Harvard Apparatus Regenerative Technology, Inc.
Form 10-K
March 30, 2016

UNITED STATES

SECURITIES AND EXCHANGE COMMISSION

Washington, D.C. 20549

FORM 10-K

x **Annual report pursuant to Section 13 or 15(d) of the Securities Exchange Act of 1934**

For the fiscal year ended December 31, 2015

or

¨ **Transition report pursuant to Section 13 or 15(d) of the Securities Exchange Act of 1934**

For the transition period from to

Commission File Number 001-35853

HARVARD APPARATUS REGENERATIVE TECHNOLOGY, INC.

(Exact Name of Registrant as Specified in Its Charter)

Delaware	**45-5210462**
(State or other jurisdiction of Incorporation or organization)	(I.R.S. Employer Identification No.)

84 October Hill Road, Suite 11, Holliston, Massachusetts 01746

(Address of Principal Executive Offices, including zip code)

(774)233-7300

(Registrant's telephone number, including area code)

Securities registered pursuant to Section 12(b) of the Act:

Title of each class	**Name of each exchange on which registered**
Common Stock, $0.01 par value	**The NASDAQ Capital Market**
Preferred Stock Purchase Rights	

Securities registered pursuant to Section 12(g) of the Act:

None

Indicate by check mark if the registrant is a well-known seasoned issuer, as defined in Rule 405 of the Securities Act. YES ¨ NO x

Indicate by check mark if the registrant is not required to file reports pursuant to Section 13 or Section 15(d) of the Act. YES ¨ NO x

Indicate by check mark whether the registrant (1) has filed all reports required to be filed by Section 13 or 15(d) of the Securities Exchange Act of 1934 during the preceding 12 months (or for such shorter period that the registrant was required to file such reports), and (2) has been subject to such filing requirements for the past 90 days. YES x NO ¨

Indicate by check mark whether the registrant has submitted electronically and posted on its corporate Web site, if any, every Interactive Data File required to be submitted and posted pursuant to Rule 405 of Regulation S-T during the preceding 12 months (or for such shorter period that the registrant was required to submit and post such files). YES x NO ¨

Indicate by check mark if disclosure of delinquent filers pursuant to Item 405 of Regulation S-K is not contained herein, and will not be contained, to the best of registrant's knowledge, in definitive proxy or information statements

incorporated by reference in Part III of this Form 10-K or any amendment to this Form 10-K. ¨

Indicate by check mark whether the registrant is a large accelerated filer, an accelerated filer, a non-accelerated filer, or a smaller reporting company. See the definitions of “large accelerated filer,” “accelerated filer” and “smaller reporting company” in Rule 12b-2 of the Exchange Act. (Check one):

Large accelerated filer ¨	Accelerated filer ¨
Non-accelerated filer ¨ (Do not check if a smaller reporting company)	Smaller reporting company x

Indicate by check mark whether the registrant is a shell company (as defined in Rule 12b-2 of the Exchange Act. YES ¨ NO x

The aggregate market value of the voting and non-voting common equity held by non-affiliates of the registrant, computed by reference to the price at which the common equity was last sold, or the average bid and asked price of such common equity, as of June 30, 2015 was approximately $10,356,769. Shares of the registrant’s common stock held by each officer and director and each person known to the registrant to own 10% or more of the outstanding voting power of the registrant have been excluded in that such persons may be deemed affiliates. This determination of affiliate status is not a determination for other purposes.

At March 21, 2016, there were 14,110,540 shares of the registrant’s common stock issued and outstanding.

DOCUMENTS INCORPORATED BY REFERENCE

Portions of the Company’s definitive Proxy Statement in connection with the 2016 Annual Meeting of Stockholders (the “Proxy Statement”), to be filed within 120 days after the end of the Registrant’s fiscal year, are incorporated by reference into Part III of this Form 10-K. Except with respect to information specifically incorporated by reference in this Form 10-K, the Proxy Statement is not deemed to be filed as part hereof.

HARVARD APPARATUS REGENERATIVE TECHNOLOGY, INC.

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For the Year Ended December 31, 2015

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This Annual Report on Form 10-K contains statements that are not statements of historical fact and are forward-looking statements within the meaning of Section 27A of the Securities Act of 1933 and Section 21E of the Securities Exchange Act of 1934 (the "Exchange Act"), each as amended. The forward-looking statements are principally, but not exclusively, contained in "Item 1: Business" and "Item 7: Management's Discussion and Analysis of Financial Condition and Results of Operations." These statements involve known and unknown risks, uncertainties and other factors that may cause our actual results, performance or achievements to be materially different from any future results, performance or achievements expressed or implied by the forward-looking statements. Forward-looking statements include, but are not limited to, statements about management's confidence or expectations and our plans, objectives, expectations and intentions that are not historical facts. In some cases, you can identify forward-looking statements by terms such as "may," "will," "should," "could," "would," "seek," "expect," "plans," "aim," "anticipates," "believes," "estimates," "projects," "predicts," "intends," "think," "continue," "potential," "is likely," "permit," "objectives," "optimistic," "new," "goal," "target," "strategy" and similar expressions intended to identify forward-looking statements. These statements reflect our current views with respect to future events and are based on assumptions and subject to risks and uncertainties. Given these uncertainties, you should not place undue reliance on these forward-looking statements. We discuss many of these risks in detail under the heading "Item 1A. Risk Factors" beginning on page 19 of this Annual Report on Form 10-K. You should carefully review all of these factors, as well as other risks described in our public filings, and you should be aware that there may be other factors, including factors of which we are not currently aware, that could cause these differences. Also, these forward-looking statements represent our estimates and assumptions only as of the date of this report. We may not update these forward-looking statements, even though our situation may change in the future, unless we have obligations under the federal securities laws to update and disclose material developments related to previously disclosed information. Harvard Apparatus Regenerative Technology, Inc. is referred to herein as "we," "our," "us," and "the Company."

PART I

Item 1. ***Business.***

BUSINESS

We are a biotechnology company developing bioengineered organ implants based on our novel Cellframe™ technology.

Our Cellframe technology is comprised of a biocompatible scaffold that is seeded with the recipient's own cells. We believe that this technology may prove to be effective for treating patients across a number of life-threatening medical indications who currently have unmet medical needs. We are currently developing our Cellframe technology to treat life-threatening conditions of the esophagus, trachea or bronchus with the objective of dramatically improving the treatment paradigm for those patients.

We believe that our Cellframe technology may provide surgeons with a new treatment paradigm to address damage to the esophagus, bronchi, and trachea due to cancer, infection, trauma or congenital abnormalities. Organ implants being developed based on our Cellframe technology for those indications are called Cellspan™. We announced key preliminary preclinical results of large-animal studies for the esophagus, trachea and bronchus in November 2015. While the studies pertaining to the trachea and bronchus showed promising results for restoring organ function, the most promising results were shown in the esophagus study. As such, our Cellspan esophageal implant will be our lead development product candidate.

A portion of all patients diagnosed with esophageal cancer are treated via a surgical procedure known as an esophagectomy. The current standard of care for an esophagectomy requires a complex surgical procedure that involves moving the patient's stomach or a portion of their colon into the chest to replace the portion of esophagus resected by the removal of the tumor. These current procedures have high rates of complications, and can lead to a severely diminished quality of life and require costly ongoing care. Our Cellspan esophageal implant aims to simplify the procedure, reduce complications, result in a better quality of life and reduce the overall cost of patient care to the healthcare system.

Our product candidates are currently in development and have not yet received regulatory approval for sale anywhere in the world.

The Office of Combination Products of the U.S. Food and Drug Administration, or FDA, has confirmed for us that the FDA intends to regulate our cell-seeded scaffold implant as a combination biologic-device product under the primary jurisdiction of the Center for Biologics Evaluation and Research, or CBER, and will require a BLA pathway for market approval. The initial indication for which we intend to seek FDA approval will be to restore the function of the esophagus after a portion of the esophagus has been surgically removed to treat cancer, damage caused by injury or infection or congenital abnormalities. While this FDA confirmation was based on our previous-generation tracheal product candidate, we expect that our Cellspan esophageal implant would similarly be regulated as a combination product under the primary jurisdiction of the CBER. We also intend to request expedited review from the FDA for the Cellspan esophageal implant product. Receipt of the FDA's expedited review would reduce the overall time through the regulatory process.

We plan to apply for orphan drug designation from the FDA for our Cellspan esophageal implant in the U.S. and Europe. Orphan drug status provides market exclusivity in the U.S. for seven years from the date of the product's approval for marketing. This exclusivity is in addition to any exclusivity we may obtain due to our patents. Additionally, orphan designation provides a waiver of the BLA application fee. Orphan drug status in Europe provides market exclusivity there for ten years from the date of the product's approval for marketing.

We believe that our Cellframe technology may prove to be effective for treating patients across several life-threatening medical indications who currently have unmet medical needs. We are now advancing the development of our Cellframe technology to address life-threatening conditions of three organs, including the esophagus, the trachea and the bronchus. We are currently developing our lead product candidate, our Cellspan esophageal implant, in large-animal studies with Mayo Clinic to gain third-party confirmation of our esophageal product's potential and to develop compelling data in support of our goal of filing an Investigational New Drug (IND) application with the FDA in late 2016, seeking to initiate clinical trials in humans. We currently anticipate providing an update on our ongoing large-animal research collaboration with Mayo Clinic mid-second quarter 2016.

Our Mission and Our Strategy

Our mission is to be the leading developer and supplier of bioengineered organ implants for restoring organ function for patients with life-threatening conditions of the esophagus, the bronchus and the trachea. Our business strategy to accomplish this mission includes:

Targeting life-threatening medical conditions. We are focused on creating products to help physicians treat life-threatening conditions like esophageal cancer, central lung cancer and damage to the trachea caused by cancer, trauma or infection. We are also developing products for the treatment of congenital abnormalities of the esophagus and the airways. We are not targeting less severe conditions that have reasonable existing treatment options. Solutions for life-threatening medical conditions present a favorable therapeutic index, or risk/benefit relationship, by providing the opportunity of a significant medical benefit for patients who have poor or no treatment alternatives. We believe that product candidates targeting life-threatening medical conditions may be eligible for review and approval by regulatory authorities under established expedited review programs, which may result in savings of time in the regulatory approval process. Also, we believe that products targeting life-threatening medical conditions may be more likely to receive favorable reimbursement compared with treatments for less critical medical conditions.

Developing products that have a relatively short time to market. Since the number of patients diagnosed with esophageal cancer in the U.S. each year is relatively small, we expect the number of patients that we would likely need to enroll in a clinical trial will also be relatively small. A small number of patients implies a relatively fast enrollment time and a less expensive clinical development program. Therefore, we expect to be able to conduct a clinical trial in a relatively short period of time compared to clinical trials in indications with larger patient populations. We intend to work closely with regulatory agencies and clinical experts to design and size the clinical studies appropriately based on the specific conditions our products are intended to treat.

Using our Cellframe technology as a platform to address multiple organs. We believe that preclinical data we have produced to date may suggest that our Cellframe technology is a novel and innovative approach to restoring organ function that may provide an ability to develop products that would address life-threatening conditions impacting organs like the esophagus, bronchi and trachea, and perhaps lower portions of the gastrointestinal (GI) tract. We believe that our Cellframe technology may allow physicians to treat certain life-threatening conditions in ways not currently possible, and in some combination, to save patients' lives, avoid or reduce complications experienced in the current standard of care, and improve the patients' quality of life, while at the same time reducing the overall cost of patient care to the healthcare system.

Supplying the finished organ implant to the surgeon. Our technology includes our proprietary organ bioreactor, as well as our proprietary biocompatible scaffold that is seeded with the patient's own cells. We believe there is considerable value in supplying the final cell-seeded scaffold implant to the surgeon so that the hospital and surgeon

may focus solely on performing the implantation.

Collaborating with leading medical and research institutions. We have and will continue to collaborate with leading medical and research institutions. We have a co-development agreement with Mayo Clinic for regenerative medicine organ implant products for the esophagus and airways, and we are currently conducting large-animal studies with Mayo Clinic to develop our Cellframe technology. We are also collaborating with Connecticut Children's Medical Center on a co-development project to research regenerative medicine-based solutions to esophageal atresia. We believe the use of our product candidates by leading surgeons and institutions will increase the likelihood that other surgeons and institutions will use our products.

Our Technology

Our Cellframe technology is comprised of our proprietary bioengineered organ scaffold seeded with the patient's own stem cells in our proprietary organ bioreactor prior to implantation. We believe that our Cellframe technology combines a highly-engineered, biocompatible scaffold and a robust population of cells that, by tapping into the stem cell niche of the surrounding native tissue after implantation, may potentially enable a tubular organ to remodel or regenerate tissue to close the gap created by a surgical resection of a portion of that organ. This unique combination of technologies, developed through our extensive testing performed during the last two years, may potentially provide solutions to life-threatening conditions for patients with unmet medical needs.

We believe that our new technology is unique, in that its mode of action appears to be different from other tissue engineering organ scaffold products developed previously, of which we are aware. Prior to our development of the Cellframe technology, our approach attempted to implant an organ scaffold that would be incorporated into the patient's body by the surrounding native tissue growing into the scaffold. To our knowledge, all previous research and development efforts by other investigators were based on that same concept. Our Cellframe technology appears to work very differently. We believe that the unique combination of our highly-engineered organ scaffold with a population of the patient's own mesenchymal stem cells enables an organ to develop new native tissue around our scaffold, but not into it, so the scaffold acts as a sort of frame or staging for the new tissue. As a result, our scaffold is not incorporated into the body. Instead, it is retrieved from the body via an endoscopic or bronchoscopic procedure, not surgically, after sufficient tissue remodeling and regeneration has occurred to restore the organ's integrity and function.

A Cellframe technology-based organ implant includes two key components: a biocompatible synthetic scaffold and the patient's own stem cells.

Biocompatible Scaffold Component

Our proprietary biocompatible scaffold component of the Cellspan esophageal implant is constructed primarily of polyurethane (PU; a plastic polymer). This material was chosen based on extensive testing of various materials. The scaffold is made using a manufacturing process known as electrospinning. The combination of the electrospinning process, which provides accurate control over the desired microstructure of the scaffold fabric, with the PU results in a scaffold that we believe has favorable biocompatibility characteristics.

The Patient's Cells

Based on current preclinical development efforts, the cells we seed onto the scaffold are obtained from the patient's adipose tissue (abdominal fat). This fat tissue is obtained in a standard biopsy before the implant surgery. Mesenchymal stem cells are extracted and isolated from the adipose tissue biopsy. The isolated cells are then expanded, or grown, for a short period prior to surgery in order to derive a sufficient cell population to be seeded on the scaffold. The cells are then seeded on the scaffold in our proprietary organ bioreactor and incubated there before the implant surgery.

We believe the Cellspan esophageal implant has the potential to provide a major advance over the current therapeutic options for treating esophageal cancer, damage from infection or trauma and congenital abnormalities. We believe our Cellframe technology has the potential to overcome the major challenges in restoring organ function for a damaged esophagus. With our Cellspan esophageal implant we are developing a surgical procedure that has the objective of reconstituting the continuity of the patient's esophagus without having to relocate another organ in its place. In addition, by reducing or eliminating complications that occur in the current standard of care, we expect to reduce the costs of addressing and treating those additional complications. Because these substantial costs can be reduced or even eliminated with our technology, we believe our products, if successfully developed, can help save lives, improve the quality of life for patients and reduce overall healthcare costs.

Further, human embryonic stem cells are not part of any of our implant product candidates. This eliminates both the medical risks and ethical controversy associated with regenerative medicine approaches that use human embryonic stem cells.

Unmet Patient Needs and Cellspan Implant Solutions

Esophageal Cancer

There are approximately 456,000 new diagnoses of esophageal cancer globally each year. According to the American Cancer Society, there are approximately 17,000 new diagnoses of esophageal cancer in the U.S. each year, and there are more than 15,000 deaths from esophageal cancer each year. Esophageal cancer is very deadly - the five-year survival rate for people with esophageal cancer is 18% in the U.S. Approximately 5,000 esophagectomy surgeries occur in the U.S. annually to treat esophageal cancer, and approximately 10,000 esophagectomies occur in Europe annually. We believe that our Cellspan esophageal implant, if approved, has the potential to provide a major advance over the current esophagectomy procedures for addressing esophageal cancer, which have high complication and morbidity rates.

The current standard of care for the esophagectomy requires either (A) a gastric pull-up, where the stomach is cut and sutured into a tubular shape, then pulled up through the diaphragm to replace a portion of the esophagus resected by the removal of the cancerous tumor; or (B) a colon interposition, where a portion of the colon is resected and used to replace the portion of the esophagus resected by the removal of the cancerous tumor. Esophagectomies have 90-day mortality rates of up to 19%. Serious complications, such as leakage at the anastomoses, which can lead to infections and sepsis, and pulmonary complications, such as impaired pulmonary function or pneumonia, occur in up to 30% of esophagectomy cases. Other complications from esophagectomies, such as a narrowing of the esophagus post-surgery, gastroesophageal reflux and dumping syndrome (repetitive nausea, dizziness and vomiting) can also pose significant quality of life issues for patients.

We believe that the Cellspan esophageal implant has the potential to provide physicians a new, simpler procedure to restore organ function while significantly reducing complication and morbidity rates compared with the current standard of care, and without creating significant quality of life issues for patients.

Esophageal Atresia

Esophageal Atresia (EA) is a rare congenital abnormality in which a baby is born without part of the esophagus. About 1 in 4,000 babies in the U.S. is born with EA. In some cases, the two sections can be connected surgically. However, in cases where the gap is too great for a simple surgical reconnection, the current standard of care is a gastric pull-up, a colon interposition, or a procedure known as the Foker process. In the Foker process, traction devices are surgically attached to the two ends of the esophagus. Traction is then applied, usually for several weeks during which time the baby remains in an Intensive Care Unit, to stimulate the ends of the esophagus to grow and

narrow the gap. If the Foker process is successful in narrowing the gap sufficiently, a second surgery is necessary to connect the two ends of the esophagus. In addition to the Foker process being complex, it is also a very expensive procedure, because the baby will normally be several months in hospital for the process.

We believe that a pediatric Cellspan esophageal implant may provide pediatric surgeons with a better procedure to treat EA that would result in a connected esophagus with higher success rates, lower complications and lower overall costs to the healthcare system.

Central Lung Cancer

Lung cancer is the most common form of cancer and the most common cause of death from cancer worldwide. There are more than 450,000 new lung cancer diagnoses annually in the U.S. and Europe. In approximately 25% of all lung cancer cases, the cancerous tumor resides only in a bronchus and not in the lobes of the lungs, and is known as central lung cancer. Approximately 33,000 central lung cancer cases diagnosed in the U.S. and Europe are Stage I and II and are considered eligible for surgical resection, often with adjuvant chemotherapy and radiation. Approximately 5,000 of those patients are treated via pneumonectomy, a surgical procedure involving the resection of the cancer tumor, the whole bronchus below the tumor and the entire lung to which it is connected. It is a complex surgery and results in a 50% reduction in the patient's respiratory capacity. The procedure has reported rates of post-surgical (in hospital) mortality of 8% to 15%. Complication rates associated with pneumonectomy are reported as high as 50%, and include post-operative pneumonia, supraventricular arrhythmias and anastomotic leakage, placing patients at significant mortality risk post-discharge.

We believe that a Cellspan bronchial implant, once developed and approved for marketing, has the potential to provide physicians a treatment alternative superior to the sleeve pneumonectomy to address central lung cancer, a simpler procedure to restore organ function of the bronchus without sacrificing one of the patient's lungs, resulting in fewer post-surgery complications, improved mortality rates and improved quality of life for the patient.

Life-threatening conditions of the Trachea

There are approximately 8,000 patients per year in the U.S. and Europe who suffer from a condition of the trachea that put the patient at high risk of death. These conditions can be due to tracheal trauma, tracheal stenosis or trachea cancer. There are approximately 40,000 tracheal trauma patients diagnosed each year in the U.S. Of those, approximately 1,000 are severe enough to need surgical resection procedures. Tracheal stenosis is as a rare complication from tracheostomies, but have a devastating impact on respiratory function for patients. Approximately 2,000 patients are diagnosed with stenosis from tracheostomy in the U.S. each year. Trachea cancer is a very rare but extremely deadly cancer. Trachea cancer patients in the U.S. have a median survival of 10 months from diagnosis and a 5-year survival of only 27%. There were approximately 200 cases of primary trachea cancer diagnosed in the U.S. in 2013. Based on these facts, we estimate that there are approximately 8,000 patients in the U.S. and Europe with conditions of the trachea that put them at high risk of death, but for whom there is currently no clinically effective tracheal implant or replacement method currently available.

We believe that a Cellspan tracheal implant may potentially provide physicians a treatment to re-establish the structural integrity and function of a damaged or diseased trachea to address life-threatening conditions due tracheal trauma, stenosis or cancer.

Our History

We were incorporated under the laws of the State of Delaware on May 3, 2012 by Harvard Bioscience, Inc. ("Harvard Bioscience") to provide a means for separating its regenerative medicine business from its other businesses. Harvard Bioscience has been designing and manufacturing devices for life science researchers for over 100 years. Harvard Bioscience first explored the regenerative medicine market in 2007 and began focusing on providing devices to scientists involved in regenerative medicine research in 2008. Since early 2009, Harvard Bioscience's regenerative medicine business initiative operated as a division of Harvard Bioscience. During this first phase of development of our company, the business was built on the basis of Harvard Bioscience's expertise in physiology and applying that know-how to developing new organ bioreactors and other equipment to be used in regenerative medicine researchers' laboratories.

Harvard Bioscience decided to separate its regenerative medicine business into our company, a separate corporate entity (the "Separation"), and it spun off its interest in our business to its stockholders in November 2013. Since the Separation we have been a separately-traded public company and Harvard Bioscience has not been a stockholder of our common stock or controlled our operations. Following the Separation, we continued to innovate our bioreactors based on our physiology expertise, we developed our materials science capabilities and we investigated and developed a synthetic tracheal scaffold. In April 2014, our first Chief Medical Officer, Saverio LaFrancesca, M.D., joined our company. By that time we had built and staffed cell biology laboratories at our Holliston facility, to give ourselves the ability to perform and control our scientific investigation and developments internally. At that point, we began the second phase of our company's development.

In mid-2014, under Dr. LaFrancesca's leadership, we increased the pace of our scientifically-based internal analysis and development of our first-generation tracheal implant product, the HART-Trachea. From large-animal studies conducted thereafter we found that the product elicited an unfavorable inflammatory response after implantation, which required additional development and testing. These requirements extended our expectations regarding our regulatory milestones and we announced the additional testing and extended milestone expectations in January 2015. During 2015 we isolated and tested all major variables of the organ scaffold and the cell source and protocols, examining the effects of alternatives against the then-existing product approach. Through extensive *in vitro* preclinical studies, and small-animal and large-animal studies, we made dramatic improvements, and discovered that the mechanism of action of this new approach was very different from our hypothesis regarding that of the first-generation product. We call this new implant approach our Cellframe™ technology. Our Cellframe technology uses a different scaffold material and microstructure, a different source and concentration of the patient's cells and several other changes from our HART-Trachea product. We believe that our Cellframe technology, although built on learnings from our earlier-generation product, represents a new technology platform resulting from our rigorous science and development.. We see the development of our Cellframe technology platform as the beginning of a new, third phase in our company's progression.

Leading up to the time of the Separation, we engaged in activities with a surgeon, Dr. Paolo Macchiarini, then employed by the Karolinska Institutet in Sweden, one of the world's most respected medical institutions, and who was at that time considered to be a world-renowned regenerative medicine pioneer. We provided organ bioreactors and organ scaffolds to Dr. Macchiarini's laboratories to conduct cell biology research and in return Dr. Macchiarini was to provide us with scientific data to advance the development of our bioreactors and tracheal scaffold. We also provided bioreactors and tracheal scaffolds in support of several compassionate care human surgeries performed by Dr. Macchiarini. We collaborated with Dr. Macchiarini in an effort to advance our product research and development with the assistance of a highly-acclaimed researcher and a well-respected institution. Regarding compassionate use human surgeries, we relied on the due process that involved a team of physicians and the Institutional Review Boards of the institutions where the surgeries were performed. We developed no part of any clinical protocol in any manner. Further, all surgeries involving any of our products or product candidates were conducted under the compassionate use system governed by the rules and regulations of each institution. Dr. Macchiarini was not employed by or affiliated with our company, and we did not pay him any wages or consulting fees. In June 2014, shortly after our Chief Medical Officer joined our company we ceased support of any human surgeries with Dr. Macchiarini. In addition, in November 2014, we formally announced that we would no longer be supporting or providing products to the human surgeries being performed in Russia, based in part on our belief that, due to the design of the Russian hospital's study and the nature and extent of the follow-up medical data made available to us, additional surgeries in Russia would provide less meaningful product development data than the work being done in our U.S. research and preclinical programs at that time.

Since the time we withdrew from involvement with Dr. Macchiarini, his work has become the subject of at least two investigations by the Karolinska Institutet. Many of the claims Dr. Macchiarini made publicly and published in peer-reviewed articles in reputable medical journals about the post-surgery quality of life, or even the necessity, of certain of his compassionate care surgeries where he used either a HART bioreactor or a HART-Trachea scaffold, or both, have been called into question. We discontinued development of our HART-Trachea product in 2014, and that first-generation product was significantly different from our new Cellframe technology and Cellspan products currently in development. We have focused our development efforts on our Cellframe technology and Cellspan products, which we have and will continue to develop internally, and with our collaborators, via a rigorous scientific development process. As a result, we believe that prior statements by Dr. Macchiarini or others regarding the patients whose surgeries utilized our HART bioreactor or HART-Trachea scaffold, or such products, are not pertinent to our Cellframe technology or Cellspan products, or their respective future development.

Clinical Trials

In order to market our product candidates, we will need to successfully complete clinical trials. The initial indication for which we intend to seek FDA approval will be to restore the function of the esophagus subsequent to esophageal damage or stenosis due to cancer, injury or infection.

Because esophageal cancer affects only approximately 17,000 patients per year in the U.S. we anticipate that our clinical trials will involve relatively few patients. Therefore, once commenced, we expect to be able to conduct a clinical trial in a relatively short period of time compared to clinical trials in indications with larger patient populations. We intend to work closely with regulatory agencies and clinical experts to design and size the clinical studies appropriately based on the specific conditions our products are intended to treat. We also intend to request expedited review from the FDA for the Cellspan esophageal implant product. Receipt of expedited review would reduce the overall time through the regulatory approval process.

We intend to pursue regulatory approval for the Cellspan esophageal implant in the U.S., Canada and Europe initially. Following clinical trials in other foreign markets, we expect to pursue regulatory approval for the Cellspan esophageal implant in those foreign markets, as well.

Research and Development

Our primary research and development activities are focused in three areas: materials science, cell biology and engineering. In materials science, we focus on designing and testing biocompatible organ scaffolds, testing the structural integrity and the cellularization capacities of the scaffolds. In cell biology, we focus on developing and

testing isolation and expansion protocols, cell characterization and fate studies, investigating the effects of various cell types and concentrations, evaluating the biocompatibility of scaffolds, experimenting with different cell seeding methodologies, and developing protocols for implantation experiments. Our engineering group supports the materials science and cell biology groups across an array of their activities, i.e. designing, engineering and making our proprietary organ bioreactors. All three of our R&D groups combine to plan and execute the in vitro studies. A fundamental part of our R&D effort in developing the Cellframe technology has been dedicated to the discovery and development of small and large animal model studies. The large-animal model employs the use of Yucatan mini-pigs. Our Cellspan scaffolds were implanted in the cervical portion as well as the thoracic portion of the esophagus and the airways in studies to date. As of December 31, 2015, we employed 12 full-time scientists and engineers and we also hire other consultants and part-time employees from time to time.

In addition to our in-house engineering and scientific development team, we collaborate with leaders in the field of regenerative medicine who are performing the fundamental research and surgeries in this field to develop and test new products that will advance and improve the procedures being performed. As these procedures become more common, we will work with our collaborators to further enhance our products to make them more efficient and easier to use by surgeons. In the U.S., our principal collaboration is with Mayo Clinic. Collaboration typically involves us developing new technologies specifically to address issues these researchers and clinicians face. In certain instances, we have entered into agreements that govern the ownership of the technologies developed in connection with these collaborations. These agreements are discussed below in “Intellectual Property and Related Agreements.”

We incurred approximately $5.1 million and $4.8 million of research and development expenses in 2014 and 2015, respectively. As we have not yet applied for or received regulatory approval to market any clinical products and sales of our research bioreactor products have not been significant in relation to our operating costs, no significant amount of these research and development costs have been passed on to our customers.

Manufacturing

For our scaffolds we use a process called electrospinning to create the fabric part of the scaffold. Electrospinning is a well-known fabrication process. It is useful for cell culture applications as it can create extremely thin fibers (much thinner than a human hair) that can make a fabric with pores approximately the same size as a cell. The electrospinning process parameters can be tuned to create a structure that is very similar to the natural structure of the collagen fibers in human extracellular matrix. Our Cellspan scaffolds are made from polyurethane, an inert polymer that is not bioresorbable. However, we also perform studies on the use of scaffolds made from bioresorbable materials. While we do not manufacture the cells, as they will come from the patient's adipose tissue, for regulatory purposes we are responsible for the quality control of the cells and the seeding of the cells onto the scaffold in the bioreactor. For this we have, in collaboration with our partners, developed standard operating procedures for the seeding of cells on the scaffold. For U.S. clinical trials we anticipate that the seeding will be performed in an automated version of our bioreactor at a pre-qualified third-party contract manufacturer using current Good Manufacturing Procedures (cGMP) using our proprietary protocol and under the supervision of our staff.

For our scaffolds, our primary materials are medical-grade plastic resins and solvents used to liquefy the resins in our manufacturing process. These materials are readily available from a variety of suppliers and do not currently represent a large proportion of our total costs. For our bioreactors, we perform final assembly and testing of components that we buy from third parties like machine shops, parts distributors, molding facilities and printed circuit board manufacturers. These operations are performed primarily at our Holliston, MA headquarters.

Sales and Marketing

We expect that most surgeries using the Cellspan esophageal implant product will be performed at a relatively small number of major hospitals in the U.S., Canada and European countries that will establish themselves as specialized centers of excellence. We believe that a relatively small number of centers of excellence in each country would be able to treat a very large percentage of that country's patients annually, given the expected number of patients to be treated each year. So, we expect our markets to be served by a concentrated number of treatment centers. Further, our three Cellspan product candidates are for the esophagus, the bronchi and the trachea, three organs all treated by thoracic surgeons. Therefore, all three products, once approved, would be marketed primarily to physicians practicing in a single surgical specialty, so we expect that the total number of physicians using our products will be a much smaller population than if our products were to be used by physicians in multiple areas of surgical specialties. Due to

our expectation of a population of physicians in one surgical specialty being the primary users of our products in a concentrated number of centers of excellence in each national market, we expect to be able to support our markets with a fairly small field sales force.

We expect to price the product commensurate with the medical value created for the patient and the costs avoided with the use of our product. We further expect to be paid by the hospital that buys the product from us. Finally, we expect that the hospital would seek reimbursement from payers for the entire transplant procedure, including the use of our products.

Harvard Bioscience is the exclusive distributor for the research versions of our organ bioreactors. Harvard Bioscience can only sell those products to the research markets in accordance with the terms of our distribution agreement. We retain all rights to manufacture and sell all our products for clinical use.

Intellectual Property and Related Agreements

We actively seek to protect our products and proprietary information by means of U.S. and foreign patents, trademarks and contractual arrangements. Our success will depend in part on our ability to obtain and enforce patents on our products, processes and technologies to preserve our trade secrets and other proprietary information and to avoid infringing on the patents or proprietary rights of others.

We have rights in the patent and the patent applications listed below. The patent or patents that may issue based on the patent applications are scheduled to expire as provided below:

Patent/Technology	Jurisdiction	Expiration
Patent application covering aspects of synthetic scaffolds and organ and tissue transplantation	U.S.	2032
Patent application relating to methods and compositions for producing elastic scaffolds for use in tissue engineering	U.S.	2033
Patent application relating to support configurations for tubular tissue scaffolds, and airway scaffold configurations	U.S., Europe	2033
Patent application relating to methods and compositions for promoting the structural integrity of scaffolds for tissue engineering	U.S.	2033
Issued Patent covering methods for analyzing engineered tissues	U.S.	2033
Patent application covering aspects of clinical scale bioreactors and tissue engineering	U.S., Europe	2030
Issued Patent covering aspects of liquid distribution in a rotating bioreactor	Germany	2031
Issued Patent covering aspects of liquid distribution in a rotating bioreactor	Germany	2021
Patent application covering aspects of liquid distribution in a rotating bioreactor	U.S.	2032
Patent application relating to bioreactors with supports to facilitate culturing organs	U.S.	2034
Patent application relating to bioreactor adaptors for tubular tissue scaffolds	U.S.	2034
Patent applications relating to engineered hybrid organs	U.S.	2034
Patent applications relating to infrared-based methods for evaluating tissue health including methods for evaluating burns	U.S.	2033
Patent application covering aspects of syringe devices and methods for delivering cells to tissues	U.S.	2030
Patent application relating to meshes and patches for tissue repair	PCT – international stage	2034
Provisional applications relating to methods and compositions for esophageal repair	U.S.	2036

We also rely on unpatented proprietary technologies in the development and commercialization of our products. We also depend upon the skills, knowledge and experience of our scientific and technical personnel, as well as those of our advisors, consultants and other contractors. To help protect our proprietary know-how that may not be patentable,

and our inventions for which patents may be difficult to enforce, we rely on trade secret protection and confidentiality agreements to protect our interests. To this end, we require employees, consultants and advisors to enter into agreements that prohibit the disclosure of confidential information and, where applicable, require disclosure and assignment to us of the ideas, developments, discoveries and inventions that arise from their activities for us. Additionally, these confidentiality agreements require that our employees, consultants and advisors do not bring to us, or use without proper authorization, any third party's proprietary technology.

Exclusive License Agreement and Sponsored Research Agreement — InBreath Bioreactor

We have an exclusive license agreement with Sara Mantero and Maria Adelaide Asnaghi to intellectual property rights relating to our InBreath Bioreactor. Under this agreement, we have worldwide rights to intellectual property (including patents, data, and know-how) relating to the hollow organ bioreactor, related techniques, and improvements thereof. We have exclusive worldwide rights to make, use and sell the hollow organ bioreactor, and the right to grant sublicenses and distribution rights. Under this agreement, we are obligated to pay the licensor royalties at various percentage rates in the low to mid-single digits pertaining to any applicable bioreactors we sell. This agreement terminates on the expiration date of the last to expire patent rights that may exist pertaining to inventions of Dr. Mantero or Ms. Asnaghi relating to the hollow organ bioreactor technology or improvements, or August 6, 2016 if on such date no such patent rights exist.

We have entered into a sponsored research agreement with Sara Mantero, Maria Adelaide Asnaghi, and the Department of Bioengineering of the Politecnico Di Milano, or PDM. Under the terms of this agreement, PDM is required to use its facilities and best efforts to conduct a research program relating to the development of bioreactors, clinical applications, and automated seeding processes. We are required to provide engineering support to PDM with respect to bioreactor designs. Intellectual property developed by PDM or its employees, including Dr. Mantero or Ms. Asnaghi, under this sponsored research agreement will be owned by Dr. Mantero or Ms. Asnaghi and covered by our exclusive license agreement described above. In addition, we have an option to an exclusive license for intellectual property relating to new technology that may not be covered by the exclusive license agreement. We will own any inventions and discoveries that we solely develop in connection with the research program and any inventions and discoveries that are jointly developed in connection with the research program will be owned jointly by the parties. The sponsored research agreement will continue until terminated by a party thereto upon 90 days prior written notice.

Sublicense Agreement with Harvard Bioscience

We have entered into a sublicense agreement with Harvard Bioscience pursuant to which Harvard Bioscience has granted us a perpetual, worldwide, royalty-free, exclusive, except as to Harvard Bioscience and its subsidiaries, license to use the mark “Harvard Apparatus” in the name Harvard Apparatus Regenerative Technology. The mark “Harvard Apparatus” is used under a license agreement between Harvard Bioscience and Harvard University, and we have agreed to be bound by such license agreement in accordance with our sublicense agreement. We currently have no affiliation with Harvard University.

Separation Agreements with Harvard Bioscience

On November 1, 2013, to effect the Separation, Harvard Bioscience distributed all of the shares of our common stock to the Harvard Bioscience stockholders (the “Distribution”). Prior to the Distribution Harvard Bioscience contributed the assets of its regenerative medicine business, and approximately $15 million in cash, to our company to fund our operations following the Distribution.

In connection with the Separation and immediately prior to the Distribution, we entered into a Separation and Distribution Agreement, Intellectual Property Matters Agreement, Product Distribution Agreement, Tax Sharing Agreement, Transition Services Agreement, and Sublicense Agreement with Harvard Bioscience to effect the Separation and Distribution and provide a framework for our relationship with Harvard Bioscience after the Separation. These agreements govern the current relationships among us and Harvard Bioscience and provided for the allocation among us and Harvard Bioscience of Harvard Bioscience’s assets, liabilities and obligations (including employee benefits and tax-related assets and liabilities) attributable to periods prior to the Separation.

Government Regulation

Any product that we may develop based on our Cellframe technology, and any other clinical products that we may develop, will be subject to considerable regulation by governments. We were in the past informed by the FDA that our previous-generation tracheal product candidate would be regulated under the Biologics License Application, or BLA, pathway in the U.S. and we were informed by the European Medicines Agency (EMA) that the previous generation tracheal product would be regulated under the Advanced Therapy Medicinal Products, or ATMP, pathway in the EU. Although our Cellframe technology differs in design and performance from the first generation product candidate, we expect that Cellframe-based products will be regulated by the FDA and EMA under the same pathways as the first generation tracheal product candidate. This expectation is based on the fact that the Cellframe technology is centered on the delivery of the patient's own cells seeded on an implanted synthetic scaffold in order to restore organ function and our belief that the cells provide the primary mode of action. Of course, it is possible that some of our current and future products may use alternative regulatory pathways.

Combination Product/Biologic

Government Regulation Combination Products/Biologics

We believe that products derived from our Cellframe technology may be defined as combination products consisting of two or more regulated components, a biologic and a medical device. In the U.S., a combination product usually is assigned by the FDA to one of the agency's centers, such as the CBER or the Center for Devices and Radiological Health, or CDRH, with the chosen center to take the lead in pre-marketing review and approval of the combination product. Other FDA centers also may review the product in regard to matters that are within their expertise. The FDA selects the lead center based on an assessment of the combination product's "primary mode of action." Some products also may require approval or clearance from more than one FDA center.

To determine which FDA center or centers will review a combination product submission, companies may submit a Request for Designation to the FDA. Those requests may be handled formally or informally. In some cases, jurisdiction may be determined informally based on FDA experience with similar products. However, informal jurisdictional determinations are not binding on the FDA. Companies also may submit a formal Request for Designation to the FDA Office of Combination Products. The Office of Combination Products will review the request and make its jurisdictional determination within 60 days of receiving a Request for Designation. We believe that regenerative medicine products containing cells will be reviewed by CBER, possibly with CBER's consultation with CDRH.

Domestic Regulation of Our Products and Business

The testing, manufacturing, and potential labeling, advertising, promotion, distribution, import and marketing of our products are subject to extensive regulation by governmental authorities in the U.S. and in other countries. In the U.S., the FDA, under the Public Health Service Act, the Federal Food, Drug and Cosmetic Act, and its implementing regulations, regulates biologics and medical device products.

The labeling, advertising, promotion, marketing and distribution of biopharmaceuticals, or biologics and medical devices also must be in compliance with the FDA and U.S. Federal Trade Commission, or FTC, requirements which include, among others, standards and regulations for off-label promotion, industry sponsored scientific and educational activities, promotional activities involving the internet, and direct-to-consumer advertising. The FDA and FTC have very broad enforcement authority, and failure to abide by these regulations can result in penalties, including the issuance of a warning letter directing us to correct deviations from regulatory standards and enforcement actions that can include seizures, injunctions and criminal prosecution. Recently, promotional activities for FDA-regulated products of other companies have been the subject of enforcement action brought under healthcare reimbursement laws and consumer protection statutes. In addition, under the federal Lanham Act and similar state laws, competitors and others can initiate litigation relating to advertising claims. Further, we are required to meet regulatory requirements in countries outside the U.S., which can change rapidly with relatively short notice.

The FDA has broad post-market and regulatory enforcement powers. Manufacturers of biologics and medical devices are subject to unannounced inspections by the FDA to determine compliance with applicable regulations, and these inspections may include the manufacturing facilities of some of our subcontractors. Failure by manufacturers or their suppliers to comply with applicable regulatory requirements can result in enforcement action by the FDA or other regulatory authorities. Potential FDA enforcement actions include:

- untitled letters, warning letters, fines, injunctions, consent decrees and civil penalties;
- unanticipated expenditures to address or defend such actions;
- customer notifications for repair, replacement, refunds;
- recall, detention or seizure of our products;
- operating restrictions or partial suspension or total shutdown of production;
- operating restrictions;
- refusal to grant export approval for our products; or
- criminal prosecution.

In addition, other government authorities influence the success of our business, including the availability of adequate reimbursement from third party payers, including government programs such as Medicare and Medicaid. Medicare and Medicaid reimbursement policies can also influence corresponding policies of private insurers and managed care providers, which can further affect our business.

Biologics Regulation

Biological products must satisfy the requirements of the Public Health Services Act and the Food, Drug and Cosmetics Act and their implementing regulations. In order for a biologic product to be legally marketed in the U.S., the product must have a BLA approved by the FDA.

The BLA Approval Process

The steps for obtaining FDA approval of a BLA to market a biopharmaceutical, or biologic product in the U.S. include:

- completion of preclinical laboratory tests, animal studies and formulation studies under the FDA's GLP regulations;
- submission to the FDA of an IND application, for human clinical testing, which must become effective before human clinical trials may begin and which must include Institutional Review Board, or IRB, approval at each clinical site before the trials may be initiated;
- performance of adequate and well-controlled clinical trials in accordance with Good Clinical Practices, or GCP, to establish the safety and efficacy of the product for each indication;
- submission to the FDA of a BLA, which contains detailed information about the chemistry, manufacturing and controls for the product, extensive pre-clinical information, reports of the outcomes of the clinical trials, and proposed labeling and packaging for the product;

- the FDA's acceptance of the BLA for filing;

- satisfactory review of the contents of the BLA by the FDA, including the satisfactory resolution of any questions raised during the review or by the advisory committee, if applicable;

- satisfactory completion of an FDA inspection of the manufacturing facility or facilities at which the product is produced to assess compliance with cGMP regulations, to assure that the facilities, methods and controls are adequate to ensure the product's identity, strength, quality and purity; and

- FDA approval of the BLA.

Preclinical studies include laboratory evaluations of product toxicity, as well as animal studies.

An IND will automatically become effective 30 days after receipt by the FDA, unless before that time the FDA raises concerns or questions about issues such as the conduct of the trials as outlined in the IND. In that case, the IND sponsor and the FDA must resolve any outstanding FDA concerns or questions before clinical trials can proceed.

Clinical trials are subject to extensive monitoring, recordkeeping and reporting requirements. Clinical trials must be conducted under the oversight of an IRB for the relevant clinical trial sites and must comply with FDA regulations, including but not limited to those relating to GCP. Adverse events must be reported and investigated in a timely manner. To conduct a clinical trial, a company is also required to obtain the patients' informed consent in form and substance that complies with both FDA requirements and state and federal privacy and human subject protection regulations. The sponsor, the FDA or the IRB could suspend a clinical trial at any time for various reasons, including a belief that the risks to trial subjects outweigh the anticipated benefits. A protocol for each clinical trial and any subsequent protocol amendments must be submitted to the FDA as part of the IND. In addition, an IRB at each site at which the trial is conducted must approve the protocol and any amendments. If foreign clinical trials are intended to be considered by the FDA for approval of a product in the U.S. then those foreign clinical trials performed under an IND must meet the same requirements that apply to U.S. studies. The FDA will accept a foreign clinical trial not conducted under an IND only if the trial is well-designed, well-conducted, performed by qualified investigators in accordance with international principles for GCP, or with the laws and regulations of the country in which the research was conducted, whichever provides greater protection of the human subjects. The FDA, however, has substantial discretion in deciding whether to accept data from foreign non-IND clinical trials.

Clinical trials involving biopharmaceutical products are typically conducted in three sequential phases. The phases may overlap or be combined. A fourth, or post-approval, phase may include additional clinical trials. These phases are described generally below. We note, however, that the exact number of study subjects required for each specific intended use, and our intent to combine or "telescope" various study phases together, are both areas where we will

actively seek FDA feedback to streamline the clinical evaluation process. Briefly, the phases of clinical development generally include the following:

- Phase I. Phase I clinical trials involve the initial introduction of the product into human subjects to determine the adverse effects associated with increasing doses. Such Phase I studies frequently are highly abbreviated or combined with Phase II studies (as outlined below), when the product involves the patient's own cells.

- Phase II. Phase II clinical trials usually involve studies in a limited patient population to evaluate the efficacy of the product for specific, targeted indications, to determine dosage tolerance and optimal dosage, and to identify possible adverse effects and safety risks. Products that contain the patient's own cells frequently are studied for initial safety and effectiveness determinations in combined or "telescoped" Phase I/II clinical studies.

- Phase III. If the product is found to be potentially effective and to have an acceptable safety profile in Phase II (or sometimes Phase I) trials, the clinical trial program will be expanded to further demonstrate clinical efficacy, optimal dosage and safety within an expanded patient population at geographically dispersed clinical trial sites. As noted, the exact number of subjects needed, the duration of clinical follow-up, and the endpoints by which safety and efficacy are demonstrated are based on the condition being treated.

- Post-Approval (Phase IV). Post-approval clinical trials are required of or agreed to by a sponsor as a condition of, or subsequent to marketing approval. Further, if the FDA becomes aware of new safety information about an approved product, it is authorized to require post approval trials of the biological product. These trials are used to gain additional experience from the treatment of patients in the intended therapeutic indication and to document a clinical benefit in the case of biologics approved under accelerated approval regulations. If the FDA approves a product while a company has ongoing clinical trials that were not necessary for approval, a company may be able to use the data from these clinical trials to meet all or part of any Phase IV clinical trial requirement. These clinical trials are often referred to as Phase III/IV post approval clinical trials. Failure to promptly conduct Phase IV clinical trials could result in withdrawal of approval for products approved under accelerated approval regulations.

Clinical testing may not be completed successfully within any specified time period, if at all. The FDA close