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

A Major Qualifying Project Report

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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 to enter specific countries greatly depends on the size of the potential market and the costs and time needed for regulatory approval. 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. The paper will evaluate the regulatory pathways of ten select countries. This regulatory analysis, combined with a market analysis on these same countries by the other three members of the project, will form a basis from which we can create a suggested order of entry.

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Background

Atrial Fibrillation (AF) is the most common form of arrhythmia, accounting for approximately 40% of all cases of arrhythmia. Arrhythmia is defined as an irregular heart rhythm caused by electrical imbalances in the heart. In atrial fibrillation, these irregularities are caused by electrical signals being issued too fast or randomly by the sinoatrial node, causing the heart to quiver rather than fully contract. Atrial Fibrillation is more difficult to treat than other kinds of arrhythmias and there currently exists only three options for AF patients. First, the patient may opt for medications, which include antiarrhythmic or rate control drugs along with anticoagulants, such as warfarin, for the remainder of one's life. Surgical ablation may be performed by a cardiac surgeon, operating outside the heart on the pericardium. Finally, there are catheter ablations which include the CircumBlator™. Catheter ablations were first used in the late eighties and subsequent incremental improvements have done little to change the success rate of ablations. Current catheter ablation operations have a wildly varying success rate, between 50-80%, and are highly dependent on the skill of the electro-physiologist performing them.

AblaCor's CircumBlator™ claims to fix this problem by removing significant chance of surgeon error from the procedure. The CircumBlator™ holds itself within the pulmonary vein using a stent-like device, called an anchor. The ablation is then performed using a circumferential radiofrequency ablator with an electrode array around the vein. This process improves upon existing methods by using the anchor to hold the ablator electrodes in place, which provides improved contact between the electrode and target tissue, freeing the surgeon of the task of ablating several individual points by hand. This reduces procedure time, making it more attractive economically, will reduce the number of images required and subsequent radiation exposure and improve the quality of the lesion created by the ablation. The result should be a simpler to perform operation, attracting more physicians to perform it and less reliance on highly skilled physicians to achieve a higher rate of success.

Accessing a particular market with a new medical device can be very costly. Novel devices must have substantial clinical data to demonstrate their safety and efficacy which is difficult to conduct under the budget of a startup medical company. The goal of this paper is to

minimize the cost of entry by finding the most cost-effective regulatory pathways to the largest individual markets. This will be done by comparing the approval processes, forms, fees, tests, and personnel needed to access a particular country. How likely a certain country is to accept international clinical data is a key factor in most major markets and certain countries may outright refuse approval unless clinical tests are conducted within their own boarders.

By understanding the requisite regulatory steps needed to sell a new medical device in a certain country, the cost-benefit of entering that particular country can then be determined based on the size of the market. This paper is meant to supplement a market review of the ten select countries initially chosen for analysis. As the regulatory steps are a cost to entering a certain country, fully determining the benefit of a given market relies on understanding numerous factors that surround the device. Markets are affected by AF arrhythmia demographics, wealth of a nation, number of surgeons capable of performing the operation, reimbursement policies, and many other factors. This paper will routinely use a nation's wealth (defined by annual investments in medical devices by that nation) as a rough estimate of a given nation's market size. A forthcoming full and detailed review of the markets will use this paper as a regulatory basis and combined they will outline our suggestions for the best order of entry.

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 United States, European Union, 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.

Given this above information, determining the optimal order of entry becomes dependent on the knowledge of several diverse types of data. Understanding and organizing this information in such a way that it becomes clear which countries are worth pursuing requires a variety of skills taught in the Management major. With the knowledge gained through classes like Business Law and Achieving Strategic Effectiveness we can define regulatory pathways and estimate market sizes of a given country. This data can then be collected and evaluated using techniques found in data analysis and our knowledge of entrepreneurial startups and their limitations.

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 afterward registering a device in an individual European nation is quick and economical. Europe, like most other nations uses a three tier device classification system based on complexity of the device and the risk associated with it. Class I devices are simple tools such as elastic bandages, sterile gloves, or medical grade scalpels. Class II devices are riskier and subject to more device specific controls, these include power wheelchairs and infusion pumps. Class III devices are defined as any device in which the guidelines for class I and II are deemed insufficient to demonstrate safety and require a pre-market approval, this is the class the CircumBlator™ belongs to. Due to the rigorous requirements for class III device approval, device registration may not be required in certain European countries (as yearly approval from a Notified Body is considered proof of device safety).

To gain approval for a class III device the applicant 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 are based on ISO 13485 requirements (USA and Brazil have similar requirements that predate ISO 13485). 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 (Bouchez). Post-market surveillance must also be conducted to ensure successful yearly audits.

Regulatory Approval Process in the United States

Regulatory approval in the United States 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 United States remains one of the most sought after

markets due to its status as the single largest buyer of medical devices in the world. 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 CircumBlato^{rTM} 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 United States 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 (sharps.org). 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 United States can vary between two to five years.

Table 1

Recent Device Approvals or Rejections in the US and EU	US Trial Size	EU Trial Size	Status
Sharp's AF catheter ablator	210	N/A	Rejected
Distal Protection system for cortorary artery	800	22	Both Approved
Left atrial appendage exclusion for prevention of stroke (in AF patients)	700	250	EU Approved
MACPAF Cryo AF Ablator	N/A	108	Rejected
Source: clinicaltrials.gov			

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 worldwide, behind the United States, 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 (Nagasaka). Combined with the costs of maintaining Japanese personnel, the costs of running clinical trials in Japan is comparable to clinical trials in the United States. 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 rights 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 clear 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 United States and then Japan is also recommended, as they represent a combined 54% of medical device purchases worldwide.

Table 2

Annual Investment in Medical Devices by Country (US Dollars adjusted for inflation) From Selected Market Data	
U.S.	80,130,000,000
EU Composite	54,760,000,000
Japan	19,100,000,000
Canada	2,736,000,000
South Korea	3,600,000,000
Australia	1,084,000,000
Brazil	1,209,000,000
India	420,000,000
Russia	1,059,000,000
China	16,000,000,000

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) and European CE guidelines. 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 (pharmout.com.au).

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 (TGA.gov).

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 on the Brazilian Market. All electrical devices must obtain INMETRO Certification for electrical safety, although this test 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 (Flood). 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. All forms sent in during the approval process must follow the international STED format that Canada as adopted (Wisdahl). 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 (Sun). 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 (Tariah).

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 electro-physiologist). The agent must also hold a valid Indian wholesale license, called Forms 20B and 21B (Mukherji). 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 (CDSCO.gov).

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 heavily 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 impact of regulatory approval is the designation of the distributor before entering the market, as 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 (ita.doc.gov). 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 possesses little overlap with other European approvals. 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 (Ludmila). 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 (Makstrong).

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 possess similar age spreads and have nearly identical annual expenditures on medical devices, but Brazil has nearly five times the population and four times the reported instances of arrhythmia when compared to Australia (see Appendix B). 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 (Koster).

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. 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 and is a fairly large buyer of medical devices. Additional nations which rely heavily on medical device imports and have relatively simple regulatory processes include Columbia, Costa Rica, and the Philippines (emergogroup.com).

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^{TM} 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 loose enough to work within the frameworks of the regulatory processes of its 30 member nations. The United States 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 AblaCor would be pursuing European approval first and the reasons became increasingly clear when compared to the other two regional powers. The European pathway to initial market access for U.S. medical device startups is the clear best choice.

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, and 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, for example, rather than China's or Japan's four tier systems. 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).

Conclusions

When comparing regulatory processes to one another, a large number of factors and a large number of countries must be considered in order to get an accurate representation. No effort to harmonize regulatory standards globally has ever been successful largely because national authorities always hold the final say on device approval in any given country. The European model for device regulation, while only officially applicable in the EFTA, provides the closest thing to an international model for countries which desire access to the newest medical technologies immediately. Although nearly half of all clinical trials are conducted in the US, the majority are conducted by major US companies, which possess the large amount of capital and long-term stability needed to receive an FDA Letter of Approval. The directives of the CE Mark emphasize the promotion of trade, by limiting safety concerns to proof of parity and proof of safety in man, rather than requiring devices to be substantial improvements over existing ones. These factors combined with fewer bureaucratic delays then the FDA approval process makes CE Marking the closest thing to an international guideline for device approval.

Canada, Australia, and South Korea were chosen as follow ups to CE Marking as they most closely follow the directives necessary for European approval. All three accept STED documentation, clinical data obtained during CE Marking, and recognize Notified Bodies as guaranteers of quality. Their additional requirements are minimal and can be fulfilled through the use of a European Notified Body (Canada-specific ISO 13485 certification and Korean type testing may both the done through a Notified Body). This makes the realistic costs of entering these three countries minimal assuming prior EU approval. The real cost of entering any one of

these three markets with a CE Mark in hand is equivalent to regulatory fees, distributor fees (through an appointed liaison), and a waiting period less than six months. Canada and Australia are ranked slightly ahead of South Korea as they have no type testing requirement and easier requirements for a distributor/regulatory liaison.

US approval is not initially recommended primarily because of the prohibitive costs and time associated with approval. Despite purchasing nearly half of all medical devices and conducting nearly half of all clinical trials globally, the United States actually lags three to five years behind other developed nations in seeing new medical technologies. Large, established medical corporations can afford to pursue US and EU clinical trials concurrently; meaning new technologies developed in the US may actually reach European markets first. Even with these drawbacks, continued success and mainstream acceptance of the CircumBlator™ will be contingent on pursuing FDA approval at some point. Japanese approval faces similar problems; but with similar expected cost as US clinical trials, two to three years needed for approval, and only a quarter the size of the US market, approval should only be sought in Japan after everything else.

With this information it makes sense to pursue approval in smaller nations that accept CE Marking rather than begin US approval immediately following EU approval. The cost to access small but wealthy nations that adhere to some level of CE directives can be as little as thousands of dollars. Large emerging economic powers are slightly more difficult to access and at present offer a theoretical return equivalent to Australia or Singapore. For this reason it does not make sense to pursue approval in India or Brazil until all small wealthy nations have been exhausted. India and Brazil have more potential for growth than any of the other observed countries, but due to their simplistic and fast regulatory processes, actual approval can be acquired easily at a later date when these markets have grown. Other rising economic powers, Russia and China, are not recommended for different reasons. Russia relies entirely on device testing, giving their approval process a lengthy and expensive step that only accesses a relatively minor market. China is the largest single market to be eliminated from consideration for purely regulatory reasons. The approval process in China takes an unknown length of time and is fraught with potential IP complications.

Overall, access to a majority of markets cannot be done at once. The United States 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 but growing markets and economies make India and Brazil good candidates for device registration. 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. AblaCor can maintain continued CE Mark approval by conducting clinical trials in the United States, Japan, or even Russia 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 European Union 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 when referring to medical devices.

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	10000	44.3668054571226	80130000000
EU Composite	503,500,000	2500000			899	43118	30.319808646350	54760000000
Japan	127,520,000	2,083,677		10144			10.575389794472	19100000000
Canada	34,938,400	350000	1232			1430	1.5148830616584	2736000000
South Korea	50,004,441	16945					2.2080606480658	3600000000
Australia	21,662,093	400000	27	752	6	1944	0.6001948972360	1084000000
Brazil	193,946,886	1500000		8000			0.6694055634301	1209000000
India	1,210,193,422	1205073	30	3500	20	15000	0.2325478384124	420000000
Russia	143,200,000	9000			71	3727	0.5863527639971	1059000000
China	1,347,350,000	9000			no info	no info	8.8589652728561	16000000000
Israel	7,913,900				12	no info	0.2823795180722	510000000
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		

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

Number of Atrial Fibrillation Ablations and Performing EPs in Europe in 2012 by Country

	Minimum Ablating EPs	# Afib Ablations Last Year
Austria	18	510
Belgium	38	1898
Bulgaria	1	3
Croatia	5	46
Cyprus	2	3
Czech rep	20	1590
Denmark	10	1074
Estonia	2	115
Finland	7	476
France	130	6488
Germany	200	15000
Greece	23	340
Hungary	10	606
Iceland	1	15
Ireland	11	450
Italy	170	
Latvia	2	69
Lithuania	3	66
Luxemburg	1	27
Malta	1	4
Netherlands	15	2147
Norway	4	1147
Poland	47	1176
Portugal	18	467
Romania	14	67
Slovakia	4	94
Slovenia	2	118
Spain	60	1445
Sweden	10	1428
Switzerland	21	1595
United Kingdom	49	4654
Total	**899**	**43118**