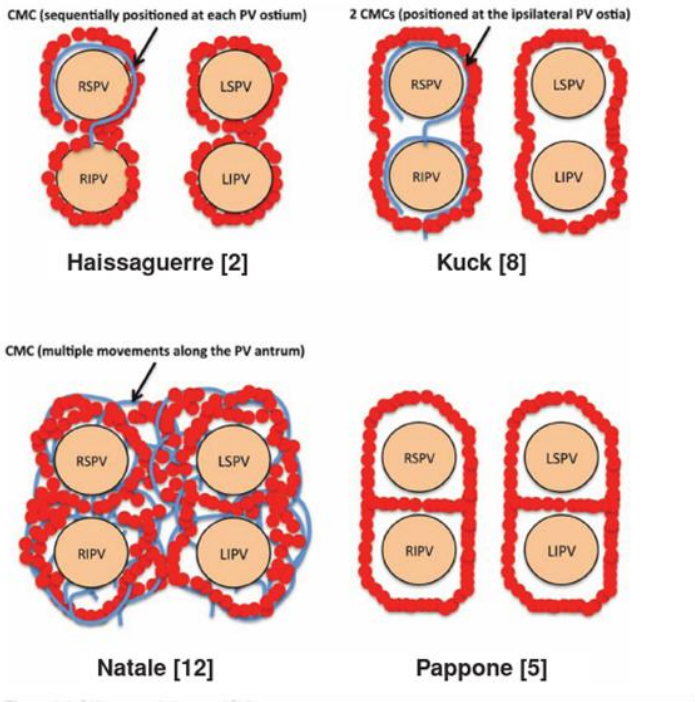

Figure 1: Pulmonary Vein Isolation (Appendix A)

2-2-2 Energy Types

Radiofrequency Energy

Radiofrequency (RF) energy is the most common type of energy used in AF ablation today. Radiofrequency energy is converted into heat that is used to ablate and create lesions ("Catheter Ablation Technology"). Use of this type of energy requires direct contact with the tissue. The depth of the lesion created using RF energy is dependent on the amount of energy used and the type of ablator used (Singh et al. 187).

Laser Energy

Laser energy catheter emits light onto the cells that are targeted for ablation. The energy of the light causes the cells to enter into an excited state and vibrate ("Catheter Ablation Technology"). These vibrations create heat and lead to the formation of scar tissue. Laser energy catheters do not require direct contact with target cells and minimize the risk of damage to surrounding healthy cells.

Cryothermy

Cryo energy exposes affected cells to frigid conditions. This exposure to cold has varying effects of the cells depending on the temperature they are exposed to. When exposed to temperatures between 0 and -20°C electrical conductivity slows down and eventually stops; between -60 and -80°C scar tissue is formed (Singh et al. 195).

2-5-3 Setbacks

Though there has been much advancement on ablation techniques and their efficacy over the past decade, there is still much advancement that needs to be made. Studies have found that after one ablation AF reoccurs in 30-50% of patients a year or more after the ablation (Lewalter et al.). After reading the reviews and opinions of various electrophysiologists and cardiologist, it was found that most of the difficulty of achieving a successful ablation in the first procedure lies in the fact that it is difficult to ablate in a continuous line. Though current technology helps address some of this concern, there is still room for significant improvement.

The difficulty of the procedure and achieving a successful ablation makes it hard for new electrophysiologists to perform. Much of the success rates of catheter ablation is based on the skill and training of the electrophysiologist (Mandrola). By making the procedure simpler to learn and execute, more professionals would be able to perform ablations and meet the rising demand for this treatment.

2-3 Circumblator

The CircumBlator is a device that is being developed by AblaCor Medical Corporation. The CircumBlator will provide electrophysiologists with a one-touch ablation solution for PVI. This device is designed to improve the minimally invasive procedure, catheter ablation, used to treat atrial fibrillation. The CircumBlator aims to burn the faulty heart tissue and eliminate the unwanted electrical activity that causes AF.

Most cardiac ablations are performed inside the heart by using catheters. There are different ways of performing cardiac catheter ablations including point ablation, balloon ablation and circular array ablation. The ablation points are centered in the left atrium and create lesions. These lesions block the trigger points of atrial fibrillation and create a barrier to the arrhythmia. The goal of cardiac ablations is to electrically isolate the pulmonary vein and treat the arrhythmia.

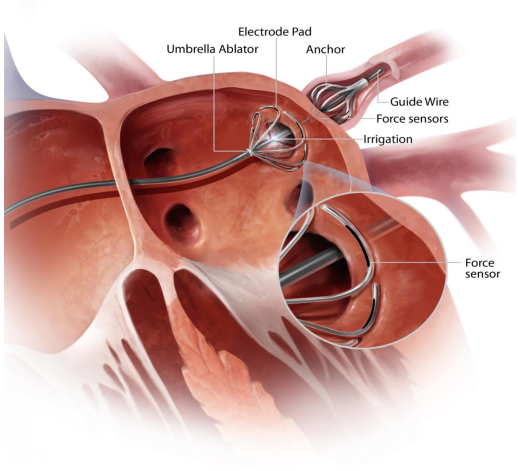

Figure 2: The CircumBlator (Appendix C)

The CircumBlator performs these cardiac ablations in a much more efficient way. The CircumBlator contains a guide wire, anchor, force sensors, electrode pad and an umbrella ablator. In order to perform the procedure, electrophysiologists push the guide wire through a vein and once the wire reaches the designated area, the anchor is pulled back causing it to open up and secure the wire in the right area. The anchor has force and temperature sensors to ensure there is no unnecessary damage. Once it is fully anchored and secure, the umbrella ablator and electrode pad can enter. When the electrode pad and ablator is safely secure on the ablation area, the electrophysiologist will start the actual procedure by pressing a button to start the ablator and electrode pad. The electrode pad also has force sensors to make sure the energy doesn't exceed the energy taken to get the anchor through the vein.

This procedure is more efficient that normal cardiac ablations for many reasons. The CircumBlator is safer and more consistent because of the anchor and electrode pad. The anchor provides a more stable platform which allows the umbrella ablator to be locked in against the tissue. In other ablators, electrophysiologists have to make sure to actively maintain contact between the ablator and tissue, thereby relying on physician skill to generate successful ablations. The electrode pad increases consistency because the energy level remains constant throughout the procedure. Also, all the electrodes are making contact with the tissue and adapt to the contours of the topography around the vein. The CircumBlator reduces the length cardiac ablations procedures by one to two hours. With the CircumBlator™, ablation procedures will be more economically attractive, because they will be shorter and more effective as a result of maintaining continuous ablator-tissue contact.

3 Methodology

3-1 Market Data

The Team created a Google document that compiled all the market data that was considered to be prevalent to AF and ablation. The Team chose countries and regions that were thought to be good markets for AblaCor to implement their CircumBlator. The countries initially chosen to start research were Australia, Brazil, Canada, China, India, Israel, Japan, South Korea, Switzerland, the US, and every country in the EU. The Team researched various criteria that would aid in the understanding of ideal markets to distribute the CircumBlator. The Team looked into the population of each market to determine if there was a significant population that were or potentially could be living with AF. Along with looking at the population, the population of each region over the age of 65 was considered as most cardiac arrhythmia cases tend to occur with people over the age of 65. The number of arrhythmia cases that occurred within the past year was considered to determine the prevalence of the entire cardiac arrhythmia market. The percentage of arrhythmia cases that were atrial fibrillation was researched to determine the prevalence of AF within each region in comparison to other forms of arrhythmia. The total number of cardiologists and electrophysiologists in each market was a critical criterion. Data from this category was used to determine the number of qualified professional available in each region to perform cardiac ablations. It was also used to estimate the size and scope of the market for novel ablation devices. Not all electrophysiologists perform ablations and as a result the number of electrophysiologist known to be performing ablations was also taken into account. There are multiple types of cardiac ablations so the number of atrial fibrillation ablations per year and the cost of the procedure were also researched.

After collecting data from each of the categories, the Team created another table for atrial fibrillation cases for the last five years within select European countries. These countries were Great Britain, France, Germany, Russia and Ireland. This was used to determine if there was a trend in the number of individuals being affected by AF in certain areas.

The Team conducted our research by looking at reputable journals, national census websites and organizational documents about AF as well as medical databases that were about AF and cardiac ablation. Some of the databases and websites that we used were the Atrial Fibrillation Association of the US, Atrial Fibrillation Association of the United Kingdom and the European Society of Cardiology. The team also met Rachel Zyirek, a research and instruction librarian at WPI. She guided the Team in the use of IBIS World, The American Heart Association and the Whitebook to assist in researching biomedical devices, marketing, medical procedures, and insurance. She also helped locate information on marketing a biomedical device and health insurance policies in international markets.

3-2 Regulatory

Much of the research on the regulatory approval processes of each region was conducted by Matthew Hammond as shown in Appendix H. This information was gathered mostly by Hammond and in part by the team. The researched was centered on the procedures required in order for a medical device to be brought to market. This information will aid the team in the decision for an initial market as the quickest and most cost effective procedure will be the most advantageous. Additionally, some regulatory approvals are accepted in other countries and by obtaining an approval in a major region can open windows into others.

3-3 Determining Initial Markets

After collecting all of the research on market data and regulatory hurdles for entering foreign markets, the team must determine which or regions are best suited for this product. By entering into too many markets, the strategy becomes too thinly spread and can suffer from a lack of strength in each individual market. As a team, it was decided that it would be best to determine three foreign markets outside of the US to enter. In order to successfully accomplish this task, each aspect of the information that was gathered must be analyzed for relevance to the devices success in the medical device market and for its significance in priority for markets to enter.

3-3-1 Population and Affected Citizens

The population of the citizens is an indicator of the overall pool of potential consumers of the medical device. By looking at various aspects of the population and the prevalence of Atrial Fibrillation based on the proportion of sufferers to the overall population, the team can determine if the issue is at a large enough scale to become relevant to a wide number of physicians. Additionally, by looking at this prevalence, we can compare it with the number of electrophysiologists and cardiologists to deduce the potential for adoption in medical institutions. The market that is most suitable for entry would be one with a large pool of citizens and a fair to large proportion of those citizens either in need of the device or aware of Atrial Fibrillation. However, a smaller population can also be suitable based on the relevance of the condition amongst the citizens.

To best define a metric by which this can be assessed, a combination of total population, the amount of Arrthymia cases, the amount of those cases that are Atrial Fibrillation, and the prevalence of these cases per capita must flow into different pools that set apart the large

population ideal, the small population ideal, and the lesser desired markets. By beginning with the population, it can be divided simply by what would be considered a large population and what would be a smaller population. A simple initial division of the markets into two groups will keep the breakdown easy. From each group of populations, what must be determined is what criteria are more relevant to the larger and smaller populations. For the smaller populations, it would be best to see a larger percent of Atrial Fibrillation per capita as opposed to overall numbers. For the larger populations, the overall number of cases and the amount that are Atrial Fibrillation can at the very least show case the potential for marketing.

With the smaller population's criteria set aside, the larger population markets are left with three criteria: the number of Arrthymia cases, the number of Atrial Fibrillation cases, and the percent of Arrthymia cases that are Atrial Fibrillation. Since the device is intended to treat Atrial Fibrillation specifically, the number of Arrthymia cases can be overlooked initially, with the exception of special cases. The first criteria would be the overall number of Atrial Fibrillation cases. A high number of cases show that there is prevalence in the market. If a market has a low number of Atrial Fibrillation cases, then there is a lack of prevalence and the population may be too small to adopt the device as well as desired. However, a high number of Arrthymia cases would show a prevalence of the overall condition and can have potential.

From looking at the number of Arrthymia cases, if the amount is under a set threshold, then there is overall too miniscule of a presence and the market is undesirable. If the market shows a large number of Arrthymia cases, then the percent of these cases that is Atrial Fibrillation can then be observed. A low ratio decreases the relevance of the device and may put the market into an undesirable category. But if the ratio of cases is high, then the market can find its place back with the larger population ideals.

3-3-2 Current Cardiac Ablation Climate

After eliminating the initial undesirable markets and splitting the rest into the large and small population ideals, or markets that fit into large and small scale markets respectively, the markets must then be further sorted by the current climate of cardiac ablation procedures. It is quite apparent that with a larger population, there may also be a larger number of electrophysiologists or cardiologists to conduct the procedure. Thus, for the larger population markets, the total amount of ablation procedures conducted per year must instead be observed. With a suitable enough number of procedures being conducted, it shows that there is prevalence in not just the condition, but also that method of treatment. For the markets that do not meet the suitable number of procedures, the number of electrophysiologist and cardiologists can be observed along with the number of them that are conducting ablations. If there is a substantial amount of electrophysiologists and/or cardiologists, then the markets can return to ideal status. If there is not a substantial number or insufficient data, then the number of recorded electrophysiologists and cardiologists conducting can be observed. This would show that even without sufficient data or insignificant numbers, there is at least a record of a substantial amount of professionals conducting the procedure. Without this record or an insignificant number in this regard, the market can be seen as unfit for initial release.

As for the small population ideal group, it has already been determined that a large portion of the population have Atrial Fibrillation, showing a prevalence of the condition. To further support this observation, the number of ablations conducted by electrophysiologists per year can be observed, this would show that a simpler and more cost effective procedure would benefit their large workloads. Should this number be too small or unfounded based on

insufficient data, and then the market would go under the same route as for the large population ideal that has an insubstantial number of ablations per year.

3-3-3 Medical Device Market Share and Annual Investment

The final step for the decision flow based on the market research is to look at how the market share and annual investment in medical devices fair in each locale. A high number in either category shows dominance of the market externally or the strength of the medical device industry internally. This information serves to prove two advantages: a quick development of the presence of an ablation device in the market and the ability of the success in this market to open avenues into others.

For the large population ideals, it is expected that there would be a large amount of money put into investments for the medical device industry. As such, it would be best to base the entry decision from the percent share of the medical device market that the locale has globally. A high enough share shows a potential from expansion from this market, which is advantageous for the later stages of the marketing strategy. Countries or regions with a low share of the medical device market can still be seen as significant if they have an even more substantial amount in the annual investments in medical devices.

For the small population ideals, the annual investment in medical devices is the focus as a smaller country or region may not have as much dominance in the global market. Those with high numbers show a great potential for internal growth, while those with too minute of a number show a lack of potential for one device amongst the myriad of different ones.

This step in the decision flow would separate the markets into internal growth (early strategy) ideals and external expansion (late strategy) ideals. The desired ratio of the three

countries or regions outside of the US would be 2 internal growth ideals and 1 external growth ideal.

3-3-4 Regulatory Measures

Once the markets are split into the internal growth and external expansion ideals, the regulatory measures that a firm must undergo to reach final approval must be analyzed. Since each criterion must be properly evaluated, the decision flow at this point will be based on a scoring system centered on how ideal these regulatory measures are. The highest scoring market in each category will be the end choices for initial entry. The other markets will also be evaluated based on any extraneous criteria that may display an importance for that country or region to be used. These countries or regions will then be added onto the current list of ideal markets as secondary options.

4 Results and Analysis

4-1 Market Data

At the conclusion of collecting data for each of the regions targeted for possible entry, there were many gaps in specific region information. The majority of these gaps were regarding the number of qualified persons performing ablations and the volume these professional were performing. Despite the lack of information, the original list of countries and regions was then organized into markets for initial entry, markets for expansion, and those where further information and market monitoring was needed. In order to overcome the lack of data for certain and regions this ranking was primarily based on population size, reported number of AF cases, the number of AF ablations performed each year, and the number of electrophysiologist or cardiologist who have the ability to perform the procedure without additional education.

Based on the criteria we found that the US and the EU would be the most ideal areas for entry and thus should be pursued first. Each of these regions has seen a significant increase in their elderly populations, and as life expectancies continue to increase the prevalence of AF is also anticipated to increase. In addition to the prevalence of elderly, both regions also are reported to perform the most AF ablations per year, with 43,118 in the EU and 10,000 in the US To perform these ablations there are a minimum of 2,388 active cardiology professionals performing ablations in the two regions. From the population data alone we found the US and the EU to be the best regions for initial entry; however, medical device spending in both areas accounts for more than 74% of the total market. Based on this information these two regions are not only ideal for immediate entry, but they also have the potential for continued and sustained growth.

Japan, Canada, South Korea, Australia, Brazil, and India were found to be countries that could be considered for expansion. Most of these countries, such as Japan and Canada, were also found to have rapidly increasing elderly populations. The aging population makes these markets suitable for entry; however, the lack of information available in regards to the number professionals who are or have the ability to perform ablations detracts from the attractiveness of these markets. The lack of information on the number of AF ablations being performed makes it difficult to determine the size and potential growth of the market. Without information in regards to the number of electrophysiologists we felt that we could not accurately determine the ease of implementation amongst professionals in these countries as well. Though the number of AF cases can indicate the disease's presence in the populations, factors such as medical tourism need to be taken into considerations. For markets in this tier, further explorations of the regulatory

processes were taken into consideration to determine the overall attractiveness of the county's market.

Finally Russia, China, and Israel were all found to be countries that were not suitable for immediate entry or entry in the near future. For all three of these nations there was not substantial or reliable enough information to provide a recommendation for entry. More extensive information regarding the size and scope of the AF market is necessary before these nations can even be considered for potential entry.

4-2 Regulatory

At the conclusion of the collection of basic market data three main markets emerged that would be most ideal based on population; the US, EU, and Japan. The regulatory processes for these and all additional regions clarified some of the top market picks while eliminating others.

4-2-1 Regulatory Processes by Market

The US regulatory process for medical devices is conducted by the FDA and is similar to other regulatory processes. However, despite approval in foreign markets the FDA requires clinical trials to be done within the US. These trials must include between 500 and 1,000 patients and is expected to cost $5-10 million. The unique aspect of the US regulatory process in addition to the local clinical trials that must be done causes the approval process to take between five and ten years on average.

The EU requires medical devices receive a CE Mark before they can distributed throughout the member countries. Despite being accepted throughout the EU, certain member countries have stricter interpretations of the CE guidelines. Like the FDA, CE guidelines also require clinical trials that are done within the EU. Based on the approval of similar catheter

ablation devices within the last ten years it can be deduced that the Circumblator will need between 200 and 300 patients for their trial. Once a CE Certificate has been received the firm can begin registering the device for distribution in specific EU countries. The CE certificate is valid for one year and requires auditing every year thereafter. In order to comply with the yearly audits it is essential that post-market surveillance is conducted. This regulatory process generally costs $2-3 million.

The Japanese regulatory process for medical devices, while in compliance with ISO 13485, is unique from the FDA and CE approval processes. Unlike the previous two markets, medical device classification is not based on the type of device, but rather the risk associated with it. Similarly to the US, Japan requires local clinical trials; however the number of patients required varies depending on the level of risk associated with the device. For high risk devices between 400 and 600 participants are required. A benefit to getting approval in Japan is that the approval certificates do not expire; however the process of approval is long and cost associated with completing clinical trials within Japan are high.

Outside of these three markets the process for regulatory approval in generally faster and more cost effective. Many of the countries targeted for international market entry follow a similar approval style to that of the CE Mark. This being the case many of these countries will accept clinical trial data from foreign countries, thus shortening the time and cost to approval. Many of the countries that do not currently have regulatory processes similar to those of the US, EU, and Japan are currently in the process of reformatting and refining them do be similar.

4-2-2 Market Analysis

Taking into consideration both the market data and the regulatory requirements of each market considered, it was found that basing countries and regions targeted for entry solely on the

potential for AF cases was not an effective strategy. This plan did not guarantee device implementation. As opposed to the previous methods for target market determination, annual medical device spending provides a better insight into the potential for product implementation within the region.

Taking this newly defined path into consideration, it was found that the original three markets for consideration were also those with the highest annual medical device spending, making up more than 75% of total medical device spending. Medical device spending not only gives a clear insight into the benefits of entering a specific country or region, it also allows for better comparison between markets. For example when looking at markets with similar population compilations and number of ablating professionals, the market with the higher medical device spending is likely to provide a better, more receptive market for entry.

Considering this method of determination, large emerging markets such as Brazil, Russia, India and China, fall behind countries with higher expenditures despite less stringent regulatory processes and larger AF affected populations. Conversely, smaller markets can receive higher consideration despite the number of people affected by AF. Countries with regulatory processes similar to those of the CE Mark would fall into this category for further consideration.

4-4 Determining Initial Markets

The development of a successful decision flow diagram required an understanding of the data that we had collected and how each category showcases a market's suitability for the device and its potential acceptance. Each threshold would not only filter out countries into those that are desirable and those that may not be the best at the moment. Additionally, the decision flow diagram will designate each market into a strategic category. One of the categories is the Internal

Growth Ideals may be an apt idea. These markets spend quite a bit on investments for biomedical devices and thus can hasten the presence of the device and its success within the market. The other category is the External Growth Ideals. While these countries or regions may also have a prospect of internal growth, their dominance in the global market of biomedical devices is strong enough to allow for expansion on a global scale. The Internal Growth Ideals are an early strategy option, setting the foundation and example of the device's success and can be used to gauge how successful the device will be on a global scale. The External Growth Ideals are more of a later strategy option, not to say that entry into these markets should be delayed by any means, but that the success in these markets could mean a boost to expansion later on.

4-4-1 The Decision Flow Diagram

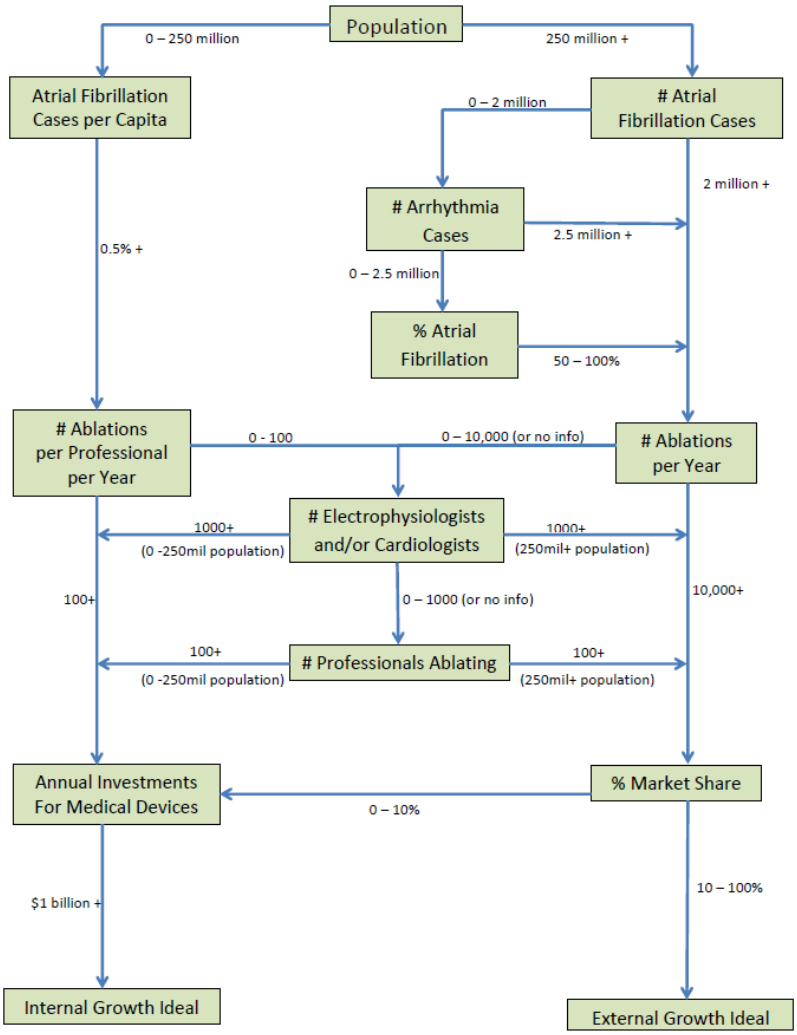

Figure 3: The Initial Market Decision Flow Chart (Appendix F)

The decision flow diagram above illustrates the flow of the decisions made based on the criteria and the values observed for each criterion.

The flow diagram begins by looking at the populations of each country or region observed. It was decided that 250 million would be the cutoff point to sort the markets into initial large and small categories. This number was generated from the average population of each country and region with the deletion of the two outliers, China and Australia. From the

separation into these sub groups, the rest of the data was observed considering what qualities an ideal market with a large and small population would have. For the smaller populated countries, the focus relied on the prevalence of Atrial Fibrillation by looking at the number of cases per capita. With at least 0.5% of the population with Atrial Fibrillation, the market has a large enough portion suffering from it that there is a need for treatments that successfully remedy the condition. If the condition is prevalent, the focus then moves on to a potentially high patient count for professionals that conduct treatments. The markets that have professionals with high counts of treatments per year may have the need for a quicker and more cost effective procedure allowed by the use of the CircumBlator™. For the larger markets, the aim is to find the ones with a higher general prevalence of Atrial Fibrillation. If there is not a high enough prevalence of the condition, a high number of Arrhythmia cases with a majority of those cases being Atrial Fibrillation can still show a need for treatment options. And if the country or region is already conducting many treatments, the potential for adoption of a more efficient procedure is significant enough to investigate further.

If there is not enough evidence to show a need of the device based on either the amount of ablations conducted or the number conducted by each professional, then the amount of professionals must be evaluated. The prevalence of the treatment may not be high, but there still may be a multitude of clinics and professionals conducted other treatments. If these values show a sizeable market of buyers of the CircumBlator™, then the decision relies on either the annual investment for medical devices in the smaller countries or the global market share of the larger ones. Those seen with a high annual investment in medical devices are internal growth ideals, meaning that the internal funding of the industry can lead to further developments of the device's success in the market. The countries or regions with the highest global market share are the

external growth ideals, meaning that from the success within these countries or regions can expand into other markets.

4-4-2 Regulatory Scoring

After reviewing the results of the regulatory research, it was determined that instead of a scoring system, it would be more strategic to start in a country or region where regulatory approval can spread to others. The country and region that have this advantage are the US and the EU. Approval from the US Federal and Drug Administration can extend approval to other countries such as Brazil. Additionally, the CE mark in the EU is widely accepted around the world. With the potential to find success and being required to pass only two approval processes to expand, the US and the EU are ideal choices.

4-4-3 The Initial Market Choices

The top scoring markets found through the decision flow chart are the US, the EU, and Japan. Other countries that have made it through the decision chart as the internal growth ideals are Canada, Brazil, and Australia. Another country that also fit the external growth ideals was China. However, with the advantages brought upon by FDA approval and CE marking acceptance, the US and the EU were deemed to be the best initial markets to enter. Additionally, for the EU, Germany was also ranked as an internal growth ideal and would be a suitable starting point for entering the EU.

5 Conclusions and Recommendations

5-1 Markets for Entry

Given the both the market data and regulatory processes, it is clear that the two primary markets to be considered to begin approval and distribution of the Circumblator are the US and EU, more specifically Germany. These markets comprise the majority of annual investments in medical devices and can support additional international growth in the future. However, we recommend that to begin device approval should be sought in Germany.

We recommend Germany as a beginning market because not only is it a large investor in medical devices, but also the regulatory procedures are swifter and less expensive than pursuing similar action within the US. The CE Mark being the standard for many other medical device regulatory processes around the world means that distribution of the device into those markets would be relatively simple once the original CE Certification had been received. By receiving a CE Mark, the CircumBlator would have the ability to enter into other large market with high numbers of arrhythmia, aging populations, and high investments in medical devices

By pursuing Germany as the primary distribution market as opposed to the US, AblaCor can save at least $5,000,000 in regulatory fees and 2 years. With the time and money saved AblaCor can distribute the Circumblator throughout the EU and use the profits from this distribution to fund US based clinical trials.

5-1-2 The German Market

Germany is Europe's largest market for medical devices and the world's third largest, behind the US and Japan. Although in decline, Germany's population of Germany still accounts for around 20% of the population. Germany counts 2,000 hospitals; 2,000 medical supply stores; 1,200 rehabilitation

centers; 21,500 pharmacies; and 150,000 doctors' offices. Government funding of hospital projects has remained static; major areas of opportunity are seen for private hospitals and clinics, which have a 20% market share. Demand will mainly be driven by demographics and a substantial increase in the number of patients and by the need for more efficient procedures. The German medical market expects a sales growth of approximately 6% this year, with continued upwards trends predicted for next year as well. The medical technology sector continues to be strong on innovation and growth and will provide excellent potential for US suppliers of innovative and price-competitive products. US medical device exporters to Germany continue to hold a 27-30% import market share, depending on product.

The "Medical Technology Action Plan" pools the Federal Ministry of Education and Research's varied funding activities and programs under three main topics: Medical technology in rehabilitation and care (intelligent implants); Molecular imaging; Medical technology for regenerative medicine. Incentives are provided as R&D project grants/cash incentives with a maximum 50% of eligible project costs. The EU is subsidizing transnational R&D through its 7th Research Framework Program. A budget of 6.1 billion Euros for the period 2007 to 2013 has been earmarked for health research.

For US companies, the German market which is the largest in the EU continues to be attractive in numerous sectors and remains an important element of any comprehensive export strategy to Europe. While US investors must reckon with a relatively higher cost of doing business in Germany, they can count on high levels of productivity, a highly skilled labor force, quality engineering, a first-class infrastructure, and a location in the heart of Europe.

The most successful market entrants are those that offer innovative products featuring high quality and modern styling. Germans are responsive to the innovation and high technology evident in US products, such as computers, computer software, electronic components, health care and medical devices, synthetic materials, and automotive technology. Germany boasts one of the highest Internet access rates in the EU and new products in the multi-media, high-tech and service areas offer great potential as increasing numbers of Germans join the Internet generation. Certain agricultural products also represent

good export prospects for US producers. Price is not necessarily the determining factor for the German buyer, given the German market's demand for quality. The German market is decentralized and diverse, with interests and tastes differing dramatically from one German state to another. Successful market strategies take into account regional differences as part of a strong national market presence. Experienced representation is a major asset to any market strategy, given that the primary competitors for most American products are domestic firms with established presences. US firms can overcome such stiff competition by offering high-quality products, services at competitive prices, and locally based after-sales support. For investors, Germany's relatively high marginal tax rates and complicated tax laws may constitute an obstacle, although deductions, allowances and write-offs help to move effective tax rates to internationally competitive levels.

5-1-2 German Reimbursement

Before applying for German reimbursement, make sure that the medical device is CE- certified. Once certified, the medical device is eligible to apply for reimbursement in Germany. All applications for medical devices are submitted to the umbrella organizations of the Statutory Health Insurance (SHI). You must provide information about the device such as suitability, safety, quality, requirement and medical benefits.

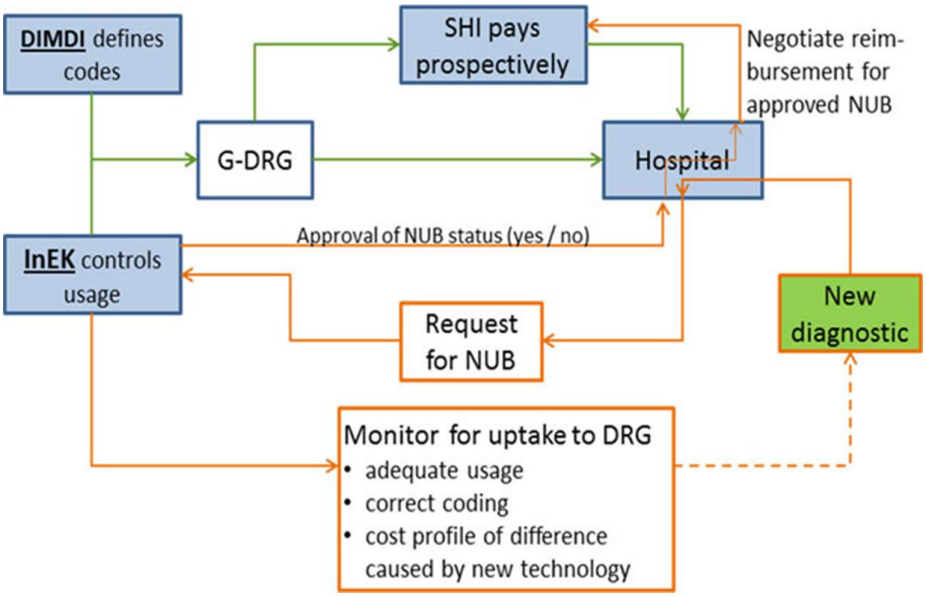

Figure 4: German Reimbursement Process (Appendix G)

Germany's hospital funding is regulated by the Hospital Financing Act. The Act makes each state responsible for covering large investment costs and the procurement of assets with a long economic life typically three or more years. These types of investments need to be negotiated and agreed between the state and the hospital in question. Inpatient hospital activity is the responsibility of each patient's SHI or private insurer. Only the top 3% of people in Germany have private insurance. The principal mechanism of inpatient activity reimbursement to hospitals by the SHIs or private insurers is called the German DRG or G-DRG.

German Diagnostic Related Groups (G-DRG) is the German modification of the World Health Organization's ICD-10 classification system. Every year the Deutsche Institut für Medizinische Dokumentation und Information (German Institute for Medical Documentation and Information) or DIMDI reviews the annual ICD-10 released by the World Health Organization and modifies the G-DRG in order to be somewhat similar to the ICD-10 but also works for the German health care system.

While the DIMDI has the responsibilities of maintaining the G-DRG's diagnostic and procedural codes, the Institut für das Entgeltsystem im Krankenhaus Siegburg (Institute for the Hospital Remuneration System) also known as the InEK is responsible for the collection and processing of hospital

costing data, the updating of the funding units associated with each funding code and the updating of the funding codes themselves. They are also responsible for certifying the logic system available to German hospitals. The Statutory Health Insurance or private insurer will then pay the hospital for the procedure based on where the procedure falls within the G-DRG code.

The reimbursement of newly introduced technologies depends on the availability of specific diagnostic and procedure codes, as well as the adequate uptake and correct coding of the new technology by the hospitals that participate in InEK's calculation system. InEK is updating G-DRG on an annual basis. Because of this, it may take longer to successfully fund a new technology or create new funding codes for it.

Recognizing the need for a mechanism allowing innovation within the G-DRG system, the InEK has created an "on-top" funding process for innovative products. This process, known as NUB (Neue Untersuchungs- und Behandlungsmethoden) Application can be filed by hospitals only for technologies that have just been introduced in Germany. Every hospital will need to apply separately (electronic application at InEK) and the "on-top" payment (if the application is approved) will be available only to the hospitals that applied for it and not to every hospital in Germany. Approved applications are subsequently monitored by InEK and should the new technology be adequately used; correctly coded; and, exhibit a cost profile of sufficient difference, the InEK may integrate it permanently to the G-DRG. It should be noted that InEK makes no decision on the actual amount of the "on-top" payment. That will need to be directly negotiated between the successful hospital applicants and the SHIs. The NUB pathway has the potential to accelerate market access for new technologies but requires significant effort from its users.

5-2 Next Steps

For future teams looking to expand the scope of the target market for the CircumBlator™, this is a general guideline for approaching that task. Each step in the guideline provides a basic objective that should be reached in order to make a fully educated decision as to

where to enter and how to enter that market. Future teams may take these guidelines and add more to it if they wish to make a more definitive decision.

5-2-1 Narrow List

When generating a list of countries and regions to research, the future team should first narrow a primary list down to about three. By utilizing a metric, such as the annual investment in medical devices, the team can find the strongest markets to conduct extensive research on. The number of narrowed down countries and region can be changed dependent on the budgeted time to research. The metric of annual investment in medical devices is useful in narrowing down markets due to the overall financial acceptance of medical devices within. Those with the highest annual investments supply a financial foundation in the industry that can increase the ease at which the device finds success. Of course, any other evidence that may highlight a market as one with a high need, either through political changes or changes in the market, can include that country or region to the list. Regulatory means can also be a way of narrowing the markets. If a CE mark has already been obtained, then looking into countries that accept it will help, especially if there is no additional approval process beyond having the CE mark.

5-2-2 Gather Data

Once the team has determined the markets that it will research, the team should look into these values with these thoughts in mind:

Number of Atrial Fibrillation Cases

This value shows the basic population of the target users and possibly consumers of the device. Attempt to look into the concentration of cases and other factors of the prevalence of Atrial Fibrillation beyond the number of cases. Are there regions in the market that are experiencing predominantly more cases than the rest? Is there a correlation between the aspects

of the market or regions in the market and the number of cases? By answering questions such as these with your research, the team can make more sense of the value and paint a picture of the environment surrounding Atrial Fibrillation in the country or region.

Number of Electrophysiologists, Cardiologists, and Clinics

The purpose of researching these quantities is primarily to gauge the size of the target market. Are these professionals or clinics providing treatment for Atrial Fibrillation? Are they conducting cardiac ablations? By focusing the research into a detailed account of the history of treatment of Atrial Fibrillation in the market, the team can understand the target market's current state and the potential impact the introduction of the device will have in the country or region. Additionally, this research will aid the team in finding the first customers of the device.

Number of Ablations per Year

The team can use this research to focus their entry efforts and gauge the competition within the market. Focus the research on more than just the total number and look into which clinics have the most traffic and if there are any growing frustrations with how ablations are currently being operated. Since this research should uncover other companies that market cardiac ablation devices in the country or region, this is also an opportune time to research those companies as they will become direct competitors.

Reimbursement Process

Countries or regions often have differing medical reimbursement systems, especially when comparing a majorly private healthcare system and a social one. For example, the reimbursement process in the US will vary widely based on the policies of the individual health insurance companies. By understanding the processes in the markets the team is researching, the sponsoring company can better understand the flow of money and how they will earn revenue.

Percent Share of the Medical Device Market

This value will aid in ranking the markets based on the strategic potential they have in expanding to other markets. A market that has a major share of the medical device market is one that has the leverage needed to expand. Another possibility is that having such a large share means that other countries respect success in that one, leading to greater success and acceptance when expanding to those countries.

5-2-3 Prioritize the List

After gathering all of the necessary data, the team can use, transform and use, or generate a new decision flow and prioritize the markets from the most ideal to the least.

5-2-4 Research Regulatory Processes

Starting from the highest priority market, research the regulatory process required to obtain approval in the country or region. This information can often be obtained in full by the or region's department or ministry of health. The key points to focus on are the average times to approval, the trial size required for clinical testing, and the average cost to approval. This information is critical, especially if you still require a form of internationally accepted approval, such as FDA approval or a CE Mark.

5-2-5 Compare Regulatory Process to Resources

After gathering the regulatory data and conducting a cost analysis, the team should compare the results between the markets listed. If any of the markets fall out of the range that the sponsoring company can handle, then move the market down the list. After comparing and moving the countries and regions around, the team should have one or two definitive ideal countries or regions. These markets are ones that show a potential for an accepting market and a regulatory process that will not bring the company into failure.

5-2-6 Final Market

Once the final market has been decided for entry, begin the process toward approval. If an international approval is accepted and has already been obtained, you may be able to almost directly enter the market.

5-3 Conclusion

What the team found that were the most important points in the process of deciding an initial market are the market data, the regulatory process, and the reimbursement process. By combining these three factors, the atmosphere around medical device markets can be properly assessed. The decision to enter Germany involved adequate analysis, but by following the guidelines with proper focus will allow for future teams to make a decision after finding exhaustive information.

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7 Appendices

Glossary of Terms

Competent authority – Any governmental regulatory agency responsible for the registration of medical products within that country. Most often refers to device registration in European countries after obtaining a CE Mark.

DIMDI- German Institute for Medical Documentation and Information

EFTA – The European Free Trade Association is the area in which CE Mark directives apply. Includes the EU and neighboring Norway, Switzerland, Lichtenstein, and Iceland.

External Market Growth – Largely populated market with high global market share. This market has potential for expansion and often also has high annual investments in medical devices and internationally accepted regulatory approvals. Ideal for a later strategy or overall focus.

G-DRG - German Diagnostic Related Group, it is the German modification of the World Health Organization's ICD-10 classification system.

GHTF – The Global Harmonization Taskforce is a voluntary organization of medical professionals that promote am international unified approach to medical product registrations.

InEK - Institute for the Hospital Remuneration System

Internal Growth Ideal – Market with high annual investments in medical devices. Shows potential for quick growth within the market. Ideal for early strategy.

ISO – International organization for Standardization, international guidelines for nation's regulatory processes. ISO 13485 and 14155 are the most commonly adhered to guidelines.

ISO 13485:2003 Certification - A widely accepted certificate demonstrating compliance with the quality management systems outlined in ISO13485. Accepted in nearly every nation.

Large Scale Market – A largely populated market. High potential for large annual investments in medical devices and global market share.

Notified body – Third party authorized to issue a CE Mark by the EU. May also be qualified to carry out other certifications (such as Brazilian INMETRO certification).

QMS - The organizational structure, procedures, processes and resources needed to ensure consistent performance in manufacturing. Proof of sufficient quality management systems is required in all regulatory process and is usually fulfilled by ISO standards.

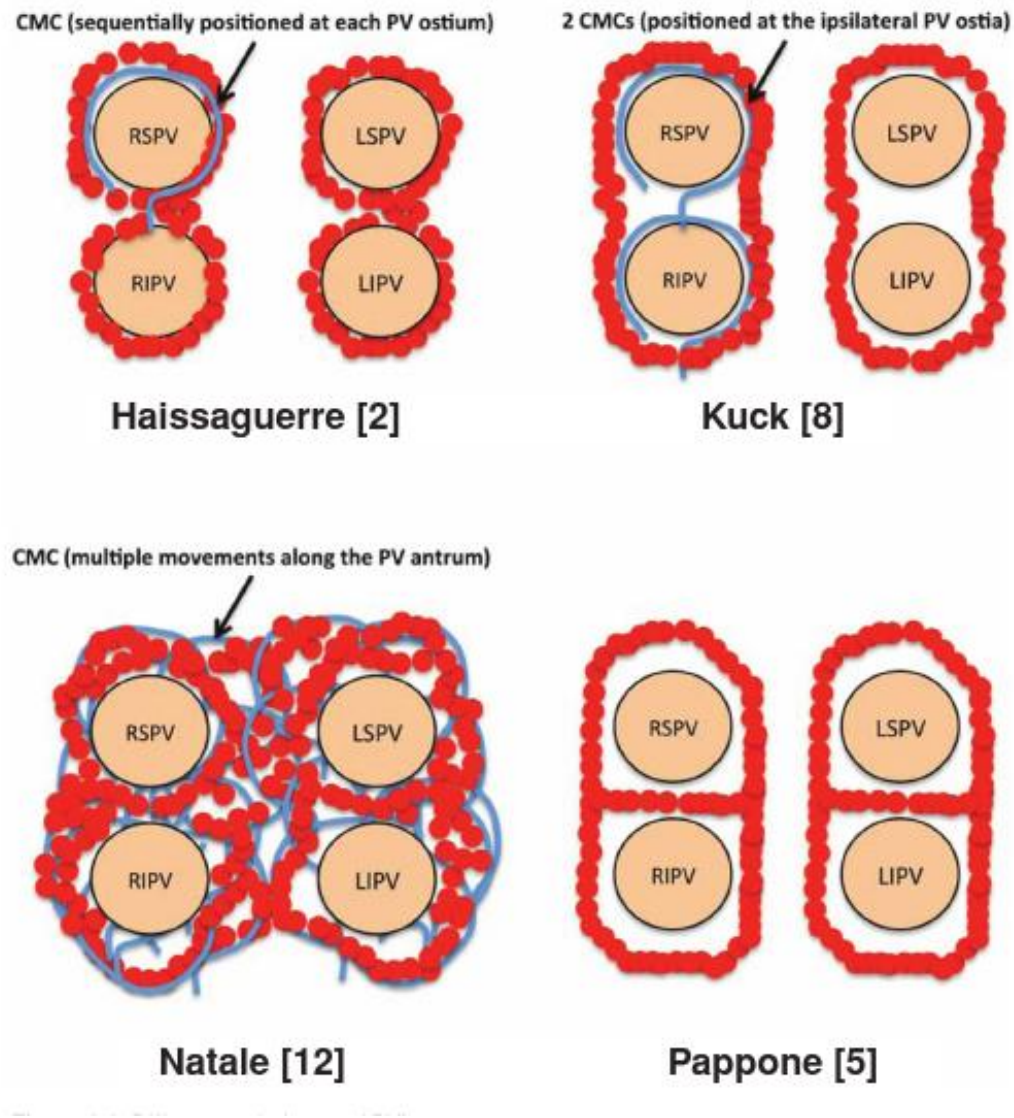
Regulatory Liaison – A person or company responsible for handling regulatory and sometimes distribution of a device in a country you are not based in. Requirements, importance, and legal capabilities for a liaison vary greatly by country.

SHI - Statutory Health Insurance

Small Scale Market – Smaller population markets. May have high annual investments in medical devices or concentrated prevalence of cases.

STED Documentation – Suggested standardized technical file documentation promoted by the GHTF. Not universally adopted but frequently accepted in place of technical documentation.

Appendix A: Pulmonary Vein Isolation

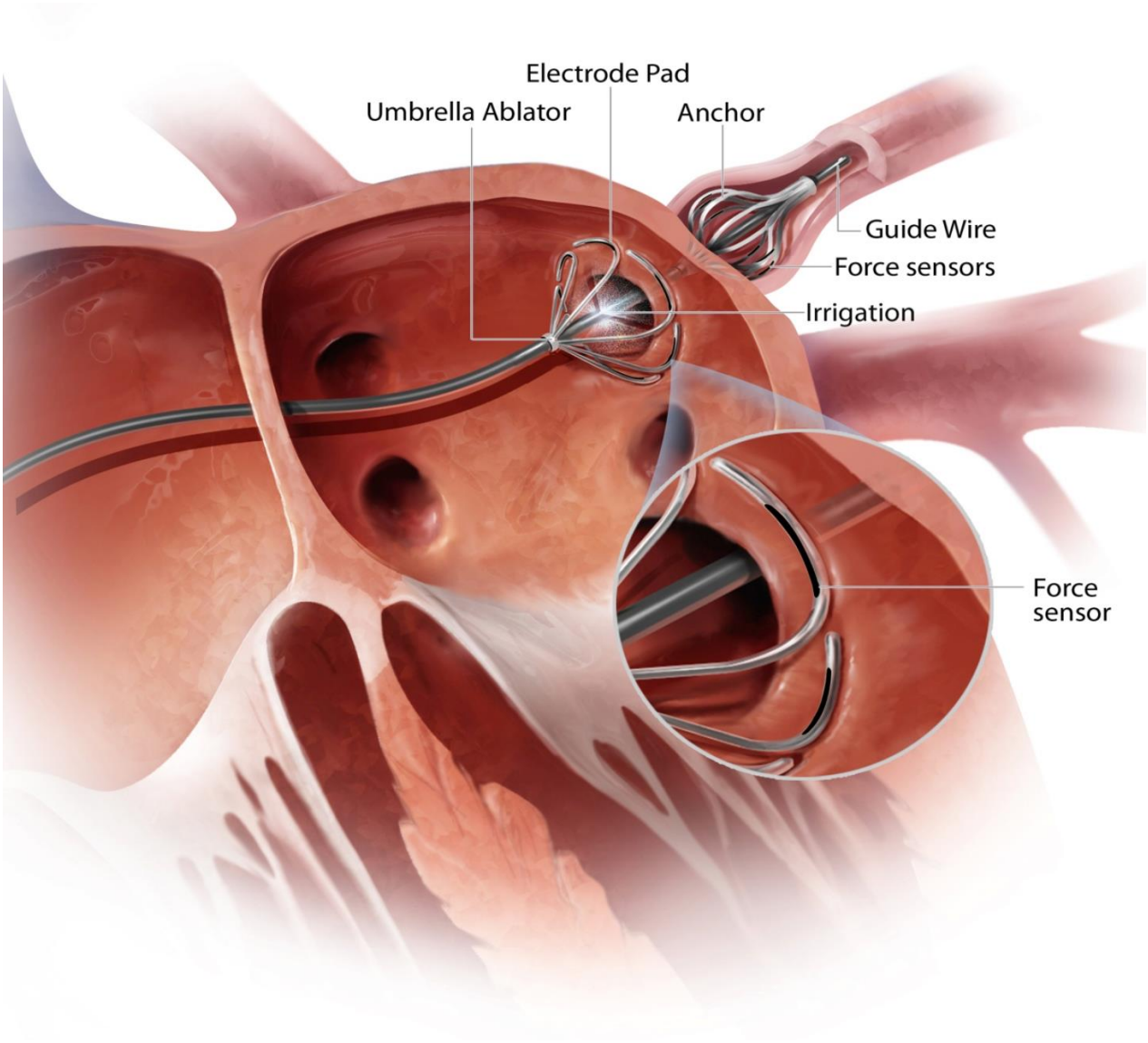


Source: Techniques and Technologies for Atrial Fibrillation Catheter Ablation

Appendix B: AblaCor™

AblaCor Medical Corporation (formally Automated Medical Instruments) is a company based in Needham, Massachusetts and was by founded by WPI alum, Martin Sklar. AblaCor Medical Corporation is an early stage medical device company that is dedicated to the development of revolutionary, minimally invasive products that will transform catheter ablation into a first-line treatment for patients with atrial fibrillation. AblaCor is designing a device called the CircumBlator which is a one-touch ablation solution for pulmonary vein isolation. It is also designed to improve the catheter ablation procedure. AblaCor recently was a finalist in the MassChallenge which is a competition designed to help early-stage entrepreneurs with the resources they need to launch and succeed as soon as possible.

Appendix C: CircumBlator



Appendix D: Market Data

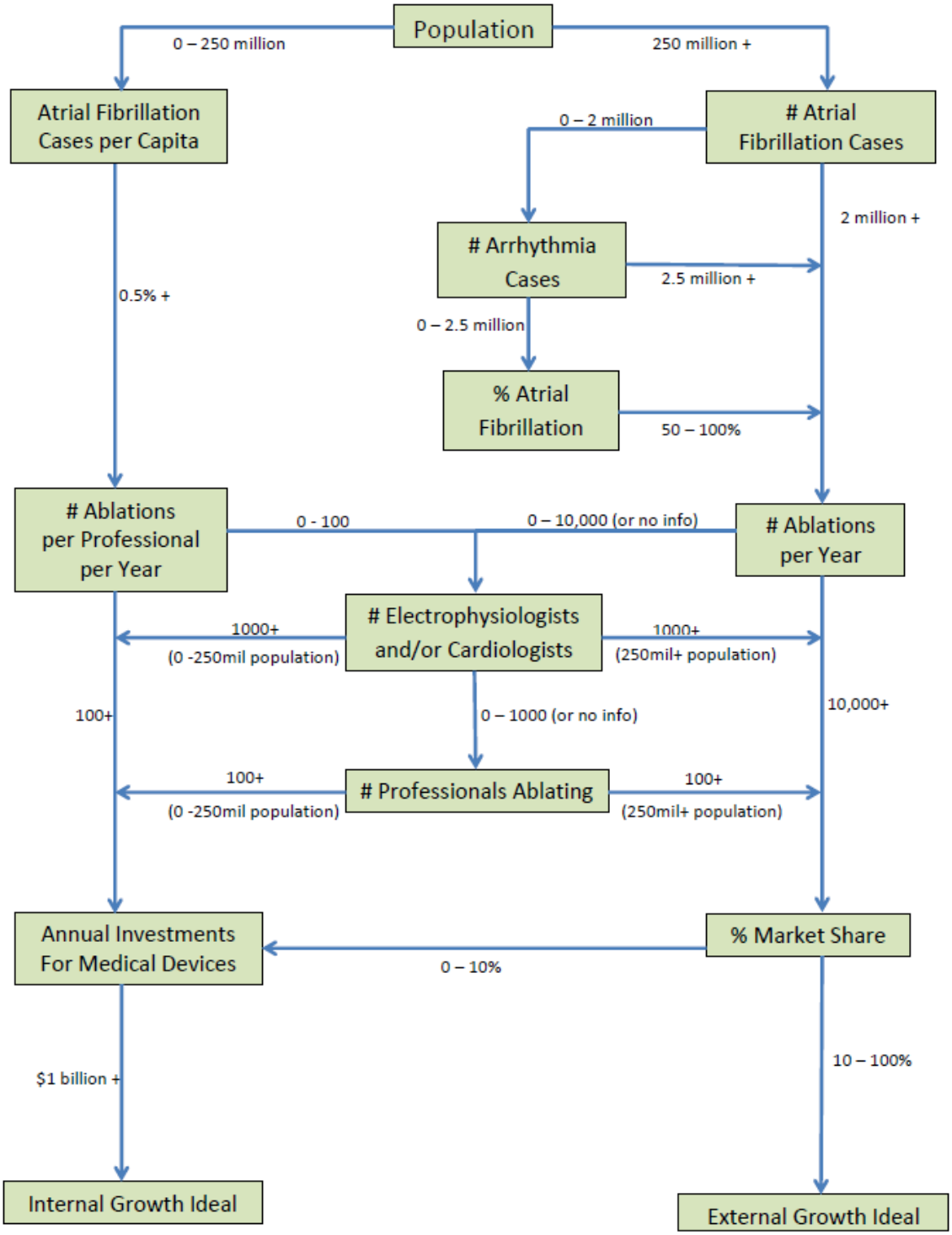
	Population	# Arrthymia Cases	AFibCases	Percent Arrhythmia Cases that are AFib	Percent AFib per Capita
U.S.	314,519,000	4,000,000	2200000	55	0.699480794483004
EU Composite	503,500,000	4,500,000	2500000	55.5555555555556	0.496524329692155
Japan	127,520,000	3,800,000	2,083,677	54.8336	1.634
Canada	34,938,400	1,100,000	350000	31.8181818181818	1.00176310306139
South Korea	50,004,441		16945		0.033886990157534
Australia	21,662,093	1,055,396	400000	37.9004657967246	1.8465436373115
Brazil	193,946,886	2,730,000	1500000	54.945054945055	0.773407622538472
India	1,210,193,422	2,000,000	1205073	60.25365	0.099576892263095
Russia	143,200,000	16,380	9000	54.945054945055	0.006284916201117
China	1,347,350,000	16,500,000	9000	0.05454545454545	0.00066797788251
Israel	7,913,900	no info			
Switzerland	8,000,001	4,679	16945		0.211812473523441
Ireland	4,588,252	1,000			
Great Britain	62,262,000	15,078	46000		0.073881340143266
France	65,350,000	31,175	600000		0.918133129303749
Germany	81,844,000	50,000	1000000		1.22183666487464
Italy	59,464,644	19,000			

	# EPs	# Cardiologists	# EPs Ablating	AF Ablations per Year	Ablation/EP/Year	cert for invasive EP	Cost/Proedure	% Share of Medical Device Market	Most recent annual investment in medical devices (adjusted for inflation)
U.S.	2421		1489	50000	33.5795836131632		$17,000-$21,000	44.3668054571226	80130000000
EU Composite			899	60000	66.7408231368187			30.3198086463501	54760000000
Japan		10144					Y1,063,200-2,029,640	10.575389794472	19100000000
Canada	1232			1430			$16,274 - $21,294	1.5148830616584	2736000000
South Korea								2.2080606480658	3600000000
Australia	27	752	6	1944	324		17,467-20,500	0.60019489723600	1084000000
Brazil		8000						0.66940556343019	1209000000
India	30	3500	20	15000	750			0.23254783841247	420000000
Russia			71	3727	52.4929577464789	yes - cardiology		0.58635276399716	1059000000
China			no info	no info				8.85896527285613	16000000000
Israel			12	no info		yes - EP specialization		0.28237951807228	510000000
Switzerland			21	1595	75.952380952381	yes - cardiology			
Ireland			11	450	40.9090909090909	yes - cardiology			
Great Britain	65	650	49	4654	94.9795918367347	yes - cardiology			
France		6200	130	6488	49.9076923076923	yes - cardiology			
Germany	305	4000	200	15000	75	none - pending			
Italy			170	no info		no			

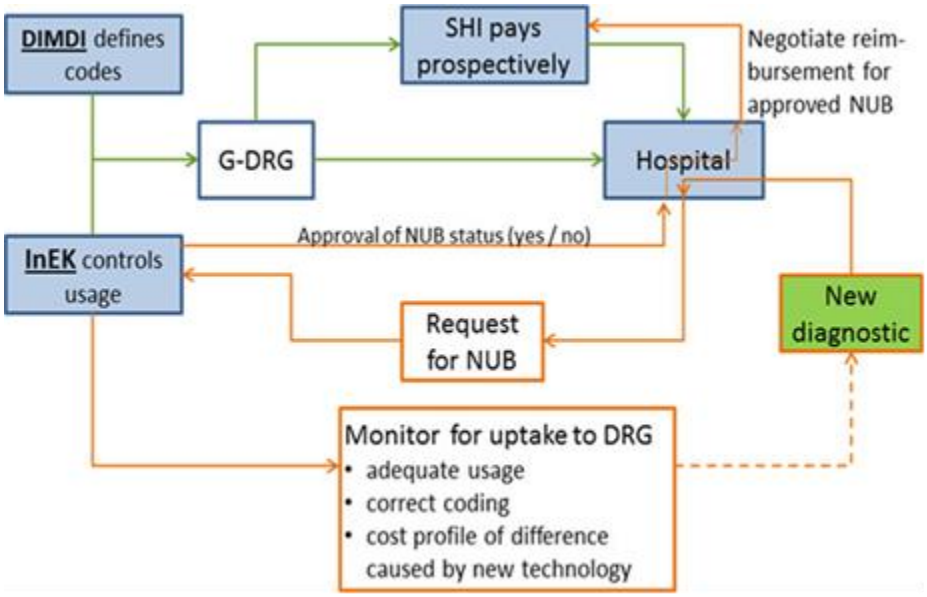
Appendix E: Regulatory Information

Country	Certification Requirements	CE Marking accepted?	Avg to acceptance	Expected Pivotal Trial Size	Cost of Approval with Clinical Trials	Comments
U.S.	PMA Letter of Approval	no	5 - 11 years	500-1000	$5,000,000 - $10,000,000	does not recognize ISO 13485
EU	CE Certificate	n/a	3 years	200-300	$2,000,000 - $3,000,000	requires technical files/design dossiers similar to FDA PMA
Brazil	INMETRO electrical safety INVISA clinical trials	yes	6 months	200 - 300	$1,600,000 - $2,400,000	requires economic report, electrical certification
China	IMDRC Certificate	yes	6-9 months	100 - 200	$600,000-$1,200,00	requires in-country clinical trials as well as local representation
Canada	Medical Device License ISO:13485:2003 certificate	yes	6 months	400 - 600	$3,000,000 - $4,000,0000	QMS very similar to Brazil/Japan
India	Registration Certificate Form 41 Import License Certificate Form 10	yes	9 months	100 - 200	$500,000-$1,000,00	accepts US/EU/AUS/JAP approvals
Korea	Certificate of Product Approval KGMP Certificate	yes	6-8 months	150	$500,000-$1,000,00	
Japan	Pre-Market Approval Certificate	no	5 years	800 - 1000	$5,000,000 - $10,000,000	local distibutor given far more independence than normal
Australia	GMDN registration	yes	3 - 6 months	200 - 300	$2,000,000 - $3,000,000	requires national distributor
Russia	Registration Certificate GOST-R Certificate	no	3 - 6 months	200 - 300	$820,000 - 1,230,000	requires type testing

Appendix F: Decision Flow Chart



Appendix G: German Reimbursement Flow Chart



Appendix H: Regulatory Analysis Report

MQP – FRH – FHO2

Regulatory Feasibility Analysis for a New Atrial Fibrillation Ablator in Selected Countries

A Major Qualifying Project Report
Submitted to the Faculty of the
Worcester Polytechnic Institute
in partial fulfillment of the requirements for the
Degree of Bachelor of Science in
Management by

_____

Matthew Hammond

Approved:

_____

Martin Sklar, President and CEO
Automated Medical Instruments
Project Sponsor

_____

Frank Hoy, Ph.D
Paul R. Beeswick Professor of
Innovation and Entrepreneurship
Project Advisor

_____

Jerome Schaufeld, Ph.D
Professor of Practice
Project Co-Advisor

Abstract

Medical device registration for class three devices, such as a catheter ablator, can be a long and difficult process. The regulatory requirements can vary greatly by country, overlap and benefit one another, or require repeating a certification depending on the country in question. Determining the order in which regulatory approval is pursued affects the size of the market in which a new device may enter. Prior approval on major facets such as clinical trials may greatly reduce the costs of entering a particular country if the data from an outside source is deemed acceptable. This creates a complex problem where start-ups who cannot afford to pursue regulatory approval in all major markets simultaneously must carefully chose and enter individual markets a few at a time. This paper compares ten nations and regions against one another and outlines a suggested order of entry.

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Acknowledgements

I would like to thank Martin Sklar for his expertise and continued interest in the success of our project for Automated Medical Instruments. His experience and input was critical in determining the scope of this project.

I would also like to thank my advisors Professor Frank Hoy and Professor Jerry Schaufeld for all their guidance and feedback. They were critical in helping us find relevant sources and contacts crucial to the research of this project.

Finally, I would like to thank my team, Kyle Cayabyab, Meagan Ward, and Jameel Galloway for all their help and research on the project. They were a great help in compiling the massive amounts of data we ended up going through. I wish them the best in the coming semester.

Background

Atrial Fibrillation is the most common form of arrhythmia, accounting for approximately 40% of all cases of arrhythmia. Currently, there exist only two options for arrhythmia patients, surgical ablation or going on anticoagulants, such as warfarin, for the remainder of one's life. The surgical ablation process is currently done by catheter point ablators, a technique that was introduced in the late eighties, and has changed little since then. Current catheter ablation operations have a wildly varying success rate, between 50-80%, and are highly dependent on the skill of the electrophysiologist performing them.

Automated Medical Instrument's Circumblator claims to fix this problem by removing significant chance of surgeon error from the procedure. The Circumblator anchors itself within the pulmonary vein using a stent-like device. The ablation is then performed using a circular radiofrequency ablator around the vein. This process improves upon existing methods by using the anchor to hold the device in place, freeing the surgeon of the task of ablating several individual points by hand. The results should be a major increase in the success rate of catheter ablation.

Project Purpose

Understanding the regulatory process of a country is a critical component in determining the cost and benefit of entering a particular nation. Regulatory systems are complex; often impact one another, and approval runs the risk of becoming increasingly costly if the applicant is not prepared. The approval process in all countries must be able to show safety and efficacy of the device making the quality of clinical data the key factor. Most nations accept clinical data from studies conducted outside their boarders but will independently determine whether or not the data is considered sufficient for "statistically significant results" as defined by ISO 14155. As a result, it is important to conduct initial clinical trials in an area with high standards and a high reputation for quality. The three regulatory systems with the highest reputations and most widely accepted sources of clinical data are in the US, EU, and Japan.

Once the first location of clinical trials has been chosen, other regulatory processes may be considered as though they had sufficient clinical data (if outside data is accepted). Whether or not clinical data from the first trial location are accepted elsewhere will greatly impact the order of entry internationally.

Methods

European CE Marking Process

The European approval process is a decentralized and highly efficient regulatory approval route designed to give all member countries access to new medical technologies. CE Marking is not a mark of quality, the process of CE Marking is actually a "self-declaration" whereby the manufacturer claims to be in compliance with the guidelines necessary for free trade within the European Economic Area (EEA). The CE Mark effectively functions as a "pre-market approval", which includes the lengthy technical documentation and collection of clinical data processes. This is the most expensive aspect of the approval process and registering a device in individual European nations with a CE Mark is quick and inexpensive or, in many cases for class III devices, not required at all.

A class III device must prepare and submit two documents to a notified body in order to receive a CE Mark. The first is proof of implementation of a Quality Management System (QMS) that complies with ISO 13485 guidelines. This is the first required step in all regulatory approval processes and in all but two of the observed countries (USA, Brazil) is based on ISO 13485 requirements. The second document is a Design Dossier, an extensive technical file that will require a large amount of clinical data. Clinical trials for a CE Mark are best conducted in European countries with the strictest interpretations of the CE guidelines such as the UK, Germany, France, Sweden, or Switzerland or in partner states that have made large efforts to comply with CE guidelines such as Canada and Australia. Clinical trials require approval from a Competent Authority (CA) from the countries they are to be conducted in. Competent Authorities are the regulatory bodies of the individual nations within the EFTA and have based their regulatory processes around CE guidelines. The size of clinical trials must demonstrate proof of safety in man and proof of parity to existing devices at a "statistically significant level" (ISO 14155). What constitutes "statistically significant levels" of data is based on precedence and the expected level of risk of the device. For example, a new catheter point ablator awarded a CE Mark in 2006 conducted a 210 patient clinical trial (sharps.org) where the more novel, less understood Cryoballoon catheter ablator required a 240 patient pivotal trial (Medtronic.com).

Based on this and other invasive electrophysiological devices approved in the last ten years we can expect a clinical trial size for the Circumblator to range between 200 and 300 patients.
With this information in hand, an authorized representative called an EC-Rep located within the EU must be appointed and submit the applications to a notified body. If the audit is successful and the device is approved the notified body will then issue a CE Certificate. This certificate is valid for one year after which continued approval is subject to yearly audits by a notified body. Upon being issued a CE Certificate, the manufacturer may produce a Declaration of Conformity and begin registering the device in the countries which require registration and begin distribution. Registration is frequently not required for class III devices as many nations rely on the yearly notified body audits to ensure quality. However, even if registration is not required, distribution must still comply with all CE directives which include translating all labeling into the local language. Post-market surveillance must also be conducted to ensure successful yearly audits.

Regulatory Approval Process in the US

Regulatory approval in the US is conducted by the FDA. The FDA approval process is separate from all other regulatory processes meaning US-based clinical trials will always be required regardless of the status of foreign approval. Unique standards must adhered to similar to ISO protocols, with random inspections in place of yearly reviews. The only international standards followed during the FDA regulatory process are the STED document formats. Despite these drawbacks, the US remains one of the most sought after markets due to its status as the single largest buyer of medical devices. The international reputation and acceptance of FDA approval is second only to Europe.
The first step in seeking regulatory approval from the FDA is implementing a Quality Management System. The FDA's QMS predates ISO standards and does not recognize ISO 13485 approval. Instead, the implemented QMS must follow the 21 CFR Part 820 requirements, also known as the current Goods Manufacturing Process (fda.gov). As the CircumBlator is a substantially novel device, a Pre-IDE trial will likely be required as the device is not substantially equivalent to existing market products. This trial is small in scope, with the goal of demonstrating safety in man and parity to existing devices. Once IDE approval is granted, pivotal trials may start. A pivotal trial conducted in the US will require 500 to a 1,000

patients at an expected cost of $5,000,000 to $10,000,000 (gmplabelling.com). Once pivotal trial data is collected, a completed PMA application may be submitted. The PMA review will theoretically take no longer than 180 days and is contingent on site inspections.
The FDA's regulatory process is regarded as one of the highest standards in the world. Part of this is the scope of pivotal trials in the US; the FDA reserves the right to reject devices due to new technologies not being "substantial improvements" over existing ones. Despite this, the FDA is plagued by bureaucratic issues that impact the approval process, including outdated infrastructure and a high turnover rate. Delays are common meaning the approval process within the US can vary between two to five years.

Regulatory Approval Process in Japan

Much like the FDA, the Japanese approval process is known internationally for its high standards. Also, like the FDA, Japanese approval is a long and difficult process that requires clinical trials conducted within the country's boarders regardless of international recognition. Japan is the fourth largest individual buyer a medical devices, behind the US, Germany, and France.
Regulatory approval in Japan begins with the appointment of a Marketing Authorization Holder, called a D-MAH, which will act as a regulatory liaison in the country. Device classification must be determined as Japan has a 4 tier classification system where tiers 3 and 4 do not clearly specify the kinds of devices in each category. Instead, device classification is done by an arbitrary approximation of risk of the device. Once this information is known, the D-MAH may submit a form for Foreign Manufacturer Accreditation to the PMDA. A quality management system must be implemented that complies with ISO 13485 as well as the Ministry of Health, Labor, and Welfare Ordinance #169. At this stage, clinical trials must be conducted in Japan. Clinical trials in Japan are costly, for high risk devices 400 to 600 Japanese patients may be needed. Combined with the costs of maintaining Japanese contacts, the costs of running clinical trials in Japan is comparable to clinical trials in the US. Once clinical data is collected a pre-market approval form may be submitted as well as technical files which follow the STED format. Pre-market Approval certificates issued by the PMDA do not expire.

Approval in Japan is unfortunately not a quick or easy option for a small company in the US. Japan places high importance on the status of home-country approval although it is not required. Additionally, the role of the D-MAH is much greater than most regulatory liaisons, they possess certain right in the country related to devices they help approve. Choosing a D-MAH that is part of an international medical device distributor or consulting firm is recommended.

Cost of Regulatory Approval between the US, EU, and Japan

Due to the huge costs associated with clinical trials, the optimal path for approval and access to all major markets is best done sequentially rather than concurrently. Outside approval only officially benefits the regulatory process in Europe, unfortunately the CE Mark is also the quickest and least expensive way to obtain one of the three major approvals. Furthermore, Japan places a high value on the status of home-country approval. The order in which approval is sought after in these three markets greatly affects access to the worldwide medical device market. Obtaining approval in one of these three bodies would normally indicate that you have sufficient clinical data to pursue regulatory approval in almost any other nation in the world without the need for additional clinical trials.

Due to Japan's foreign device constraints, smaller market, and comparable regulatory costs, it only makes sense to seek Japanese approval following US approval. This makes the question of first major market a decision between the EU and the US. Approval in the EU comes at an expected cost of $2-3 million and grants access to 30.3% of the medical device market. Approval in the US comes at an expected cost of $5-10 million, grants access to 44.4% of the medical device taking roughly twice as long to gain approval. With the metric of "cost to access 1% of the market" it becomes clear that Europe is a much more cost effective first market (US: $112,000-224,000 per 1%, EU: $66,000-100,000 per 1%). Combined with other factors, such as the acceptance of the CE Mark internationally, aging population of most European nations, and lower total capital needed to get to market, Europe becomes the best choice. Once European approval is granted in the form of a CE Mark, access to all other international markets becomes substantially easier, especially in many wealthy smaller nations that make up the list of top medical device buyers (Canada, Australia, and South Korea). Consecutively pursuing approval in

the US and then Japan is also recommended, as they represent a combined 54% of medical device purchases worldwide.

Regulatory Approval outside of the Top Three Markets

With clinical data from European trials, the regulatory timetable and cost to access markets in multiple other nations drops significantly. These countries regularly accept clinical data from outside their boarders and will likely not require additional studies if the product possesses a CE Mark. However, although many nations have streamlined their regulatory processes to better match the European model, the regulatory agencies still maintain the final say on approval within a specific nation. This section covers the regulatory processes for select countries based on their market size.

Australia

The Therapeutic Goods Administration (TGA) is the regulatory body in charge of medical device approvals in Australia. The TGA, in an effort to combat medical tourism and other failings within its old approval system, redesigned its classification system and regulatory process along the guidelines of the Global Harmonization Task Force (GHTF). Depending on the scope and requirements of clinical trials, it may be worthwhile to pursue Australian and EU approval concurrently, as the TGA is a Notified Body capable of issuing a CE Mark.

Similar to Europe in its initial steps, the registration process for Australia requires proof of compliance with ISO 13485. When submitting a Design Dossier, the European standard equivalent may be used. The Australian regulatory process differs from the European system during the submission process. Medical Device registration in Australia requires a regulatory liaison that resides in the country. Through this liaison, manufacturers evidence (CE Mark) is submitted and the device is entered into an electronic registry called the DEAL system. If approved, the approval will be posted on the TGA website and a certificate will be issued with the device's registry number. A small fee is required to submit the manufacturer's evidence and list the device online.

Brazil

Device registration in Brazil begins with the appointment of a Brazilian Registration Holder. This must be a company with locations inside Brazil that possess a Company Working Allowance permit. Highly novel or high risk devices will require the submission of an Economic Information Report assessing the impact the new device could possibly have in Brazil. All electrical devices must obtain INMETRO Certification, although this does not need to be done within Brazil, it is the only nation we observed that had such a requirement. Proof of compliance with the Brazilian Goods Manufacturing Practice must also be demonstrated and is subject to inspections every two years. With these preliminary steps completed, the Registration Holder may then submit a technical file to ANVISA for approval. Once approved, ANVISA issues a device registration certificate and a letter of authorization, both these documents must then be registered at a Brazilian consulate. All certificates issued are valid for five years.

Canada

Medical device registration in Canada is handled by Health Canada's Health Products and Food Branch. Like Australia, Canada has tailored their regulatory process to international standards and follows the European model whenever possible. First, an ISO13485:2003 Certificate must be acquired. Approval for an ISO13485:2003 Certificate must be done by a CMDCAS accredited registrar. CMDCAS accreditation is managed by Health Canada and many European notified bodies possess CMDCAS accreditation. The ISO Certificate, Pre-Market Review documents, Medical Device License application, and relevant fees must then be sent to Health Canada for review and approval. Once approved the device is legal for sale in Canada subject to yearly approval fees. Once the aforementioned steps have been completed, the approved device is totally legal for sale in Canada. However, Canada operates under a nationalized healthcare system making the Canadian government itself the largest singular buyer of medical devices in the country. Due to the country's huge landmass and relatively small population, using Health Canada as a distributor may be the easiest way to disseminate a new product across the country. In order to sell directly to the Canadian government, a Private Label Medical Device License must be acquired. This is a much faster process than normal device registration and is not subject to

yearly renewals. Depending on the level of interest, it is possible that Health Canada would purchase the rights to manufacture a PLMDL device within the country.

China

China purports a standardized regulatory process in compliance with most EU and US guidelines. In practice, approval in China can be substantially more difficult than most nations with standardized guidelines. First, a regulatory liaison, called a Legal Agent, and a distributor, called an After Sales Agent, must be appointed. Although the Legal and After Sales Agents are involved in the preparation and submission of documents, the device manufacturer is responsible for holding all of the necessary forms. A Registration Standard document must be prepared and submitted along with a prototype for type testing. Officially, a response for the SFDA should take no longer than two to three months but depending on the novelty of the device, it is entirely possible that it will be held longer causing an unknown amount of delay in registration. The results of type testing may result in the requirement of additional clinical trials to be held in China. If not needed, quality assurance documents may be submitted (ISO13485 Certificate or FDA equivalent, CE Mark or FDA Letter of Approval, etc.) along with technical files for approval. If successful, an Import Medical Device Registration Certificate is issued and is valid for four years.

India

India's regulatory body does not classify devices via the tier system used in most of the rest of the world. Instead, devices in India are only subject to certain regulatory processes if they fall into one of the specific device listings. These listings do not include invasive medical devices and are more analogous to class II devices. Instead, regulatory approval relies on the appointment of a regulatory liaison and the completion of two forms. The regulatory liaison, called the India Authorized Agent, must be an Indian born national with five years' experience in the given field (in this case, an electrophysiologist). The agent must also hold a valid Indian wholesale license, called Forms 20B and 21B. Through the agent, a device registration form must be submitted called Form 40. This form will require clinical data and approval data from the US, EU, Japan, or Australia is sufficient. Once approved the Indian governing body (CDSCO) will issue Certificate 41. Upon approval, an import license, called Form 10, will also need to be acquired. This import license specifies your in-country distributor and is held (along

with Certificate 41) by the India Authorized Agent. All forms are valid for three years and resubmission of forms is needed for continued approval.
India is currently implementing a more complex and more defined regulatory system for medical devices. Presently, medical device registration can take place in under a year when approached with clinical data already in hand. However, distribution can be difficult outside major cities as India is a large, highly diverse, and regional country. Care must be taken during the registration process as changing distributors is a difficult process.

South Korea

Companies without a presence in South Korea must appoint a Korean License holder to submit and utilize the necessary certificates for registration in the country. The License Holder in Korea is different from many other nations in that it is the device distributors rather than manufacturers that must hold the license, and licenses are valid for entire categories of medical products, not individual patents. The largest effect on regulatory approval is the importance of choosing the correct distributor before entering the market, otherwise the regulatory process must be repeated to gain access to another distributor. While South Korea requires the standard ISO 13485 QMS compliance and the submission of a technical file, the standardized SER Technical File may be used in this submission. The submission of a technical file will also require the submission of a prototype for type testing by the KFDA. Successful completion of these submissions will result in a product license issued. Once the product license is obtained the Korean License Holder must then apply for a KGMP Certificate. This Certificate is effectively a yearly audit on the distributor and proof that they hold both a business license and relevant product license. All three of these documents must be presented by the Korean License Holder when importing products into the country.

Russia

Regulatory approval in Russia is managed by the Rozsdravnadzor and is designed to specifically separate itself from Europe. Unlike most approval processes which can rely on a variety of safety guarantees like quality systems, cite inspection, and post-market surveillance, Russian regulatory approval is dependent upon product testing to ensure safety. A company must be appointed to act as a regulatory liaison within Russia. Once appointed the regulatory liaison seeks out permission to import testing samples into the country. Testing must be conducted at

authorized expertise centers and hospitals within Russia. Using the data gathered in the quality, safety, and efficacy testing, a registration dossier must be compiled and submitted to the Rozsdravnadzor. Applicants may be requested to collect additional clinical data or proof of home-country approval (although this appears to not be required, the Rozsdravnadzor reserves the right to request home-country approval before allowing the device into Russia). If approved, a GOST-R Certificate is issued which is valid for one year.

Results

Sizing Up Markets and Difficulty of Regulatory Access

Comparing the benefit of accessing a particular market against the difficulty of accessing that particular market can be difficult. There exists no metric that accurately defines the number of arrhythmia patients that we would gain by going into a specific country, so other derivatives must be considered. We initially organized ideal countries by those that theoretically had the largest number of potential arrhythmia sufferers. This made the countries with the oldest populations the most desirable but they all had difficult and involved approval processes (US, EU, Japan). As discussed earlier, the costs associated with pursuing approval in these three areas at once was not feasible. Instead of following the pathology of arrhythmia, we settled on a more concrete measurement, the annual amount spent on medical devices in a given country. This figure provided a more accurate look into what we could expect from gaining access to a particular country. Once again the US, EU, and Japan were at the top comprising over 75 % of the total market, but other nations can more readily be compared against one another. For example, Australia and Brazil, who possess similar age spreads and have nearly identical annual expenditures on medical devices, despite Brazil having nearly five times the population and four times the reported instances of arrhythmia compared to Australia. This data indicates that a countries economic status should have the most influence on whether or not it should be pursued as a market. Market size and regulatory ease do not necessarily make a country an ideal location. One such example would be India, despite its loose regulatory structure and 1.2 billion population, accounts for less than a 0.25% of the worldwide medical device market, making it a smaller market than Singapore. In fact, large and highly regionalized countries such as Brazil, India, Russia, and China have only recently begun controlling or enforcing medical device registration in the past 20 to 30 years. This has hindered their ability to buy devices internationally and often indicates that the regulatory system in place is undergoing constant changes.

Easy Access

Many nations not initially considered or eliminated during the market review may also be worth pursuing after acquiring a CE Mark. These small nations often have a high per capita income, large annual expenditure on medical devices, and adhere to GHTF or European guidelines for clinical data. The timeline for approval in these countries is usually on the order of weeks to months, rather than years. Many of these nations rival smaller European nations in market size and incur similar registration costs.

Singapore possesses a regulatory process that follows GHTF guidelines. Singapore device registration requires a regulatory liaison and clinical data. Hong Kong follows a similar process, with a registration time of two months. Malaysia does not require registration of a medical device, so access to Malaysia is gained by appointing a local distributor and going through the necessary forms to import a product. Israel, which was initially eliminated due to insufficient market data, grants approval to any existing device with an FDA Letter of Approval or CE Mark. Additional nations which rely heavily on medical device imports and have relatively simple regulatory processes include Columbia, Costa Rica, and the Philippines.

Following International Standards

In the present day, the European CE Mark has become the international standard for medical device registration throughout most of the world. The CE Mark has gained this status as it is the easiest to obtain of the three major standards most often used internationally. This means that subsequent regulatory approvals should be sought out in the countries that most recognize the CE Mark first. In our analysis, the three countries which most adhere to the European guidelines are Australia, Canada, and South Korea in that order. It is highly likely that a device as novel as the Circumblator will be required to perform multi-locational clinical trials and we recommend attempting to use trial cites in Australia and Canada when seeking a CE Mark if at all possible. Gaining access to South Korea is theoretically as easy as gaining access to Canada with a CE Mark but language and cultural barriers must be considered as well. Based on this, we recommend that approval in Australia, Canada, and South Korea be pursued either concurrently with European approval or immediately following CE Certification. Afterward, approval in Brazil and India may be worth considering as they represent some of the largest remaining markets but pose difficult distribution problems. Based on the need for type testing, distribution

issues, and bad international reputations we cannot recommend pursuing regulatory approval in the Russian Federation or Peoples Republic of China.

Discussion

Our initial analysis favoring European CE Marking over alternative major approval routes was not surprising. The CE Mark is designed to get products to market safely in as short a time as possible and must be lose enough to work within the frameworks of the regulatory processes of its 30 member nations. The US and Japan place a higher importance on quality control and (theoretically) safety when compared to the free trade-based approach of the CE Mark. Initially, we knew that Automated Medical Instruments would be pursuing European approval first and the reasons became increasingly clear when compared to the other two regional powers.

Regional influence also appears to play a larger role in international medical device markets. There is no international standard, the UN has not attempted to outline one, and the Global Harmonization Task Force is not an official body recognized by any government agency. The GHTF actually divides their guidelines along geographic regions (Europe, South East Asia, and the Americas) which hint that regional hegemonies have a larger influence over the regulatory process in a small nation than any notion of an international standard. Certainly this is true in many Latin American nations, which are more likely to have a system based on the FDA registration process. This could include the actual application process itself, using unique quality management standards instead of ISO 13485, or manifest itself in the form of random site inspections, reliance on testing, etc. The CE Mark is only applicable to countries lying within the EFTA, but many EU member-candidates have adopted guidelines that better follow CE directives. Many nations within the CEFTA (Macedonia, Montenegro, Serbia) may effectively be considered countries in which a CE Mark is a sufficient mark of quality to pursue registration. South East Asia appears to be the least reliant on any one nation from which regulatory processes are based. In fact, many South East Asian nations are turning to the European model to more readily gain access to new technologies as they hit the market. South Korea leads as having already adopted many CE directives, but a host of smaller nations, particularly those where medical tourism is popular, have streamlined registrations that accept approvals from most other countries.

While no true international standard exists, countries are increasingly gravitating to a more standardized regulatory approach. Most often this results in using the CE Mark as a

guideline. Countries which did not regulate or enforce medical device guidelines until recently are frequently reviewing the registration process and new iterations increasingly resemble an existing major standard. India's new proposed device classifications greatly resemble Europe's. Countries that still possess minor testing requirements can often have that testing done through a notified body (such as Brazil's INMETRO Certification or South Korea's type testing).

Overall, access to a majority of markets cannot be done at once. The US and Japan comprise over 50% of all medical device purchases and each requires their own lengthy approval process regardless of the status of the device elsewhere. Economic status of a nation is the largest indicator of market size, with wealthy nations investing orders of magnitude more on medical devices per capita than poorer nations. This makes the path after acquiring a CE Mark direct. Approval should be sought in Australia and Canada either concurrently with European approval or immediately following it. From there, South Korea is the largest remaining market with a CE compliant regulatory process. Large and relatively poor nations pose distribution problems and have proven to be relatively small markets despite their population or size, for this reason we cannot recommend initially pursuing approval in countries like India and Brazil. Small wealthy nations make up a much larger share of the medical device market than initially suspected and for this reason we suggest looking into approval in Singapore, Hong Kong, and Israel following South Korean approval. Nearly all regulatory processes require some kind of post-market surveillance following approval and seeking approval in a country that requires additional testing often fulfills this requirement. Automated Medical Instruments can maintain continued CE Mark approval by conducting clinical trials in the US and submitting this information with the reapplication.

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Appendix

Glossary of Terms

Competent authority – Any governmental regulatory agency responsible for the registration of medical products within that country. Most often refers to device registration in European countries after obtaining a CE Mark.

EFTA – The European Free Trade Association is the area in which CE Mark directives apply. Includes the EU and neighboring Norway, Switzerland, Lichtenstein, and Iceland.

GHTF – The Global Harmonization Taskforce is a voluntary organization of medical professionals that promote am international unified approach to medical product registrations.

ISO – International organization for Standardization, international guidelines for nation's regulatory processes. ISO 13485 and 14155 are the most commonly adhered to guidelines.

ISO 13485:2003 Certification: A widely accepted certificate demonstrating compliance with the quality management systems outlined in ISO13485. Accepted in nearly every nation.

Notified body – Third party authorized to issue a CE Mark by the EU. May also be qualified to carry out other certifications (such as Brazilian INMETRO certification).

QMS - The organizational structure, procedures, processes and resources needed to ensure consistent performance in manufacturing. Proof of sufficient quality management systems is required in all regulatory process and is usually fulfilled by ISO standards.

Regulatory Liaison – A person or company responsible for handling regulatory and sometimes distribution of a device in a country you are not based in. Requirements, importance, and legal capabilities for a liaison vary greatly by country.

STED Documentation – Suggested standardized technical file documentation promoted by the GHTF. Not universally adopted but frequently accepted in place of technical documentation.

Selected Market Data

	Population	AFibCases	# EPs	# Cardiologists	# EPs Ablating	AF Ablations per Year	% Share of Medical Device Market	Most recent annual investment in medical devices (adjusted for inflation)
U.S.	314,519,000	2200000	2421		1489	100000	44.3668054571228	80130000000
EU Composite	503,500,000	2500000			899	43118	30.3198086463503	54760000000
Japan	127,520,000	2,083,677		10144			10.5753897944728	19100000000
Canada	34,938,400	350000	1232			1430	1.51488306166584	27360000000
South Korea	50,004,441	16945					2.20806064806588	36000000000
Australia	21,662,093	400000	27	752	6	1944	0.60019489723606	10840000000
Brazil	193,946,886	1500000		8000			0.66940556343015	12090000000
India	1,210,193,422	1205073	30	3500	20	15000	0.23254783841247	4200000000
Russia	143,200,000	9000			71	3727	0.58635276399716	10590000000
China	1,347,350,000	9000		no info	no info		8.85896527285613	160000000000
Israel	7,913,900				12	no info	0.28237951807228	5100000000
Switzerland	8,000,001	16945			21	1595		
Ireland	4,588,252				11	450		
Great Britain	62,262,000	46000	65	650	49	4654		
France	65,350,000	600000		6200	130	6488		
Germany	81,844,000	1000000	305	4000	200	15000		
Italy	59,464,644				170	no info		

Regulatory Costs and Timetables

Country	Certification Requirements	CE Marking accepted?	Avg to acceptance	Expected Pivotal Trial Size	Cost of Approval with Clinical Trials	Comments
U.S.	PMA Letter of Approval	no	5 - 11 years	500-1000	$5,000,000 - $10,000,000	does not recognize ISO 13485
EU	CE Certificate	n/a	3 years	200-300	$2,000,000 - $3,000,000	requires technical files/design dossiers similar to FDA PMA
Brazil	INMETRO electrical safety INVISA clinical trials	yes	6 months	200 - 300	$1,600,000 - $2,400,000	requires economic report, electrical certification
China	IMDRC Certificate	yes	6-9 months	100 - 200	$600,000-$1,200,0	requires in-country clinical trials as well as local representation
Canada	Medical Device License ISO:13485:2003 certificate	yes	6 months	400 - 600	$3,000,000 - $4,000,0000	QMS very similar to Brazil/Japan
India	Registration Certificate Form 41 Import License Certificate Form 10	yes	9 months	100 - 200	$500,000-$1,000,0	accepts US/EU/AUS/JAP approvals
Korea	Certificate of Product Approval KGMP Certificate	yes	6-8 months	150	$500,000-$1,000,0	
Japan	Pre-Market Approval Certificate	no	5 years	800 - 1000	$5,000,000 - $10,000,000	local distibutor given far more independence than normal
Australia	GMDN registration	yes	3 - 6 months	200 - 300	$2,000,000 - $3,000,000	requires national distributor
Russia	Registration Certificate GOST-R Certificate	no	3 - 6 months	200 - 300	$820,000 - 1,230,000	requires type testing

Historic and Country Specific European Information

Five Year Rise in Arrhythmia in European Nations 2007	2008	2009	2010	2011	
Great Britain	7300	12057	14005	14222	15078
France	18227	22139	26050	28800	31175
Germany	30202	39500	40000	42000	50000
Russia	9022	11200	13384	14048	16380
Ireland	1600	700	800	800	1000