BioCardia, Inc.
Form 10-K
March 16, 2018

UNITED STATES

SECURITIES AND EXCHANGE COMMISSION

Washington, D.C. 20549

Form 10-K

(Mark One)

ANNUAL REPORT PURSUANT TO SECTION 13 OR 15(d) OF THE SECURITIES EXCHANGE ACT OF 1934

For the fiscal year ended December 31, 2017

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 0-21419

BIOCARDIA, INC.

(Exact Name of Registrant as Specified in its Charter)

Delaware	**23-2753988**
(State or Other Jurisdiction of Incorporation or Organization)	**(I.R.S. Employer Identification Number)**

125 Shoreway Road, Suite B

San Carlos, California 94070

(Address of Principal Executive Offices, Including Zip Code)

(650) 226-0120

(Registrant's Telephone Number, Including Area Code)

Securities Registered Pursuant to Section 12(g) of the Act: Common Stock

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

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

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 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 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
		Emerging growth company

If am emerging growth company, indicate by check mark if the registrant has elected not to use the extended transition period for complying with any new or revised financial accounting standards provided pursuant to Section 13(a) of the Exchange Act.

Indicate by check mark whether the registrant is a shell company (as defined in Rule 12b-2 of the Exchange Act). Yes No

The aggregate market value of the voting and non-voting common equity held by non-affiliates of the registrant, computed by reference to the average bid and asked price of such common equity, on June 30, 2017 was approximately $147,668,470. Shares of the registrant's common stock held by each executive officer, director and holder of 10% or more of the outstanding common stock have been excluded in that such persons may be deemed to be affiliates. This calculation does not reflect a determination that certain persons are affiliates of the registrant for any other purpose.

The number of shares of the registrant's Common Stock outstanding as of March 12, 2018 was 38,241,592.

DOCUMENTS INCORPORATED BY REFERENCE

Portions of the registrant's Proxy Statement relating to the 2018 Annual Meeting of Stockholders to be held on June 15, 2018, are incorporated by reference into Part III of this Annual Report on Form 10-K where indicated. Such Proxy Statement will be filed with the Securities and Exchange Commission within 120 days after the end of the registrant's fiscal year ended December 31, 2017.

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SPECIAL NOTE REGARDING FORWARD-LOOKING STATEMENTS

This Annual Report on Form 10-K contains forward-looking statements within the meaning of Section 27A of the Securities Act of 1933, as amended, and Section 21E of the Securities Exchange Act of 1934, as amended. Any and all statements contained in this Annual Report that are not statements of historical fact may be deemed forward-looking statements. Terms such as “may,” “might,” “would,” “should,” “could,” “project,” “estimate,” “pro-forma,” “p “potential,” “strategy,” “anticipate,” “attempt,” “develop,” “plan,” “help,” “believe,” “continue,” “intend,” “expect,” “future” a similar import (including the negative of any of the foregoing) may be intended to identify forward-looking statements. However, not all forward-looking statements may contain one or more of these identifying terms. Forward-looking statements in this Annual Report may include, without limitation, statements regarding (i) the plans and objectives of management for future operations, including plans or objectives relating to the development of our cell therapy systems, (ii) a projection of income (including income/loss), earnings (including earnings/loss) per share, capital expenditures, dividends, capital structure or other financial items, (iii) our future financial performance, including any such statement contained in a discussion and analysis of financial condition by management or in the results of operations included pursuant to the rules and regulations of the SEC and (iv) the assumptions underlying or relating to any statement described in points (i), (ii) or (iii) above.

The forward-looking statements are not meant to predict or guarantee actual results, performance, events or circumstances and may not be realized because they are based upon our current projections, plans, objectives, beliefs, expectations, estimates and assumptions and are subject to a number of risks and uncertainties and other influences, many of which we have no control over. Actual results and the timing of certain events and circumstances may differ materially from those described by the forward-looking statements as a result of these risks and uncertainties. Factors that may influence or contribute to the inaccuracy of the forward-looking statements or cause actual results to differ materially from expected or desired results may include, without limitation:

- our ability to obtain regulatory approval for our cell therapy systems;
- market acceptance of our cell therapy systems;
- the benefits of our cell therapy systems versus other products;
- our ability to successfully sell and market our cell therapy systems;
- competition from existing technologies or products or new technologies and products that may emerge;

the implementation of our business model and strategic plans for our business and our cell therapy systems;

the scope of protection we are able to establish and maintain for intellectual property rights covering our cell therapy systems;

estimates of our future revenue, expenses, capital requirements and our need for additional financing;

our financial performance;

developments relating to our competitors and the healthcare industry; and

other risks and uncertainties, including those listed under the section titled “Risk Factors.”

You should not rely upon forward-looking statements as predictions of future events. Although we believe that the expectations reflected in the forward-looking statements are reasonable, we cannot guarantee that the future results, levels of activity, performance or events and circumstances reflected in the forward-looking statements will be achieved or occur. Except as required by law, we undertake no obligation to update publicly any forward-looking statements for any reason after the date of this Annual Report to conform these statements to actual results or to changes in our expectations.

You should read this Annual Report on Form 10-K and the documents that we reference in this Annual Report on Form 10-K and have filed with the SEC as exhibits to this Annual Report on Form 10-K with the understanding that our actual future results, levels of activity, performance and events and circumstances may be materially different from what we expect. We qualify all forward-looking statements by these cautionary statements.

PART I

ITEM 1. BUSINESS

Description of Business

We are a clinical-stage regenerative medicine company developing novel therapeutics for cardiovascular diseases with large unmet medical needs. Our lead therapeutic candidate is the investigational CardiAMP Cell Therapy System, which provides an autologous bone marrow derived cell therapy (using a patient's own cells) for the treatment of two clinical indications: heart failure that develops after a heart attack and chronic myocardial ischemia. The CardiAMP Cell Therapy System is being developed to provide a comprehensive biotherapeutic solution, incorporating a proprietary molecular diagnostic to characterize the potency of a patient's own bone marrow cells and determine if they are an optimal candidate for therapy, a proprietary point of care processing platform to prepare cells at the patient's bedside, an optimized therapeutic formulation that builds on the total experience in the cardiac stem cell field to-date, and a proprietary interventional delivery system that easily navigates a patient's vasculature to securely deliver cells in a routine cardiac catheterization procedure. Our second therapeutic candidate is the investigational CardiALLO Cell Therapy System, an allogenic "off the shelf" cell therapy derived from bone marrow cells from a donor that meets specified criteria, which has potential to be advanced for many clinical indications including heart failure. We are committed to applying our expertise in the fields of autologous and allogeneic cell-based therapies to improve the lives of patients with cardiovascular conditions.

Market Overview

Adult bone marrow contains a large reservoir of stem and progenitor cells capable of differentiating into blood cells, blood vessel cells, and connective tissue cells. In addition, numerous pre-clinical cardiac studies have shown that cell-to-cell communication in which bone marrow-derived stem cells promotes microcirculatory adaptation, immune modulation and cell protection, facilitating cardiac recovery, in part via recruitment of other reparative cell types.

Bone marrow cell homing to the heart is believed to be part of the body's natural repair process. After a heart attack or an acute injury to the heart, cells from bone marrow are known to home to the heart. For example, a population of bone marrow cells that express the surface marker CD34 has certain receptors, including CXC-4 and CXC-7 receptors, that home to the SDF-1 ligand in injured heart tissue. In heart failure, the heart may have fewer of these homing signals and a decreased ability to stimulate or recreate this signaling process, leading to a lower likelihood of heart tissue repair. A number of other bone marrow derived cells with unique cell surface markers have also been

shown to have beneficial effects in animal models of heart failure and chronic myocardial ischemia disease when delivered directly to the heart.

Bone marrow derived cell-based therapy has been shown to have the potential to provide therapeutic benefit for patients with heart failure and chronic myocardial ischemia. In the past decade, intramyocardial delivery of bone marrow derived cell-based therapies in preclinical and clinical studies of heart failure and chronic myocardial ischemia has predominantly resulted in benefits, such as improvement in ventricular function, reduction in the area of dead heart tissue and increase in heart muscle blood flow, reduction in pain symptoms, reduced major adverse event rates, and reduced mortality.

Recent systematic review and meta-analysis of the scientific literature from 23 randomized controlled trials prior to 2013, covering more than 1,200 participants, was published by Fisher in Circulation Research in January 2015. The review found evidence that bone marrow cell treatment, including intramyocardial delivery of bone marrow cells, has improved left ventricle ejection fraction, or LVEF, and chronic ischemic heart disease. The authors of the review found evidence for a potential beneficial clinical effect in terms of mortality and performance status after at least one year post-treatment in people who suffer from chronic ischemic heart disease and heart failure. Results in heart failure trials indicate that bone marrow derived cell-based therapy leads to a reduction in deaths and readmission to hospital and improvements over standard treatment as measured by tests of heart function. This review concluded that further research is required to confirm the results. Published scientific papers provide clinical support for efficacy from randomized controlled clinical trials of intramyocardial delivery of bone marrow derived cells in closely related clinical conditions of chronic myocardial ischemia, diastolic heart failure, and subacute myocardial infarction.

Heart Failure

Heart failure is a clinical condition in which the output of blood from the heart is insufficient to meet the metabolic demands of the body. In 2015, the American Heart Association, or AHA, report on heart disease statistics estimated that there are 5.7 million Americans over the age of 20 that have heart failure. Heart failure is increasingly prevalent due to the aging population and the increase in major cardiovascular risk factors, including obesity and diabetes. The AHA also estimates that one in five adults will develop heart failure after the age of 40. During heart failure progression, the heart steadily loses its ability to respond to increased metabolic demand, and mild exercise soon exceeds the heart's ability to maintain adequate output. Towards the end stage of the disease, the heart cannot pump enough blood to meet the body's needs at rest. At this stage, fluids accumulate in the extremities or in the lungs making the patient bedridden and unable to perform the activities of daily living. The long-term prognosis associated with heart failure is approximately 50% mortality at five years following the initial diagnosis.

Hospitalizations for heart failure are expensive, and the risk of death increases with each recurrent heart failure-related hospitalization. In 2014, the Journal of the American College of Cardiology reported that the one- and six-month readmission rates after heart failure-related hospitalization are close to 25% and 50%, respectively. In 2010, the AHA estimated that the direct and indirect cost of heart failure in the United States was $39 billion, half of which was related to repeated hospitalizations, and by 2030 the total cost of heart failure in the United States is projected to increase to $70 billion. There is growing pressure on hospitals to reduce readmissions for heart failure.

Heart failure is classified in relation to the severity of the symptoms experienced by the patient. The most commonly used classification system, established by the New York Heart Association, or NYHA, is as follows:

- ***Class I (mild):*** patients experience no or very mild symptoms with ordinary physical activity;
- ***Class II (mild):*** patients experience fatigue and shortness of breath during moderate physical activity;
- ***Class III (moderate):*** patients experience shortness of breath during even light physical activity; and
- ***Class IV (severe):*** patients are exhausted even at rest.

Despite guideline-directed therapies employing a wide range of pharmacologic, device, and surgical options, many patients deteriorate over time and develop advanced heart failure symptoms that cannot be effectively managed by existing medical therapies. At the end stage of heart failure, current treatment options include heart transplant surgery or implantation of a left ventricular assist device, or LVAD, a battery operated mechanical circulatory device used to partially or completely replace the function of the left ventricle of the heart. LVADs are used for patients awaiting a

heart transplant or as a destination therapy for patients with NYHA Class IV heart failure who may never receive a heart transplant. Both of these end-stage treatment options require invasive open-chest surgery and can cost in excess of $150,000 per procedure, as reported by the Journal of Heart and Lung Transplantation.

There are approximately 2.9 million NYHA Class II and Class III heart failure patients, of which we estimate approximately 60% are patients with ischemic systolic heart failure. Of this subset of 1.7 million patients, we estimate that approximately 70%, or over 1.2 million patients, will have a cell potency score sufficient to qualify for treatment with the CardiAMP Cell Therapy System.

Chronic Myocardial Ischemia

Refractory angina is a condition characterized by severe pain in the chest, often also spreading to the shoulders, arms, and neck, caused by an inadequate blood supply to the heart. In the U.S. alone, it is estimated that between 600,000 and 1.8 million patients suffer this condition, with approximately 75,000 new cases diagnosed each year. There is a growing population of patients with chronic angina that suffer with severely limiting symptoms and are not amenable to current therapies. These patients have significant impairments in quality of life, suffer from poor perceived health status and represent a significant burden to the health care system due to high use of health care resources. We believe the CardiAMP Cell Therapy System has the potential to provide a treatment for these patients not met by current therapeutic alternatives.

Product Pipeline and Development Status

CardiAMP Cell Therapy System

The CardiAMP Cell Therapy System, or CardiAMP, is our lead therapeutic program being advanced for two clinical indications. This investigational cell therapy system is comprised of (i) a cell potency screening test, (ii) a point of care cell processing platform, and (iii) a biotherapeutic delivery system. In the screening process, the physician extracts a small sample of the patient's bone marrow in an outpatient procedure performed under local anesthesia. The clinic sends the sample to a centralized diagnostic lab, which tests for identified biomarkers from which we generate a potency assay score for the patient. During the treatment for patients who are assessed as meeting the indication specific CardiAMP cell potency assay score , a clinician harvests and then prepares the patient's own bone marrow mononuclear cells, or autologous cells, using our point of care cell processing platform, which a cardiologist then delivers into the heart using our proprietary biotherapeutic delivery system. We designed the entire procedure to be performed in approximately 60 to 90 minutes, which we believe is substantially faster than alternative cell-based therapies in development. The patient then leaves the hospital the same or next day.

CardiAMP Cells Preclinical Experience

Extensive preclinical data with bone marrow mononuclear cells and the media in which they have been incubated have shown compelling results in animal models of heart disease. Rats treated with media from cells showed reduced fibrotic scar at 28 days, increased microvascular density in central infarct and border zones, and demonstrated enhanced cardiac function. Swine studies have shown that there is a dose response relationship, with higher doses of bone marrow mononuclear cells resulting in reduced fibrosis and increased microvascular change in infarcted

myocardium 60 days after treatment. The highest dose tested in this series of 200 million cells, with >20 million cells per segment, resulted in the highest capillary density and the least fibrosis.

CardiAMP Cells Phase I Heart Failure Study: Transendocardial Autologous Marrow Cells in Myocardial Infarction

The CardiAMP Phase I Transendocardial Autologous Marrow Cells in Myocardial Infarction or TABMMI trial enrolled 20 patients with ischemic systolic heart failure in an open label safety trial of bone marrow cells delivered with the Helix biotherapeutic delivery system at a dosage of 100 million cells. Results showed improvement in cardiac function as measured by left ventricular ejection fraction, improved exercise tolerance, and superior survival as compared to historical controls. The Phase I TABMMI study was submitted to the Argentine Administración Nacional de Medicamentos, Alimentos y Technología Médica.

In our TABMMI Phase I trial of CardiAMP cells, we enrolled 20 patients with previous evidence of having had a heart attack and who presented with a low ejection fraction of less than or equal to 40% and greater than or equal to 20%. Baseline evaluations included informed consent, history and physical examination, electrocardiogram, 24-hour Holter monitoring, echocardiography, routine blood tests and exercise tolerance testing. Reduced regional heart wall motion was coincident with the diseased coronary vessel in each patient. A total of 20 patients with heart failure (NYHA Class I, II and III) each received three to ten transendocardial infusions of cells using our Helix biotherapeutic delivery system in an open-label dose-escalation two cohort trial. Dosage administration ranged from 30 million to 130 million autologous bone marrow derived mononuclear cells, with an average of 96 million cells.

Bone marrow cells delivered in TABMMI demonstrated an excellent safety profile in this heart failure population, with no treatment related toxicities observed. The 20 patients who received CardiAMP cells, demonstrated improvements from baseline to both six-month and 12-month follow-up across a number of parameters important in heart failure, including statistically and clinically significant improvements in left ventricular, or LV, function (ejection fraction). The difference of average ejection fraction was statistically significant over baseline at all follow-up time points of 6 months, 12 months, and 24 months. Average exercise tolerance time showed an increase at all follow-up time points, but was only statistically significant at 12 months and 24 months.

A total of 12 adverse events were observed in six patients, although none were related to the investigational delivery or cell transplantation procedure. The complete results of the 20 patients at two-year follow-up have been published in the journal Eurointervention in 2011.

CardiAMP Cells Phase II Heart Failure Trial: Transendocardial Autologous Cells in Heart Failure Trial (TAC-HFT)

In our co-sponsored Phase II Transendocardial Autologous Cells in Heart Failure Trial, patients with ischemic systolic heart failure were randomized on a one to one basis into two double-blind, placebo-controlled trials: TACHFT-BMC and TACHFT-MSC. The IND for the TACHFT trial was filed with the U.S. Food and Drug Administration, or FDA Center for Biologics Evaluation and Research in 2008 by the University of Miami, the co-sponsor of the trial.

In the safety dose escalation roll-in cohort stage of the study, eight patients received treatment with either CardiAMP cells, or autologous bone marrow mesenchymal cells, or MSC, at dosages of 100 million or 200 million cells. In the randomized, placebo-controlled efficacy stage of the study, 29 patients received treatment with either CardiAMP cells or placebo and 30 patients received treatment with either MSCs or placebo. The mode of administration was 10 intramyocardial infusions per patient using our Helix biotherapeutic delivery system into the myocardium adjacent to and into the infarcted tissue. All subjects had ischemic systolic heart failure (NYHA Class I, II or III).

TACHFT-BMC met its primary safety endpoint at both dosages (100 million and 200 million cells) and treated patients had increased functional capacity, improved quality of life, symptoms and key markers of cardiac function predictive of survival, such as end systolic volume, or ESV. The TACHFT-BMC trial included a single dose of CardiAMP cells with a follow up observation period of 12 months. The Phase II, randomized, placebo-controlled study met its primary safety endpoint and demonstrated statistically significant and clinically meaningful improvements in secondary efficacy endpoints of functional capacity, as measured by the six minute walk distance (6MW), and in quality of life, as measured by the Minnesota Living with Heart Failure Questionnaire score. Phase II results were published in the journal of the American Medical Association in 2014 and were presented at the World Congress of Regenerative Medicine in 2015.

CardiAMP Heart Failure Phase III Trial

The FDA has approved the Investigational Device Exemption, or IDE, for the randomized controlled pivotal trial of autologous bone marrow mononuclear cells using the CardiAMP Cell Therapy System in patients with heart failure developed in the aftermath of a heart attack (CardiAMP Heart Failure Trial) for up to 260 patients at up to 40 clinical sites in the United States.

Our FDA accepted Phase III pivotal trial is designed to provide the primary support for the safety and efficacy of the CardiAMP Cell Therapy System. The primary endpoint is a clinical composite of six minute walk distance and major adverse cardiac and cerebrovascular events. Based on the results achieved in the Phase II trial, our Phase III pivotal trial is designed to have more than 95% probability of achieving a positive result with statistical significance. Statistical significance denotes the mathematical likelihood that the results observed are real and not due to chance.

Particularly novel aspects of this trial include a cell potency assay to screen subjects who are most likely to respond favorably to treatment, a point of care treatment method, use of a high target dose of 200 million cells and an efficient transcatheter delivery method that is associated with high cell retention. Success in the primary endpoint of the trial, may lead to a new treatment for those suffering from heart failure in the aftermath of a heart attack.

The Department of Health & Human Services Centers for Medicare & Medicaid Services, or CMS, has designated the CardiAMP Heart Failure Trial as a qualifying trial for Medicare national coverage determination that routine costs of care will be covered for Medicare beneficiaries. Private insurance plans covering 50 million insured Americans follow this CMS reimbursement policy, and are also anticipated to pay for these costs in the CardiAMP Heart Failure Trial. Covered costs today for both the treatment and control arms of the trial include patient screening, the CardiAMP Cell Therapy System and procedure, and clinical follow-up at one and two years after the procedure.

The CardiAMP Heart Failure Trial was initiated in Q4 2016, and the first patient treated in Q1 2017. The Data Safety Monitoring Board (DSMB) safety review of the 10 patient roll in cohort treated at three clinical sites was completed successfully in Q3 2017, and the trial is actively enrolling today at 10 clinical sites. Efficacy data from the primary endpoint in the open label roll in cohort are anticipated in second half of 2018. We anticipate that trial enrollment will be completed in the first half of 2019 and expect top line data will be available in the first half of 2020.

Although clinical trial results show support for safety and efficacy in both the Phase I TABMMI and Phase II TACHFT-BMC trials, the CardiAMP Cell Therapy System still remains investigational, and no claims regarding safety or efficacy can be made until the products are approved by the FDA.

We believe the remaining clinical efficacy risk is modest in light of the Phase I and II data available, the successful Phase III DSMB review of the roll in patients, and broader literature which supports CardiAMP Cell Therapy System as a therapeutic candidate for heart failure secondary to having had a heart attack. The CardiAMP Cell Therapy System has the potential to significantly benefit patients who have limited options, and provide a cost-effective therapy to help reduce the substantial heart failure hospitalization and care costs. Unlike other autologous cell therapies, CardiAMP Cell Therapy System, is not expected to have any significant manufacturing or distribution complexities that would prevent it from being a commercial success.

By way of comparison, previous IDE clinical trials that led to FDA approval of Cardiac Resynchronization Therapy (CRT) devices for the treatment of heart failure followed the same IDE regulatory pathway and had similar endpoints to the proposed CardiAMP Heart Failure Trial. CRT is intended for patients that are NYHA III and IV versus the CardiAMP Heart Failure Trial indication of NYHA II and III. Results from 5 out of 6 randomized pivotal CRT trials showed both smaller improvements in functional capacity as measured by the six minute walk test and smaller improvement in quality of life than the CardiAMP Phase II results. Although the benefits with CRT were less than observed in CardiAMP placebo controlled Phase II trial, these results for the permanently implantable CRT devices were sufficient to obtain FDA approval.

CardiAMP Chronic Myocardial Ischemia Phase III Pivotal Trial

In 2017, we submitted for approval of an IDE for the CardiAMP Cell Therapy System in a second related clinical indication of chronic myocardial ischemia based on the strength of our Phase I and II heart failure trial data, and the strength of the clinical data showing support for the efficacy of one component of our cell therapy (the CD34+ cells) in chronic myocardial ischemia. In January 2018, the FDA approved the IDE for the randomized controlled pivotal trial of autologous bone marrow mononuclear cells using the CardiAMP Cell Therapy System in patients with refractory chronic myocardial ischemia for up to 343 patients at up to 40 clinical sites in the United States. This therapeutic approach uses the same novel aspects as the CardiAMP Heart Failure Trial. An update to the statistical analysis plan to enable an adaptive trial design is anticipated. Success in the primary endpoint of the trial, which is exercise tolerance, may lead to a new treatment for those suffering from chronic myocardial ischemia and having refractory angina.

BioCardia has applied for CMS designation of the CardiAMP Chronic Myocardial Ischemia Trial as a qualifying trial for Medicare national coverage determination similar to the designation received for the CardiAMP Heart Failure Trial. If approved by CMS for coverage, it is anticipated that this second pivotal trial will build on and benefit from the experience and infrastructure from the CardiAMP Heart Failure Trial. With CMS reimbursement and additional

funding to support this program, there is potential for this trial to be activated in 2018.

CardiAMP Cell Therapy System - Other Indications

In the future, we may also explore the continued development of CardiAMP for use immediately after a heart attack and for treatment of heart failure with preserved ejection fraction, a form of heart failure wherein the amount of blood pumped from the heart's left ventricle with each beat (ejection fraction) is greater than 50%.

CardiALLO Cell Therapy System

Our second therapeutic candidate is the CardiALLO Cell Therapy System, or CardiALLO, which will use an allogeneic “off the shelf” mesenchymal stem cell product candidate for the treatment of ischemic systolic heart failure that may be an alternative for patients who are not optimal candidates for the CardiAMP Cell Therapy System. We anticipate preparation of an Investigational New Drug, or IND, application for submission to the FDA for a Phase II trial for CardiALLO Cell Therapy System for the treatment of ischemic systolic heart failure.

The CardiALLO Cell Therapy System will use culture expanded allogeneic bone marrow derived MSCs for the treatment of ischemic systolic heart failure. We believe this therapy presents the advantages of an “off the shelf” therapy that does not require tissue harvesting or cell processing.

CardiALLO Preclinical Experience

Preclinical work with expanded MSCs in swine has been performed with our collaborators at three universities. Early studies showed cells could be efficiently delivered and tracked in the heart using iron oxide incubation techniques with magnetic resonance imaging. Immunohistochemistry stains also detailed that cells could be identified in the hearts after delivery. Randomized swine studies demonstrated that bone marrow derived mesenchymal stem cells, could be safely injected by using our Helix biotherapeutic delivery system three days after myocardial infarction. Cellular transplantation resulted in long-term engraftment, reduction in scar formation and near-normalization of cardiac function. As an additional finding, transplanted cells derived from an allogeneic donor were not rejected by the recipient, a major practical advance for the potential widespread application of this therapy. Studies have also been performed evaluating a variety of delivery strategies. Together, these findings demonstrate the safety of directly injecting cellular grafts into damaged myocardium during the peri-infarct period and provided signals of efficacy.

CardiALLO related Phase I /II Studies: POSEIDON, TAC-HFT-MSC, and TRIDENT

We have co-sponsored three clinical trials for MSCs for the treatment of ischemic systolic heart failure. In substantially similar trial designs, the POSEIDON Phase I/II trial compared autologous MSCs to allogeneic MSCs, the TACHFT-MSC Phase II trial compared autologous MSCs to placebo, and the TRIDENT Phase II compared allogenic MSCs at different doses. The first two trials shared common arms of autologous MSCs, enabling a bridge to placebo, leading us to conclude that allogeneic MSC therapy has potential to be superior to placebo. The IND for the TACHFT trial was filed with the FDA Center for Biologics Evaluation and Research in 2008 by the University of Miami, our co-sponsor for the trial. The POSEIDON trial and the TRIDENT trials were submitted by amendment under the same IND filed for the TACHFT study, and was co-sponsored by the University of Miami, the National Institutes of Health and us. The results from all three of these studies can be submitted to the FDA in support of an IND for the CardiALLO Cell Therapy System.

POSEIDON Phase I/II, TACHFT-MSC Phase II, and TRIDENT Phase I/II trials, inform and support our clinical efforts for the CardiALLO Cell Therapy System. We are developing an optimized formulation and dosage strategy of CardiALLO cells for a planned clinical trial which we intend to initiate after we complete enrollment in the CardiAMP Heart Failure Trial.

CardiALLO Development

CardiALLO is being advanced with an anticipated improved cell production strategy to be detailed in the Chemistry Manufacturing and Controls (CMC) of the IND in development. We believe the new CMC will reduce the likelihood of immune response to transplanted allogenic cells further, may enhance efficacy, and will enable commercial scale up

and global distribution. CardiALLO will require more extensive clinical development than the CardiAMP Cell Therapy System, beginning with a Phase II trial that follows previous work, to confirm the results with the modified cell culture and dosage strategy.

We are performing our own CMC development work in BioCardia laboratories to accelerate the effort and secure additional intellectual property, and in parallel are developing an agreement with an established institution to culture and supply the MSC cells for CardiALLO clinical development. We expect to demonstrate support for the safety and efficacy of MSCs in our target patient population in a Phase II randomized controlled study. We expect the CardiALLO Phase II Heart Failure Trial will enroll patients with control, low dose and high dose groups using the Helix biotherapeutic delivery system and a similar inclusion criteria as the CardiAMP Heart Failure Trial. We intend to begin enrolling the CardiALLO Heart Failure trial after the CardiAMP Heart Failure Trial completes enrollment. In the United States, CardiALLO Cell Therapy System is expected to be regulated by the FDA as a biologic combination product with our Helix biotherapeutic delivery system.

The completed clinical studies show support for the safety and efficacy of both the CardiAMP Cell Therapy System and CardiALLO Cell Therapy System development programs; however, both product candidates remain investigational, and no claims regarding safety or efficacy can be made until the constituent products are approved by the FDA. As we engage in clinical trials of our therapeutic candidates, we have compensated and intend to compensate all parties performing the trials or studies (including all the parties identified in this Annual Report on Form 10-K) only on terms that are standard and customary in clinical study arrangements.

These two therapeutic candidates provide compelling and synergistic approaches to replicating the natural response of bone marrow cells to cardiac injury. CardiAMP harnesses the potential of autologous minimally processed bone marrow cells, using an anticipated companion diagnostic to identify patients most likely to benefit from the therapy. CardiALLO utilizes mesenchymal stem cells from a donor that meets specified criteria and may be appropriate for patients who are not optimal candidates for the CardiAMP therapy.

Cell Processing and Cell Delivery Product Platforms

BioCardia has developed and secured exclusive rights to enabling cell processing and cell delivery products, which are used as part of our CardiAMP and CardiALLO therapies, and which we believe validate our approach and development expertise: (i) the CardiAMP cell processing platform, (ii) the Helix transendocardial biotherapeutic delivery system, and (iii) our Morph vascular access products.

- ***CardiAMP cell processing platform***—processes bone marrow aspirate at the point of care to concentrate mononuclear cells and prepare the dosage form. We expect the CardiAMP cell processing platform to be approved in the United States for ischemic systolic heart failure and/or chronic myocardial ischemia as part of the CardiAMP Cell Therapy System clinical development. The platform is currently cleared for use in the United States and in European Union for the preparation of a cell concentrate from bone marrow and is under investigational use for the treatment of heart failure and chronic myocardial ischemia under BioCardia IDEs in the Unites States.

- ***Helix biotherapeutic delivery system***—delivers therapeutics into the heart muscle with a penetrating helical needle from within the heart. This is a leading delivery platform in the field, which has increased safety and performance. We expect Helix to be approved in the United States as part of CardiAMP Cell Therapy System. The system is CE marked for commercial use in Europe and is under investigational use in the United States as part of our CardiAMP Cell Therapy System and CardiALLO Cell Therapy System development programs. We believe the Helix biotherapeutic delivery system is the world's safest and most efficient platform for cardiac therapeutic delivery. It has been used in more than 300 clinical procedures and is designed to be used in any catheterization laboratory in the world without the need for additional capital equipment.

  We supply our Helix biotherapeutic delivery system to selected partners developing other cell, gene, and protein therapeutic programs. These programs provide additional data, intellectual property rights, and opportunities to participate in the development of combination products for the treatment of cardiac diseases.

- ***Morph vascular access products***— provides enhanced control for Helix in biotherapeutic delivery and for other common interventions. We have secured all necessary approvals in the United States and Europe. Currently there are six Morph product model numbers approved for commercial sale in the United States via a 510(k) clearance and three in Europe under CE mark. The Morph products are valued by physicians performing difficult vascular procedures worldwide and they have been used in more than 12,000 clinical procedures to date.

Business Strategy

We are committed to applying our expertise in the fields of autologous and allogeneic cell-based therapies to improve the lives of patients with cardiovascular conditions. We are pursuing the following business strategies:

Complete the ongoing 260 patient, 40 center Phase III pivotal IDE trial of CardiAMP Cell Therapy System for patients with ischemic systolic heart failure.

Complete the recently FDA approved 343 patient, 40 center Phase III pivotal IDE trial of CardiAMP Cell Therapy System for patients with chronic myocardial ischemia.

Obtain FDA approval and commercialize CardiAMP Cell Therapy System using a highly-targeted cardiology sales force in the United States.

Advance our CardiALLO Cell Therapy System for the treatment of ischemic systolic heart failure. CardiALLO has the potential to benefit patients for whom the CardiAMP Cell Therapy System is not optimal due to the lower potency of their bone marrow cells. CardiALLO allogeneic culture-expanded bone marrow derived cells have performed well in a head to head trial with autologous mesenchymal bone marrow cells. This therapy may present advantages for patients or physicians who wish to avoid bone marrow aspiration, and our development work builds on our clinical development capabilities established through our CardiAMP program. This program positions us to provide therapy to patients ineligible for CardiAMP.

Expand CardiAMP and CardiALLO Cell Therapy Systems into additional cardiac indications. CardiAMP and CardiALLO Cell Therapy Systems have potential therapeutic benefits for multiple cardiovascular indications in addition to ischemic systolic heart failure and ischemic heart disease.

Continue to develop and partner our Helix biotherapeutic delivery system for use with other biotherapeutics. We plan to continue to make our Helix biotherapeutic delivery system available for use by qualified partners seeking to advance their own biotherapeutic candidates for similar indications.

Continue to develop and commercialize Morph catheter products. We plan to continue to enhance the performance of our Morph catheter products to benefit the CardiAMP and CardiALLO Cell Therapy Systems, to enhance Helix partnering, and to grow revenues.

Manufacturing

The CardiAMP cell processing platform is manufactured for us by our partner Zimmer Biomet. We currently produce CardiALLO cells for preclinical development in our San Carlos, California tissue culture facility. We currently manufacture our Helix biotherapeutic delivery system and Morph vascular access products in our San Carlos, California device manufacturing facility using components we source from third party suppliers.

Sales and Marketing

Our sales and marketing strategy is to market the CardiAMP and CardiALLO cell therapy systems, if approved by the FDA, for heart failure and chronic myocardial ischemia indications using a dedicated direct sales model focused on selected cardiologists. These physicians are typically affiliated with leading hospitals and medical centers and we believe that they tend to have well-established referral networks of interventional cardiologists and cardiac catheterization laboratories. We believe they represent a concentrated customer base suitable to a specialist care sales model. We believe that the CardiAMP and CardiALLO cell therapy systems will be adopted first by leading cardiologists at high-volume U.S. hospitals and medical centers, and progressively by a broader segment of the market. Cardiologists and interventional cardiologists, have a history of early adoption of innovative products and technologies, in part because the rate of innovation in this sector has been sustained, and in part because of the large unmet medical needs of heart failure patients.

Competition

The biotechnology and pharmaceutical industries in which we operate are subject to rapid change and are characterized by intense competition to develop new technologies and proprietary products. We face potential competition from many different sources, including larger and better-funded companies. While we believe that the CardiAMP Cell Therapy System's unique benefits provide us with competitive advantages, particularly given that CardiAMP is designed to be administered in a safe and short procedure, we have identified several companies which are active in the advancement of cell-based and gene-based therapeutic products in the heart failure and chronic myocardial ischemia indications. Not only must we compete with other companies that are focused on cell-based therapy treatments, any products that we may commercialize will have to compete with existing therapies and new therapies that may become available in the future.

Some of the companies that have historically been developing cell-based and gene-based therapies for cardiac indications include Abbott Laboratories, Athersys, Astra Zeneca, Baxter/Baxalta, Caladrius Biosciences, Celixr, Cesca Therapeutics, CapriCor Therapeutics, Celyad, CellProthera, Cytori Therapeutics, Juventas Therapeutics, Mesoblast, Osiris Therapeutics, Tenaya Therapeutics, Vericel Corp, Vestion, and Uniqure, some of which are in the clinical stages of development with their product candidates. There are also academic programs at University of Wisconsin, Stanford University and University of Washington that are also developing cell-based and gene-based therapies for cardiac indications.

However, these competitors may require delivery platforms for their own therapeutic programs. Because the clinical need is so large and our biotherapeutic delivery products have potential to enable multiple biotherapeutics, we view these companies also as potential collaborators and partners. To date, we have entered into agreements to provide our biotherapeutic delivery system to thirteen of these entities for various pre-clinical and clinical studies. One is active in the clinic today. None of these relationships are believed to be material to our business at this time.

Intellectual Property

We strive to protect and enhance the proprietary technologies that we believe are important to our business, and seek to obtain and maintain patents for any patentable aspects of our therapeutic candidates or products, including our anticipated companion diagnostic, their methods of use and any other inventions that are important to the development of our business. Our success will depend significantly on our ability to obtain and maintain patent and other proprietary protection for commercially important technology, inventions and know-how related to our business, defend and enforce our patents, maintain our licenses to use intellectual property owned by third parties, preserve the confidentiality of our trade secrets and operate without infringing the valid and enforceable patents and other proprietary rights of third parties. We also rely on know-how, continuing technological innovation and in-licensing opportunities to develop, strengthen, and maintain our proprietary position in the fields targeted by our therapeutic candidates.

We have a large patent portfolio of issued and pending claims covering the CardiAMP Cell Therapy System, the CardiALLO Cell Therapy System, the Helix biotherapeutic delivery system and the Morph vascular access catheter products. As of December 31, 2017, we had developed or secured rights to over 75 issued or pending U.S. patents or patent pending applications. We have sole ownership of the patents that we consider to be material, other than the patents that we license exclusively from Biomet Biologics, LLC. We have also pursued international protection for some of these U.S. patents where appropriate. Our issued U.S. patents expire between 2018 and 2032, without taking into consideration patent term extension. Among these are five issued material US patents related to the CardiAMP Cell Therapy System and the CardiALLO Cell Therapy System, which expire between 2027 and 2029 without taking into consideration patent term extension. We maintain trade secrets covering a significant body of know-how and proprietary information related to our core therapeutic candidates, biotherapeutic delivery systems and technologies. As a result, we believe our intellectual property position provides us with substantial competitive advantages for the commercial development of novel therapeutics for cardiovascular diseases.

U.S. Regulatory Protection for CardiAMP and CardiALLO

In addition to patent and trade secret protection, we may receive a 12-year period of regulatory exclusivity from the FDA upon approval of CardiAMP Cell Therapy System and CardiALLO Cell Therapy System pursuant to the Biologics Price Competition and Innovation Act. The exclusivity period, if granted, will run from the time of FDA approval. This exclusivity period, if granted, will supplement the intellectual property protection discussed above, providing an additional barrier to entry for any competitor seeking approval for a bio-similar version of the CardiAMP or CardiALLO cell therapy systems.

In addition, it is possible to extend the patent term of at least one patent covering CardiAMP and CardiALLO Cell Therapy Systems following FDA approval. This patent term extension, or PTE, is intended to compensate a patent owner for the loss of patent term during the FDA approval process. If eligible, we may use a PTE to extend the term of one or more of the patents discussed above beyond the expected expiration date. Because CardiAMP and CardiALLO cell therapy systems may involve multiple simultaneous approvals under the IDE and IND applications, each pre-market approval, or PMA or biologics license application, or BLA, associated with the system approval is anticipated to have the ability to have an extended patent term.

Trademarks

We have registered our name, logo and the trademarks “BioCardia,” “CardiAMP,” “CardiALLO,” and “Morph” in the United States. We have registered the trademarks “CardiAMP” and “CardiALLO” for use in connection with a biological product, namely, a cell-based therapy product composed of bone marrow derived cells for medical use. We also have rights to use the “Helix” trademark in the United States. We have registered Morph for use in connection with steerable vascular access technology. We intend to pursue additional registrations in markets outside the United States where we plan to sell our therapies and products.

Patent Term

The term of individual patents and patent applications will depend upon the legal term of the patents in the countries in which they are obtained. In most countries, the patent term is 20 years from the date of filing of the patent application (or parent application, if applicable). For example, if an international Patent Cooperation Treaty, or PCT, application is filed, any patent issuing from the PCT application in a specific country expires 20 years from the filing date of the PCT application. In the United States, however, if a patent was in force on June 8, 1995, or issued on an application that was filed before June 8, 1995, that patent will have a term that is the greater of 20 years from the filing date, or 17 years from the date of issue.

Under the Hatch-Waxman Act, the term of a patent that covers an FDA-approved drug, biological product may also be eligible for PTE. PTE permits restoration of a portion of the patent term of a U.S. patent as compensation for the patent term lost during product development and the FDA regulatory review process if approval of the application for the product is the first permitted commercial marketing of a drug or biological product containing the active ingredient. The patent term restoration period is generally one-half the time between the effective date of an IND and the submission date of a BLA plus the time between the submission date of a BLA and the approval of that application. The Hatch-Waxman Act permits a PTE for only one patent applicable to an approved drug, and the maximum period of restoration is five years beyond the expiration of the patent. A PTE cannot extend the remaining term of a patent beyond a total of 14 years from the date of product approval, and a patent can only be extended once, and thus, even if a single patent is applicable to multiple products, it can only be extended based on one product. Similar provisions may be available in Europe and certain other foreign jurisdictions to extend the term of a patent that covers an approved drug. When possible, depending upon the length of clinical trials and other factors involved in the filing of a BLA, we expect to apply for PTEs for patents covering our therapeutic candidates and products and their methods of use. For additional information on PTE, see “Government Regulation.”

Proprietary Rights and Processes

We may rely, in some circumstances, on proprietary technology and processes (including trade secrets) to protect our technology. However, these can be difficult to protect. We seek to protect our proprietary technology and processes, in part, by entering into confidentiality agreements with those who have access to our confidential information, including our employees, consultants, scientific advisors and contractors. We also seek to preserve the integrity and confidentiality of our proprietary technology and processes by maintaining physical security of our premises and physical and electronic security of our information technology systems. While we have confidence in these individuals, organizations and systems, agreements or security measures may be breached, and we may not have adequate remedies for any breach. In addition, our proprietary technology and processes may otherwise become known or be independently discovered by competitors. To the extent that our employees, consultants, scientific advisors, contractors, or any future collaborators use intellectual property owned by others in their work for us, disputes may arise as to the rights in related or resulting know-how and inventions. For this and more comprehensive risks related to our proprietary technology and processes, please see “Risk Factors—Risks Related to our Intellectual Property.”

License Agreement with Biomet Biologics, LLC

In October 2012, we entered into a license and distribution agreement with Biomet Biologics, LLC under which we obtained an exclusive, nontransferable, worldwide distribution right, patent license and trademark license to a point of care cell processing platform. Under the terms of the agreement, we are obligated to pay a royalty based on the price of the disposables in the CardiAMP cell processing platform for the duration of the agreement. We expect the royalty payments to Biomet Biologics, LLC for the licensed product to amount to a low or mid-single digit percentage of the expected price that we will charge for the CardiAMP Cell Therapy System. The agreement has a term of 10 years or the time the last patent pursuant to the agreement expires, whichever is later. The agreement may be terminated by Biomet Biologics, LLC for a failure by us to meet any milestone requirements, including minimum purchase requirements, as well as by either party upon 30 days prior written notice in the event of a breach of any material term by the other party. We have the right to terminate the agreement upon 90 days prior written notice in the event the safety, efficacy or comparative effectiveness of the product is insufficient to meet our commercial needs.

Technology Access Program for Biotherapeutic Delivery Systems

Our preclinical work with partners and collaborators generally takes place under arrangements where we secure access to data, reports, and a non-exclusive license to delivery technology improvement inventions.

Clinical Research Agreements for Biotherapeutic Delivery Systems

Our clinical work with partners generally takes place under arrangements where we secure access to data, reports, and a non-exclusive license to technology improvement inventions. Financial terms of each agreement are anticipated to cover our costs and provide milestone payments. We hope to generate sales if any of our partners are successful with commercializing their products with our delivery platform.

Regulation

Biological products, including cell-based therapy products, and medical devices are subject to regulation under the Federal Food, Drug, and Cosmetic Act, or FD&C Act, and the Public Health Service Act, or PHS Act, and other federal, state, local and foreign statutes and regulations. Both the FD&C Act and the PHS Act and their corresponding regulations govern, among other things, the testing, manufacturing, safety, purity, potency, efficacy, labeling, packaging, storage, record keeping, distribution, reporting, advertising and other promotional practices involving biological products. FDA acceptance must be obtained before clinical testing of an investigational biological and medical device begins, and each clinical trial protocol for a cell-based therapy product is submitted to and reviewed by the FDA. FDA approval must be obtained before marketing of biological and/or medical devices. The process of obtaining regulatory approvals and the subsequent compliance with applicable federal, state, local and foreign statutes and regulations require the expenditure of substantial time and financial resources and we may not be able to obtain the required regulatory approvals on a timely basis, or at all. To date, the FDA has never approved for commercial sale a cell-based therapy product intended to treat the heart.

Within the FDA, the Center for Biologics Evaluation and Research, or CBER, regulates cell-based therapy products. For products that use medical devices, including diagnostics, to deliver cell therapies, CBER works closely with the FDA's Center for Devices and Radiological Health, or CDRH.

U.S. Biological Product Development Process

Our CardiALLO therapeutic candidate will be regulated in the United States as a biological product. The process required by the FDA before a biological product may be tested and marketed in the United States generally involves the following:

- completion of nonclinical laboratory tests and animal studies according to good laboratory practices, or GLP, regulations and applicable requirements for the humane use of laboratory animals or other applicable regulations;
- submission to the FDA of an IND application, which must become effective before human clinical trials may begin and must be updated annually or when significant changes are made;
- approval by an independent Institutional Review Board, or IRB, or ethics committee at each clinical site before the trial begins;
- performance of adequate and well-controlled human clinical trials according to the FDA's regulations, commonly referred to as good clinical practices, or GCPs, and any additional requirements for the protection of human research subjects and their health information, to establish the safety, purity and potency of the proposed biological product for its intended use;
- preparation of and submission to the FDA of a BLA for marketing approval, after completion of all pivotal clinical trials;
- satisfactory completion of an FDA Advisory Committee review, if applicable;
- a determination by the FDA within 60 days of its receipt of a BLA to file the application for review;
- satisfactory completion of an FDA inspection of the manufacturing facility or facilities where the biological product is produced to assess compliance with GMP, to assure that the facilities, methods and controls are adequate to preserve the biological product's identity, strength, quality and purity and, if applicable, the FDA's current good tissue practices, or GTPs, for the use of human cellular and tissue products;
- potential FDA audit of the nonclinical study and clinical trial sites that generated the data in support of the BLA; and
- FDA review and approval, or licensure, of the BLA for particular indications for use in the United States, which must be updated annually when significant changes are made.

The testing and approval process requires substantial time, effort and financial resources, and we cannot be certain that any approvals for our therapeutic candidates or product candidates will be granted on a timely basis, if at all. Before testing any biological product candidate, including a cell-based therapy product, in humans, the product candidate enters the preclinical testing stage. Preclinical tests, also referred to as nonclinical studies, include laboratory evaluations of product chemistry, toxicity and formulation, as well as animal studies to assess the potential safety and activity of the product candidate. The conduct of the preclinical tests must comply with federal regulations and requirements including GLPs.

The clinical trial sponsor must submit the results of the preclinical tests, together with manufacturing information, analytical data, any available clinical data or literature and a proposed clinical protocol, to the FDA as part of the IND. Some preclinical testing may continue even after the IND is submitted. The IND automatically becomes effective 30 days after receipt by the FDA, unless the FDA places the trial on a clinical hold within that 30-day time period. In such a case, the IND sponsor and the FDA must resolve any outstanding concerns before the clinical trial can begin. The FDA may also impose clinical holds on a biological product candidate at any time before or during clinical trials due to safety concerns or non-compliance. If the FDA imposes a clinical hold, trials may not recommence without FDA authorization and then only under terms authorized by the FDA. Accordingly, we cannot be sure that submission of an IND will result in the FDA allowing clinical trials to begin, or that, once begun, issues will not arise that suspend or terminate such trials.

Clinical trials involve the administration of the biological product candidate to healthy volunteers or patients under the supervision of qualified investigators, generally physicians not employed by or under the trial sponsor's control. Clinical trials are conducted under protocols detailing, among other things, the objectives of the clinical trial, dosing procedures, subject selection and exclusion criteria, and the parameters to be used to monitor subject safety, including stopping rules that assure a clinical trial will be stopped if certain adverse events should occur. Each protocol and any amendments to the protocol must be submitted to the FDA as part of the IND. Clinical trials must be conducted and monitored in accordance with the FDA's regulations comprising the GCP requirements, including the requirement that all research subjects provide informed consent. Further, each clinical trial must be reviewed and approved by an independent institutional review board, or IRB, at or servicing each institution at which the clinical trial will be conducted. An IRB is charged with protecting the welfare and rights of trial participants and considers such items as whether the risks to individuals participating in the clinical trials are minimized and are reasonable in relation to anticipated benefits. The IRB also approves the form and content of the informed consent that must be signed by each clinical trial subject or his or her legal representative and must monitor the clinical trial until completed. Clinical trials also must be reviewed by an institutional biosafety committee, or IBC, a local institutional committee that reviews and oversees basic and clinical research conducted at that institution. The IBC assesses the safety of the research and identifies any potential risk to public health or the environment.

For purposes of BLA approval, human clinical trials are typically conducted in three sequential phases that may overlap or be combined:

- ***Phase I.*** The biological product is initially introduced into healthy human subjects and tested for safety. In the case of some products for severe or life-threatening diseases, especially when the product may be too inherently toxic to ethically administer to healthy volunteers, the initial human testing is often conducted in patients with the disease or condition. These studies are designed to test the safety, dosage tolerance, absorption, metabolism and distribution of the investigational product in humans, the side effects associated with increasing doses and, if possible, to gain early evidence on effectiveness.

- ***Phase II.*** The biological product is evaluated in a limited patient population with a specified disease or condition to identify possible adverse effects and safety risks, to preliminarily evaluate the efficacy of the product for specific targeted diseases and to determine dosage tolerance, optimal dosage and dosing schedule. Multiple Phase II clinical trials may be conducted to obtain information prior to beginning larger and more expensive Phase III clinical trials.

- ***Phase III.*** Clinical trials are undertaken to further evaluate dosage, clinical efficacy, potency, and safety in an expanded patient population at geographically dispersed clinical trial sites, to provide statistically significant evidence of clinical efficacy and to further test for safety. These clinical trials are intended to establish the overall risk/benefit ratio of the product and provide an adequate basis for product approval and labeling.

Post-approval clinical trials, sometimes referred to as Phase IV clinical trials, may be required by the FDA or voluntarily conducted after initial marketing approval to gain more information about the product, including long-term safety follow-up.

During all phases of clinical development, regulatory agencies require extensive monitoring and auditing of all clinical activities, clinical data, and clinical trial investigators. Annual progress reports detailing the results of the clinical trials must be submitted to the FDA. Written IND safety reports must be promptly submitted to the FDA, the NIH and the investigators for serious and unexpected adverse events, any findings from other studies, tests in laboratory animals or *in vitro* testing that suggest a significant risk for human subjects, or any clinically important increase in the rate of a serious suspected adverse reaction over that listed in the protocol or investigator brochure. The sponsor must submit an IND safety report within 15 calendar days after the sponsor determines that the information qualifies for reporting. The sponsor also must notify the FDA of any unexpected fatal or life-threatening suspected adverse reaction within seven calendar days after the sponsor's initial receipt of the information. Phase I, Phase II and Phase III clinical trials may not be completed successfully within any specified period, if at all. The FDA or the sponsor or its data safety monitoring board may suspend a clinical trial at any time on various grounds, including a finding that the research subjects or patients are being exposed to an unacceptable health risk, including risks inferred from other unrelated trials. Similarly, an IRB can suspend or terminate approval of a clinical trial at its institution if the clinical trial is not being conducted in accordance with the IRB's requirements or if the biological product has been associated with unexpected serious harm to patients.

Human cell-based therapy products are a new category of therapeutics. Because this is a relatively new and expanding area of novel therapeutic interventions, there can be no assurance as to the length of the trial period, the number of patients the FDA will require to be enrolled in the trials in order to establish the safety, efficacy, purity and potency of human cell-based therapy products, or that the data generated in these trials will be acceptable to the FDA to support marketing approval.

Concurrently with clinical trials, companies usually complete additional animal studies and must also develop additional information about the physical characteristics of the biological product as well as finalize a process for manufacturing the product in commercial quantities in accordance with GMP requirements. To help reduce the risk of the introduction of adventitious agents with use of biological products, the PHS Act emphasizes the importance of manufacturing control for products whose attributes cannot be precisely defined. The manufacturing process must be capable of consistently producing quality batches of the product candidate and, among other things, the sponsor must develop methods for testing the identity, strength, quality, potency and purity of the final biological product. Additionally, appropriate packaging must be selected and tested and stability studies must be conducted to demonstrate that the biological product candidate does not undergo unacceptable deterioration over its shelf life.

U.S. Review and Approval Processes

After the successful completion of clinical trials of a biological product, FDA approval of a BLA must be obtained before commercial marketing of the biological product. The BLA must include results of product development, laboratory and animal studies, human trials, information on the manufacture and composition of the product, proposed labeling and other relevant information. The FDA may grant deferrals for submission of data or full or partial waivers. The testing and approval processes require substantial time and effort and there can be no assurance that the FDA will accept the BLA for filing and, even if filed, that any approval will be granted on a timely basis, if at all.

Under the Prescription Drug User Fee Act, or PDUFA, as amended, each BLA must be accompanied by a significant user fee. The FDA adjusts the PDUFA user fees on an annual basis. PDUFA also imposes an annual product fee for biological products and an annual establishment fee on facilities used to manufacture prescription biological products. Fee waivers or reductions are available in certain circumstances, including a waiver of the application fee for the first application filed by a small business. Additionally, no user fees are assessed on BLAs for products designated as orphan drugs, unless the product also includes a non-orphan indication.

Within 60 days following submission of the application, the FDA reviews a BLA submitted to determine if it is substantially complete before the agency accepts it for filing. The FDA may refuse to file any BLA that it deems incomplete or not properly reviewable at the time of submission and may request additional information. In this event, the BLA must be resubmitted with the additional information. The resubmitted application also is subject to review before the FDA accepts it for filing. Once the submission is accepted for filing, the FDA begins an in-depth substantive review of the BLA. The FDA reviews the BLA to determine, among other things, whether the proposed product is safe and potent, or effective, for its intended use, and has an acceptable purity profile, and whether the product is being manufactured in accordance with GMP to assure and preserve the product's identity, safety, strength, quality, potency and purity. The FDA may refer applications for novel biological products or biological products that present difficult questions of safety or efficacy to an advisory committee, typically a panel that includes clinicians and other experts, for review, evaluation and a recommendation as to whether the application should be approved and under what conditions. The FDA is not bound by the recommendations of an advisory committee, but it considers such recommendations carefully when making decisions. During the biological product approval process, the FDA also will determine whether a Risk Evaluation and Mitigation Strategy, or REMS, is necessary to assure the safe use of the biological product. If the FDA concludes a REMS is needed, the sponsor of the BLA must submit a proposed REMS. The FDA will not approve a BLA without a REMS, if required.

Before approving a BLA, the FDA will inspect the facilities at which the product is manufactured. The FDA will not approve the product unless it determines that the manufacturing processes and facilities are in compliance with GMP requirements and adequate to assure consistent production of the product within required specifications. Additionally, before approving a BLA, the FDA will typically inspect one or more clinical sites to assure that the clinical trials were conducted in compliance with IND trial requirements and GCP requirements. To assure GMP and GCP compliance, an applicant must incur significant expenditure of time, money and effort in the areas of training, record keeping, production, and quality control.

Notwithstanding the submission of relevant data and information, the FDA may ultimately decide that the BLA does not satisfy its regulatory criteria for approval and deny approval. Data obtained from clinical trials are not always conclusive and the FDA may interpret data differently than we interpret the same data. If the agency decides not to approve the BLA in its present form, the FDA will issue a complete response letter that describes all of the specific deficiencies in the BLA identified by the FDA. The deficiencies identified may be minor, for example, requiring labeling changes, or major, for example, requiring additional clinical trials. Additionally, the complete response letter may include recommended actions that the applicant might take to place the application in a condition for approval. If a complete response letter is issued, the applicant may either resubmit the BLA, addressing all of the deficiencies identified in the letter, or withdraw the application.

If a product receives regulatory approval, the approval may be significantly limited to specific diseases and dosages or the indications for use may otherwise be limited, which could restrict the commercial value of the product. Further, the FDA may require that certain contraindications, warnings or precautions be included in the product labeling. The FDA may impose restrictions and conditions on product distribution, prescribing, or dispensing in the form of a risk management plan, or otherwise limit the scope of any approval. In addition, the FDA may require post-marketing clinical trials, sometimes referred to as Phase IV clinical trials, designed to further assess a biological product’s safety and effectiveness, and testing and surveillance programs to monitor the safety of approved therapies and products that have been commercialized.

The FDA has agreed to certain review goals under PDUFA, and aims to complete its review of 90% of standard BLAs within ten months from filing and 90% of priority BLAs within six months from filing. The FDA does not always meet its PDUFA goal dates for standard and priority BLAs and its review goals are subject to change from time to time. The review process and the PDUFA goal date may be extended by three months if the FDA requests, or the BLA sponsor otherwise provides, additional information or clarification regarding information already provided in the submission within the last three months before the PDUFA goal date.

Fast Track Designation, Accelerated Approval, Priority Review and Breakthrough Therapy Programs

The FDA has a Fast Track program that is intended to expedite or facilitate the process for reviewing new drugs and biological products that meet certain criteria. Specifically, new drugs and biological products are eligible for Fast Track designation if they are intended to treat a serious or life-threatening condition and demonstrate the potential to address unmet medical needs for the condition. Fast Track designation applies to the combination of the product and the specific indication for which it is being studied. The sponsor of a new drug or biological product may request the FDA to designate the drug or biological product as a Fast Track product at any time during the clinical development of the product. Unique to a Fast Track product, the FDA may consider for review sections of the marketing application on a rolling basis before the complete application is submitted, if the sponsor provides a schedule for the submission of the sections of the application, the FDA agrees to accept sections of the application and determines that the schedule is acceptable, and the sponsor pays any required user fees upon submission of the first section of the application.

Other types of FDA programs intended to expedite development and review, such as priority review, accelerated approval and Breakthrough Therapy designation, also exist. A product is eligible for priority review if it has the potential to provide safe and effective therapy where no satisfactory alternative therapy exists or a significant improvement in the treatment, diagnosis or prevention of a disease compared to marketed products. The FDA will attempt to direct additional resources to the evaluation of an application for a new drug or biological product designated for priority review in an effort to facilitate the review. Additionally, a product may be eligible for accelerated approval. Drug or biological products studied for their safety and effectiveness in treating serious or life-threatening illnesses and that provide meaningful therapeutic benefit over existing treatments may receive accelerated approval, which means that they may be approved on the basis of adequate and well-controlled clinical trials establishing that the product has an effect on a surrogate endpoint that is reasonably likely to predict a clinical benefit, or on the basis of an effect on a clinical endpoint other than survival or irreversible morbidity. As a condition of approval, the FDA may require that a sponsor of a drug or biological product receiving accelerated approval perform adequate and well-controlled post-marketing clinical trials. In addition, the FDA currently requires as a condition for accelerated approval pre-approval of promotional materials, which could adversely impact the timing of the commercial launch of the product.

A product may also be eligible for receipt of a Breakthrough Therapy designation. The Breakthrough Therapy designation is intended to expedite the FDA's review of a potential new drug for serious or life-threatening diseases where "preliminary clinical evidence indicates that the drug may demonstrate substantial improvement over existing

therapies on one or more clinically significant endpoints, such as substantial treatment effects observed early in clinical development." The designation of a drug as a Breakthrough Therapy provides the same benefits as are available under the Fast Track program, as well as intensive FDA guidance on the product's development program. Where appropriate, we intend to utilize regulatory programs that can help expedite our product development and commercialization efforts. However, Fast Track designation, priority review, accelerated approval and Breakthrough Therapy designation do not change the standards for approval, but may expedite the development or approval process.

Post-Approval Requirements

Maintaining substantial compliance with applicable federal, state and local statutes and regulations requires the expenditure of substantial time and financial resources. Rigorous and extensive FDA regulation of biological products continues after approval, particularly with respect to GMP. We will rely, and expect to continue to rely, on third parties for the production of clinical and commercial quantities of any products that we may commercialize. Manufacturers of our products are required to comply with applicable requirements in the GMP regulations, including quality control and quality assurance and maintenance of records and documentation. Other post-approval requirements applicable to biological products include reporting of GMP deviations that may affect the identity, potency, purity and overall safety of a distributed product, record-keeping requirements, reporting of adverse effects, reporting updated safety and efficacy information, and complying with electronic record and signature requirements. After a BLA is approved, the product also may be subject to official lot release. As part of the manufacturing process, the manufacturer is required to perform certain tests on each lot of the product before it is released for distribution. If the product is subject to official release by the FDA, the manufacturer submits samples of each lot of product to the FDA together with a release protocol showing a summary of the history of manufacture of the lot and the results of all of the manufacturer's tests performed on the lot. In addition, the FDA conducts laboratory research related to the regulatory standards on the safety, purity, potency and effectiveness of biological products.

We also must comply with the FDA's advertising and promotion requirements, such as those related to direct-to-consumer advertising, the prohibition on promoting products for uses or in patient populations that are not described in the product's approved labeling (known as "off-label use"), industry-sponsored scientific and educational activities, and promotional activities involving the internet. Discovery of previously unknown problems or the failure to comply with the applicable regulatory requirements may result in restrictions on the marketing of a product or withdrawal of the product from the market as well as possible civil or criminal sanctions. Failure to comply with the applicable U.S. requirements at any time during the product development process, approval process or after approval may subject an applicant or manufacturer to administrative or judicial civil or criminal sanctions and adverse publicity. FDA sanctions could include refusal to approve pending applications, withdrawal of an approval, clinical hold, warning or untitled letters, product recalls, product seizures, total or partial suspension of production or distribution, injunctions, fines, refusals of government contracts, mandated corrective advertising or communications with doctors, debarment, restitution, disgorgement of profits, or civil or criminal penalties. Any agency or judicial enforcement action could have a material adverse effect on us.

Biological product manufacturers and other entities involved in the manufacture and distribution of approved biological products are required to register their establishments with the FDA and certain state agencies, and are subject to periodic unannounced inspections by the FDA and certain state agencies for compliance with GMPs and other laws. Accordingly, manufacturers must continue to expend time, money and effort in the area of production and quality control to maintain GMP compliance. Discovery of problems with a product after approval may result in restrictions on a product, manufacturer or holder of an approved BLA, including withdrawal of the product from the market. In addition, changes to the manufacturing process or facility generally require prior FDA approval before being implemented and other types of changes to the approved product, such as adding new indications and additional labeling claims, are also subject to further FDA review and approval.

U.S. Premarket Clearance and Approval Requirements for Medical Devices

Unless an exemption applies, each medical device we wish to distribute commercially in the United States will require either prior premarket notification, or 510(k) clearance, or prior approval of a PMA application from the FDA. The FDA classifies medical devices into one of three classes. Devices deemed to pose low to moderate risk are placed in either class I or II, which, absent an exemption, requires the manufacturer to file with the FDA a 510(k) submission requesting permission for commercial distribution. This process is known as 510(k) clearance. Some low-risk devices are exempt from this requirement. Devices deemed by the FDA to pose the greatest risk, such as life-sustaining, life-supporting or certain implantable devices, or devices deemed not substantially equivalent to a previously cleared 510(k) device, are placed in class III, requiring approval of a PMA application.

Regulation of CardiAMP through the PMA Pathway

Combination products are therapeutic and diagnostic products that combine drugs, devices, and/or biological products. Because combination products involve components that would normally be regulated under different types of regulatory authorities, and frequently by different centers of the FDA, they raise regulatory, policy, and review management challenges. Differences in regulatory pathways for each component of the product can impact the regulatory processes for all aspects of product development and management, including preclinical testing, clinical investigation, marketing applications, manufacturing and quality control, adverse event reporting, promotion and advertising, and post-approval modifications.

A combination product is assigned to an FDA Agency Center or alternative organizational component that will have primary jurisdiction for its premarket review and regulation. For cell-based therapy and related products, the FDA established the Office of Cellular, Tissue and Gene Therapies within CBER to consolidate the review of such products, and the Cellular, Tissue and Gene Therapies Advisory Committee to advise CBER on its review. In our case, the CardiAMP Cell Therapy System involves minimal manipulation of cells within the procedure room, enabling it to be the first cardiac cell-based therapy we are aware of that CBER has indicated it will regulate through the PMA pathway.

PMA applications must be supported by valid scientific evidence, which typically requires extensive data, including technical, preclinical, clinical and manufacturing data, to demonstrate to the FDA's satisfaction the safety and effectiveness of the cell-based therapy. After a PMA application is deemed complete, the FDA will accept the application for filing and begin an in-depth review of the submitted information. During this review period, the FDA may request additional information or clarification of information already provided. Also during the review period, an advisory panel of experts from outside the FDA may be convened to review and evaluate the application and provide recommendations to the FDA as to the approvability of the device. As part of its review of the PMA, the FDA will conduct a pre-approval inspection of the manufacturing facility or facilities to ensure compliance with the Quality System Regulation, or QSR, which requires manufacturers to follow design, testing, control, documentation and other quality assurance procedures. FDA review of an initial PMA application is required by statute to take between six to ten months, although the process typically takes longer, and may require several years to complete. If the FDA evaluations of both the PMA application and the manufacturing facilities are favorable, the FDA will either issue an approval letter or an approvable letter, which usually contains a number of conditions that must be met in order to secure the final approval of the PMA. If the FDA's evaluation of the PMA or manufacturing facilities is not favorable, the FDA will deny approval of the PMA or issue a not approvable letter. A not approvable letter will outline the deficiencies in the application and, where practical, will identify what is necessary to make the PMA approvable. The FDA may also determine that additional clinical trials are necessary, in which case the PMA approval may be delayed for several months or years while the trials are conducted and then the data submitted in an amendment to the PMA. Once granted, PMA approval may be withdrawn by the FDA if compliance with post-approval requirements, conditions of approval or other regulatory standards is not maintained or problems are identified following initial marketing.

The FDA may approve a PMA application with post-approval conditions intended to ensure the safety and effectiveness of the device including, among other things, restrictions on labeling, promotion, sale and distribution, collection of long-term follow-up data from patients in the clinical trial that supported approval, or new post-approval studies. Failure to comply with the conditions of approval can result in materially adverse enforcement action, including the loss or withdrawal of the approval. PMA supplements are required for modifications that could affect device safety or effectiveness, including, for example, certain types of modifications to the device's indication for use, manufacturing process, labeling and design. PMA supplements often require submission of the same type of information as an original PMA application, except that the supplement is limited to information needed to support any changes to the device covered by the original PMA application, and may not require as extensive clinical data or the convening of an advisory panel.

A clinical trial is almost always required to support a PMA application. We expect that the CardiAMP Cell Therapy System will require a single pivotal trial for PMA approval in the CardiAMP Heart Failure and CardiAMP Chronic Myocardial Ischemia trials. However, there is no guarantee that the FDA will grant us regulatory clearance or approval to market the CardiAMP Cell Therapy System on the basis of a single pivotal trial. Two well-controlled pivotal studies could be necessary to provide the FDA assurance of safety or effectiveness. In the United States, absent certain limited exceptions, human clinical trials intended to support product clearance or approval require an IDE application, which the FDA reviews. Some types of trials deemed to present "non-significant risk" are deemed to have an approved IDE once certain requirements are addressed and IRB approval is obtained. If the device presents a "significant risk" to human health, as defined by FDA regulations, the sponsor must submit an IDE application to the FDA and obtain IDE approval prior to commencing the human clinical trials. The IDE application must be supported by appropriate data, such as animal and laboratory trial results, showing that it is safe to evaluate the device in humans

and that the trial protocol is scientifically sound. The IDE application must be approved in advance by the FDA for a specified number of subjects, unless the product is deemed a non-significant risk device and eligible for more abbreviated IDE requirements. Clinical trials for a significant risk device may begin once the IDE application is approved by the FDA and the responsible institutional review boards at the clinical trial sites. There can be no assurance that submission of an IDE will result in the ability to commence clinical trials. Additionally, after a trial begins, the FDA may place it on hold or terminate it if, among other reasons, it concludes that the clinical subjects are exposed to unacceptable health risks that outweigh the benefits of participation in the trial. During a trial, we are required to comply with the FDA's IDE requirements for investigator selection, trial monitoring, reporting, record keeping and prohibitions on the promotion or commercialization of investigational devices or making safety or efficacy claims for them, among other things. We are also responsible for the appropriate labeling and distribution of investigational devices. Our clinical trials must be conducted in accordance with FDA regulations and federal and state regulations concerning human subject protection, including informed consent and healthcare privacy. The investigators must also obtain patient informed consent, rigorously follow the investigational plan and trial protocol, control the disposition of investigational devices and comply with all reporting and record keeping requirements, among other things. The FDA's grant of permission to proceed with clinical trials does not constitute a binding commitment that the FDA will consider the trial design adequate to support marketing clearance or approval. In addition, there can be no assurance that the data generated during a clinical trial will meet the chosen study endpoints or otherwise produce results that will lead the FDA to grant marketing clearance or approval. Similarly, in Europe, the clinical trial must be approved by the local ethics committee and in some cases, including trials of high-risk devices, by the Ministry of Health in the applicable country.

After a device is placed on the market, it remains subject to significant regulatory requirements. Medical devices may be marketed only for the uses and indications for which they are cleared or approved. Device manufacturers must also establish registration and device listings with the FDA. A medical device manufacturer's manufacturing processes and those of its suppliers are required to comply with the applicable portions of the QSR, which cover the methods and documentation of the design, testing, production, processes, controls, quality assurance, labeling, packaging and shipping of medical devices. Domestic facility records and manufacturing processes are subject to periodic unscheduled inspections by the FDA. The FDA also may inspect foreign facilities that export products to the United States.

Failure by us or our suppliers to comply with applicable regulatory requirements can result in enforcement action by the FDA or other regulatory authorities, which may result in sanctions and related consequences including, but not limited to:

- adverse publicity, untitled letters or warning letters;
- fines, injunctions, consent decrees and civil penalties;
- recall, detention or seizure of our products;
- operating restrictions, partial suspension or total shutdown of production;
- refusal of or delay in granting our requests for 510(k) clearance or premarket approval of new products or modified products;
- withdrawing 510(k) clearance or premarket approvals that are already granted;
- refusal to grant export approval for our products;
- criminal prosecution; and
- unanticipated expenditures to address or defend such actions.

Because elements of the CardiAMP Cell Therapy System are already approved or cleared and manufactured for commercial use, we believe regulatory approval risks are primarily those of clinical efficacy in each of the two indications being assessed under separate IDEs.

Regulation of Companion Diagnostics

Companion diagnostics are subject to regulation by the FDA, the EMA and other foreign regulatory authorities as medical devices and require separate regulatory clearance or approval prior to commercial use. We anticipate that the CardiAMP potency assay for each indication will require approval under a PMA submitted to the CDRH prior to commercialization. We and our third-party collaborators who may develop our companion diagnostics will work cooperatively to generate the data required for submission with the PMA application, and will remain in close contact with the CDRH to ensure that any changes in requirements are incorporated into the development plans. We further anticipate that regulatory approval of the CardiAMP potency assay for each indication will be a prerequisite to our ability to market the CardiAMP Cell Therapy System. Representatives of CDRH have participated in our meetings with CBER regarding CardiAMP Cell Therapy System to discuss the potential use of the CardiAMP potency assay, and we anticipate that future meetings will include representatives from both CBER and CDRH to ensure that the PMA submissions (for CardiAMP and the CardiAMP potency assay) are coordinated and subject to parallel review by these respective FDA centers. Accordingly, our objective is to align the development programs such that the CardiAMP potency assay will be developed and approved contemporaneously with CardiAMP.

In the United States, companion diagnostic tests used in conjunction with drug or biological products are classified as medical devices under the FD&C Act. We anticipate that our CardiAMP potency assay we are developing in conjunction with our CardiAMP therapeutic candidate will be subject to the PMA approval process.

On July 31, 2014 the FDA issued "Guidance for Industry: In Vitro Companion Diagnostic Devices," to help companies identify the need for companion diagnostics at an earlier stage in the drug development process and to plan for co-development of the drug and companion diagnostic test. The ultimate goal of the guidance is to stimulate early collaborations that will result in faster access to promising new treatments for patients living with serious and life-threatening diseases. According to the draft guidance, for novel products such as CardiAMP, the PMA for a companion diagnostic device should be developed and approved contemporaneously with the biological product. We believe our programs for the development of the CardiAMP potency assay are consistent with the draft guidance as proposed.

On July 15, 2016, FDA released the draft guidance, "Principles for Codevelopment of an In Vitro Companion Diagnostic Device with a Therapeutic Product." This guidance document is intended to be a practical guide to assist therapeutic product sponsors and IVD sponsors in developing a therapeutic product and an accompanying IVD companion diagnostic

Coverage and Reimbursement

Sales of our products will depend, in part, on the extent to which our products will be covered by third-party payors, such as government healthcare programs, commercial insurance and managed healthcare organizations. These third-party payors are increasingly reducing reimbursements for medical products and services. In addition, the U.S. government, state legislatures and foreign governments have continued implementing cost containment programs, including price controls, restrictions on reimbursement and requirements for substitution of generic products. Adoption of price controls and cost-containment measures, and adoption of more restrictive policies in jurisdictions with existing controls and measures, could further limit our net revenue and results. Decreases in third-party reimbursement for our therapeutic candidates or a decision by a third-party payor to not cover our therapeutic candidates could reduce physician usage of our products once approved and have a material adverse effect on our sales, results of operations and financial condition.

Affordable Care Act

In March 2010, the Patient Protection and Affordable Care Act, as amended by the Health Care and Education Reconciliation Act of 2010, or collectively, the Affordable Care Act, was enacted, which includes measures that have or will significantly change the way health care is financed by both governmental and private insurers. Among the provisions of the Affordable Care Act of greatest importance to the pharmaceutical industry are the following:

- The Medicaid Drug Rebate Program requires pharmaceutical manufacturers to enter into and have in effect a national rebate agreement with the Secretary of the Department of Health and Human Services as a condition for states to receive federal matching funds for the manufacturer’s outpatient drugs furnished to Medicaid patients. Effective in 2010, the Affordable Care Act made several changes to the Medicaid Drug Rebate Program, including increasing pharmaceutical manufacturers’ rebate liability by raising the minimum basic Medicaid rebate on most branded prescription drugs and biologic agents from 15.1% of average manufacturer price (AMP) to 23.1% of AMP and adding a new rebate calculation for “line extensions” (*i.e.*, new formulations, such as extended release formulations) of solid oral dosage forms of branded products, as well as potentially impacting their rebate liability by modifying the statutory definition of AMP. The Affordable Care Act also expanded the universe of Medicaid utilization subject to drug rebates by requiring pharmaceutical manufacturers to pay rebates on Medicaid managed care utilization as of 2010. Per a ruling by the U.S. Supreme Court in 2012, states have the option to expand their Medicaid programs which in turn expands the population eligible for Medicaid drug benefits. The Centers for Medicare & Medicaid Services, or CMS, has proposed to expand Medicaid rebate liability to the territories of the United States as well. In

addition, the Affordable Care Act provides for the public availability of retail survey prices and certain weighted average AMPs under the Medicaid program. The implementation of this requirement by the CMS may also provide for the public availability of pharmacy acquisition of cost data, which could negatively impact our sales.

In order for a pharmaceutical product to receive federal reimbursement under the Medicare Part B and Medicaid programs or to be sold directly to U.S. government agencies, the manufacturer must extend discounts to entities eligible to participate in the 340B drug pricing program. The required 340B discount on a given product is calculated based on the AMP and Medicaid rebate amounts reported by the manufacturer. Effective in 2010, the Affordable Care Act expanded the types of entities eligible to receive discounted 340B pricing, although, under the current state of the law, with the exception of children's hospitals, these newly eligible entities will not be eligible to receive

- discounted 340B pricing on orphan drugs when used for the orphan indication. In July 2013, the Health Resources and Services Administration (HRSA) issued a final rule allowing the newly eligible entities to access discounted orphan drugs if used for non-orphan indications. While the final rule was vacated by a federal court ruling, HRSA has stated it will continue to allow discounts for orphan drugs when used for any indication other than for orphan indications. In addition, as 340B drug pricing is determined based on AMP and Medicaid rebate data, the revisions to the Medicaid rebate formula and AMP definition described above could cause the required 340B discount to increase.

Effective in 2011, the Affordable Care Act imposed a requirement on manufacturers of branded drugs and biologic

- agents to provide a 50% discount off the negotiated price of branded drugs dispensed to Medicare Part D patients in the coverage gap (*i.e.*, "donut hole").

- Effective in 2011, the Affordable Care Act imposed an annual, nondeductible fee on any entity that manufactures or imports certain branded prescription drugs and biologic agents, apportioned among these entities according to their market share in certain government healthcare programs, although this fee would not apply to sales of certain products approved exclusively for orphan indications.

- The Affordable Care Act required pharmaceutical manufacturers to track certain financial arrangements with physicians and teaching hospitals, including any "transfer of value" made or distributed to such entities, as well as any ownership or investment interests held by physicians and their immediate family members. Manufacturers were required to begin tracking this information in 2013 and to report this information to CMS by March 2014.

As of 2010, a new Patient-Centered Outcomes Research Institute was established pursuant to the Affordable Care Act to oversee, identify priorities in, and conduct comparative clinical effectiveness research, along with funding for such research. The research conducted by the Patient-Centered Outcomes Research Institute may affect the market for certain pharmaceutical products.

There have been judicial and Congressional challenges and amendments to certain aspects of the Affordable Care Act, and with recent legislative activity we expect there could be additional challenges, amendments and attempts to repeal the Affordable Care Act. New state and federal healthcare reform measures could limit the amounts that federal and state governments will pay for our product candidates if we obtain regulatory approval for them, and could have other impacts on consequences which cannot be reasonably predicted at this time.

Other Healthcare Laws and Compliance Requirements

If we obtain regulatory approval for any of our product candidates, we may be subject to various federal and state laws targeting fraud and abuse in the healthcare industry. These laws may impact, among other things, our proposed sale, marketing and education programs. In addition, we may be subject to patient privacy regulations by both the federal government and the states in which we conduct our business. The laws may affect our ability to operate include:

- the federal Anti-Kickback Statute, which prohibits, among other things, persons from knowingly and willfully soliciting, receiving, offering or paying remuneration, directly or indirectly, to induce, or in return for, the purchase or recommendation of an item or service reimbursable under a federal healthcare program, such as Medicare and Medicaid programs;

- federal civil and criminal false claims laws and civil monetary penalty laws, which prohibit, among other things, individuals or entities from knowingly presenting, or causing to be presented, claims for payment from Medicare, Medicaid, or other third-party payors that are false or fraudulent;

- the federal Health Insurance Portability and Accountability Act of 1996, or HIPAA, which created new federal criminal statutes that prohibit executing a scheme to defraud any healthcare benefit program and making false statements relating to healthcare matters;

- the federal transparency laws, including the federal Physician Payment Sunshine Act, that requires drug manufacturers to disclose payments and other transfers of value provided to physicians and teaching hospitals and ownership and investment interest held by such physicians and their immediate family members;

- HIPAA, as amended by the Health Information Technology and Clinical Health Act, or HITECH, and its implementing regulations, which imposes certain requirements relating to the privacy, security and transmission of individually identifiable health information; and

- State law equivalents of each of the above federal laws, such as anti-kickback and false claims laws which may apply to items or services reimbursed by any third-party payor, including commercial insurers; state laws that require pharmaceutical companies to comply with the pharmaceutical industry's voluntary compliance guidelines and the relevant compliance guidance promulgated by the federal government, or otherwise restrict payments that may be made to healthcare providers and other potential referral sources; state laws that require drug manufacturers to report information related to payments and other transfers of value to physicians and other healthcare providers or marketing expenditures; and state laws governing the privacy and security of health information in certain circumstances, many of which differ from each other in significant ways and may not have the same effect, thus complicating compliance efforts.

Because of the breadth of these laws and the narrowness of the statutory exceptions and safe harbors available, it is possible that some of our future business activities could be subject to challenge under one or more of such laws. In addition, the Affordable Care Act broadened the reach of the fraud and abuse laws by, among other things, amending the intent requirement of the federal Anti-Kickback Statute and certain criminal healthcare fraud statutes. Pursuant to the statutory amendment, a person or entity no longer needs to have actual knowledge of the statute or specific intent to violate it in order to have committed a violation. In addition, the Affordable Care Act provides that the government may assert that a claim including items or services resulting from a violation of the federal Anti-Kickback Statute constitutes a false or fraudulent claim for purposes of the false claims laws or the civil monetary penalties statute.

We are also subject to the Foreign Corrupt Practices Act, or FCPA, which prohibits improper payments or offers of payments to foreign governments and their officials for the purpose of obtaining or retaining business.

Safeguards we implement to discourage improper payments or offers of payments by our employees, consultants, and others may be ineffective, and violations of the FCPA and similar state laws may result in severe criminal or civil sanctions, or other liabilities or proceedings against us, any of which would likely harm our reputation, business, financial condition and results of operations.

If our operations are found to be in violation of any of the laws described above or any other government regulations that apply to us, we may be subject to penalties, including civil and criminal penalties, exclusion from participation in government healthcare programs, such as Medicare and Medicaid and imprisonment, damages, fines and the curtailment or restructuring of our operations, any of which could adversely affect our ability to operate our business and our results of operation.

In addition to the foregoing, state and federal laws regarding environmental protection and hazardous substances, including the Occupational Safety and Health Act, the Resource Conservancy and Recovery Act and the Toxic Substances Control Act, affect our business. These and other laws govern our use, handling and disposal of various biological, chemical and radioactive substances used in, and wastes generated by, our operations. If our operations result in contamination of the environment or expose individuals to hazardous substances, we could be liable for damages and governmental fines. We believe that we are in material compliance with applicable environmental laws and that continued compliance therewith will not have a material adverse effect on our business. We cannot predict, however, how changes in these laws may affect our future operations.

Government Regulation outside the United States

In addition to regulations in the United States, we will be subject to a variety of regulations in other jurisdictions governing, among other things, clinical trials and any commercial sales and distribution of our products. Because

biologically sourced raw materials are subject to unique contamination risks, their use may be restricted in some countries.

Whether or not we obtain FDA approval or clearance for a product, we must obtain the requisite approvals or clearances from regulatory authorities in foreign countries prior to the commencement of clinical trials or marketing of the product in those countries. Certain countries outside of the United States have a similar process that requires the submission of a clinical trial application much like the PMA or IND prior to the commencement of human clinical trials. In Europe, for example, a Clinical Trial Authorization, or CTA, must be submitted to each country's national health authority and an independent ethics committee, much like the FDA and the IRB, respectively. Once the CTA is approved in accordance with a country's requirements, clinical trial development may proceed.

The requirements and process governing the conduct of clinical trials, product licensing, pricing and reimbursement vary from country to country. In all cases, the clinical trials are conducted in accordance with GCP and the applicable regulatory requirements and the ethical principles that have their origin in the Declaration of Helsinki.

To obtain regulatory approval of an investigational biological product under European regulatory systems, we must submit a marketing authorization application. The application used to file the PMAs for CardiAMP Cell Therapy System and BLA for CardiALLO Cell Therapy System in the United States are similar to that required in Europe, with the exception of, among other things, country-specific document requirements. Europe also provides opportunities for market exclusivity. For example, in Europe, upon receiving marketing authorization, new chemical entities generally receive eight years of data exclusivity and an additional two years of market exclusivity. If granted, data exclusivity prevents regulatory authorities in Europe from referencing the innovator's data to assess a generic application. During the additional two-year period of market exclusivity, a generic marketing authorization can be submitted, and the innovator's data may be referenced, but no generic product can be marketed until the expiration of the market exclusivity. However, there is no guarantee that a product will be considered by Europe's regulatory authorities to be a new chemical entity, and products may not qualify for data exclusivity.

The 10-year market exclusivity may be reduced to six years if, at the end of the fifth year, it is established that the product no longer meets the criteria for orphan designation, for example, if the product is sufficiently profitable not to justify maintenance of market exclusivity. Additionally, marketing authorization may be granted to a similar product for the same indication at any time if:

- the second applicant can establish that its product, although similar, is safer, more effective or otherwise clinically superior;
- the applicant consents to a second orphan medicinal product application; or
- the applicant cannot supply enough orphan medicinal product.

For other countries outside of Europe, such as countries in Eastern Europe, Latin America or Asia, the requirements governing the conduct of clinical trials, product licensing, pricing and reimbursement vary from country to country. In all cases, again, the clinical trials are conducted in accordance with GCP and the applicable regulatory requirements and the ethical principles that have their origin in the Declaration of Helsinki.

In Europe, we expect both CardiAMP and CardiALLO Cell Therapy Systems to be regulated as advanced therapy medicinal products, or ATMPs. To provide for a common framework for the marketing of ATMPs, Regulation (EC) No 1394/2007 of the European Parliament and of the Council on advanced therapy medicinal products, or ATMP Regulation, was adopted in 2007. The ATMP Regulation was designed to ensure a high level of human health protection as well as the free movement of ATMPs in Europe. The cornerstone of the ATMP Regulation is that a marketing authorization must be obtained prior to the marketing of ATMPs. In turn, the marketing authorization can only be granted if, after a scientific assessment of the quality, efficacy and safety profile, it is demonstrated that the benefits outweigh the risks. The application for a marketing authorization must be submitted to the EMA and the final decision is taken by the European Commission. This procedure ensures that these products are assessed by a specialized body (the Committee for Advanced Therapies, or CAT) and that the marketing authorization is valid in all the European Union Member States.

The ATMP Regulation empowered the EMA to make scientific recommendations as to whether a given product should be considered an ATMP (hereinafter “classifications”). Additionally, it provided for a new instrument, the so-called certification procedure, designed as an incentive for small and medium sized enterprises, or SMEs, that were involved in the first stages of the development of ATMPs but lacked the resources to conduct clinical trials. Specifically, the certification that the quality and preclinical aspects of the development are in conformity with the relevant regulatory requirements was expected to help SMEs attract capital and to facilitate the transfer of research activities to entities with the capacity to market medicinal products.

The ATMP Regulation builds on the procedures, concepts, and requirements designed for chemical-based medicinal products. However, ATMPs present very different characteristics. Additionally, in contrast to chemical-based medicinal products, research in advanced therapies is –for the most part- conducted by academia, non-for-profit organizations, and SMEs, which only have limited financial resources and often lack exposure to the regulatory system that governs medicines.

If we fail to comply with applicable foreign regulatory requirements, we may be subject to, among other things, fines, suspension or withdrawal of regulatory approvals, product recalls, seizure of products, operating restrictions and criminal prosecution.

The advertising and promotion of our products in the EEA is subject to the provisions of the Medical Devices Directive, Directive 2006/114/EC concerning misleading and comparative advertising, and Directive 2005/29/EC on unfair commercial practices, as well as other national legislation in the EEA countries governing the advertising and promotion of medical devices. The European Commission has submitted a Proposal for a Regulation of the European Parliament and the Council on medical devices, amending Directive 2001/83/EC, Regulation (EC) No 178/2002 and Regulation (EC) No 1223/2009, to replace, inter alia, Directive 93/42/EEC and to amend regulations regarding medical devices in the European Union, which could result in changes in the regulatory requirements for medical devices in Europe. In Germany, the advertising and promotion of our products can also be subject to restrictions provided by the German Act Against Unfair Competition (Gesetzgegen den unlauteren Wettbewerb) and the law on the advertising of medicines (Heilmittelwerbegesetz), criminal law, and some codices of conduct with regard to medical products and medical devices among others. These laws may limit or restrict the advertising and promotion of our products to the general public and may impose limitations on our promotional activities with healthcare professionals.

Sales of medical devices are subject to foreign government regulations, which vary substantially from country to country. In order to market our products outside the United States, we must obtain regulatory approvals or CE Certificates of Conformity and comply with extensive safety and quality regulations. The time required to obtain approval by a foreign country or to obtain a CE Certificate of Conformity may be longer or shorter than that required for FDA clearance or approval, and the requirements may differ. In the EEA, we are required to obtain Certificates of Conformity before drawing up an EC Declaration of Conformity and affixing the CE Mark of conformity to our medical devices. Many other countries accept CE Certificates of Conformity or FDA clearance or approval although others, such as Brazil, Canada and Japan require separate regulatory filings.

Employees

As of December 31, 2017, we had 24 full-time employees, consisting of clinical development, product development, regulatory, manufacturing, quality, finance, administration, sales, and marketing. We also regularly use independent contractors across the organization to augment our regular staff. None of our employees are covered by collective bargaining agreements and we consider relations with our employees to be good. We believe that our future success will depend in part on our continued ability to attract, hire and retain qualified personnel.

Corporate Information

We were originally incorporated as NAM Corporation in Delaware on January 12, 1994 and subsequently changed our name to clickNsettle.com, Inc., then Cardo Medical, Inc., then Tiger X Medical, Inc., and finally BioCardia, Inc. on October 26, 2016 in connection with a reverse merger transaction in which our wholly-owned subsidiary, Icicle Acquisition Corp., merged with and into BioCardia Lifesciences, Inc. (which was named BioCardia, Inc. prior to the merger), with BioCardia Lifesciences continuing as the surviving company. Following the completion of the reverse merger transaction, we assumed the business and operations of BioCardia Lifesciences and changed our name to BioCardia, Inc.

Our principal executive offices are located at 125 Shoreway Road, Suite B, San Carlos, CA 94070. Our telephone number is (650) 226-0120. Our website address is *www.biocardia.com*. Information contained in our website is not incorporated by reference into this Annual Report, and should not be considered to be a part of this Annual Report.

Our website is www.biocardia.com. Information contained on, or that can be accessed through, our website is not part of this Annual Report on Form 10-K, and you should not consider information on our website to be part of this report unless specifically incorporated herein by reference. Our Annual Report on Form 10-K, Quarterly Reports on Form 10-Q, Current Reports on Form 8-K and amendments to reports filed or furnished pursuant to Sections 13(a) and 15(d) of the Securities Exchange Act of 1934, as amended, are available free of charge on our investor relations website as

soon as reasonably practicable after we electronically file such material with, or furnish it to the Securities and Exchange Commission, or SEC. The SEC also maintains a website that contains our SEC filings. The address of the website is www.sec.gov. Further, a copy of this Annual Report on Form 10-K is located at the SEC's Public Reference Room at 100 F Street, NE, Washington, DC 20549. Information on the operation of the Public Reference Room can be obtained by calling the SEC at 1-800-SEC-0300.

ITEM 1A. RISK FACTORS

Investing in our common stock involves a high degree of risk. You should carefully consider the risks and uncertainties described below, together with all of the other information in this Annual Report on Form 10-K, including the section titled "Management's Discussion and Analysis of Financial Condition and Results of Operations" and our consolidated financial statements and related notes, before investing in our common stock. If any of the follows risks occur, our business, financial condition, results of operations and prospects could be materially harmed. In that event, the market price of our common stock could decline, and you could lose part or all of your investment.

Risks Related to Our Business

We have a history of operating losses, and we may not be able to achieve or sustain profitability. In addition, we may be unable to continue as a going concern.

We are a clinical-stage regenerative medicine company and we have not yet generated a profit. We have incurred net losses during each of our fiscal years since our inception. Our net loss for the year ended December 31, 2017 was $12.3 million and our accumulated deficit totaled $72.5 million as of December 31, 2017. We do not know whether or when we will become profitable, if ever. We currently expect operating losses and negative cash flows to continue for at least the next several years.

To date, our only approved or cleared products are our Morph universal deflectable guide catheters and Morph AccessPro sheaths, or Morph, in the United States and Europe and our Helix biotherapeutic delivery system, or Helix, in Europe. Our limited commercialization experience and number of approved products makes it difficult to evaluate our current business and predict our future prospects. Our short commercialization experience and limited number of approved products also makes it difficult for us to forecast our future financial performance and growth and such forecasts are limited and subject to a number of uncertainties, including our ability to successfully complete our Phase III pivotal trials in heart failure and chronic myocardial ischemia and obtain FDA approval for, and then successfully commercialize, the CardiAMP Cell Therapy System.

Our ability to generate sufficient revenue to achieve profitability depends on our ability, either alone or with strategic collaboration partners, to successfully complete the development of, and obtain the regulatory approvals necessary to commercialize our therapeutic candidates. We do not anticipate generating revenues from sales of the CardiAMP Cell Therapy System, the CardiALLO Cell Therapy System or any other biotherapeutic candidates within the next few years, and we may never generate sales of these products.

Our audited consolidated financial statements as of and for the year ended December 31, 2017 have been prepared on the basis that we will continue as a going concern, which contemplates the realization of assets and satisfaction of liabilities in the normal course of business. We have incurred significant losses since our inception and we expect that we will continue to incur losses as we aim to successfully execute our business plan and will be dependent on additional public or private financings, collaborations or licensing arrangements with strategic partners, or additional credit lines or other debt financing sources to fund continuing operations. Based on our cash balances, recurring losses since inception and our existing capital resources to fund our planned operations for a twelve month period, there is substantial doubt about our ability to continue as a going concern within one year after the date these financial statements are issued. As noted below, we will need to obtain additional funding from equity or debt financings, which may require us to agree to burdensome covenants, grant security interests in our assets, enter into collaboration and licensing arrangements that require us to relinquish commercial rights, or grant licenses on terms that are not favorable. No assurance can be given at this time as to whether we will be able to achieve our fundraising objectives, regardless of the terms. If adequate funds are not available, the Company may be required to reduce operating expenses, delay or reduce the scope of its product development programs, obtain funds through arrangements with others that may require the Company to relinquish rights to certain of its technologies or products that the Company would otherwise seek to develop or commercialize itself, or cease operations.

We will require additional financing in 2018 in order to continue the trial and to continue operations at the current level.

As discussed below in "*Management Discussion and Analysis – Future Funding Requirements*," our current cash resources are not sufficient to fund operations at the expected level of activity beyond the fourth quarter of 2018. We will need additional capital to continue operations at the current level and to continue the Phase III trial. While we plan to raise additional capital to fund operations, including the trials, there can be no assurances as to the availability of capital or the terms on which capital will be available.

Our success depends in large part on our ability to obtain approval for, and successfully commercialize, the CardiAMP Cell Therapy System.

The long-term viability of our company is largely dependent on the successful development and commercialization of the CardiAMP Cell Therapy System. We are currently enrolling patients in a Phase III pivotal trial that will be used to support regulatory approval, and we do not have significant long term data on the CardiAMP Cell Therapy System's safety and efficacy in either heart failure or chronic myocardial ischemia. While we expect to successfully complete our ongoing Phase III pivotal trial of the CardiAMP Cell Therapy System in heart failure, there can be no guarantee that the study will be completed, that the primary endpoints will be achieved, or that we will receive regulatory approval for the sale and marketing in the United States. A number of companies in similar fields have suffered significant setbacks during clinical trials due to lack of efficacy or unacceptable safety issues, notwithstanding promising preliminary results. Because we are depending heavily on sales of the CardiAMP Cell Therapy System to achieve our revenue goals, failure to successfully complete the study and receive U.S. Food and Drug Administration, or FDA, approval, in a timely manner or at all, will harm our financial results and ability to become profitable. Even if we obtain regulatory approval, our ability to successfully market this product will be limited due to a number of factors, including regulatory restrictions in our labeling or requirements to obtain additional post-approval data, if any. In addition, there can be no guarantee that the CardiAMP Cell Therapy System will be accepted by the medical community as a valid alternative to currently available products. If we cannot sell the CardiAMP Cell Therapy System as planned, our financial results will be harmed.

Although we have obtained FDA acceptance of Phase III pivotal trials of the CardiAMP Cell Therapy System for the treatment of ischemic systolic heart failure and chronic myocardial ischemia, this does not guarantee any particular outcome from regulatory review. To the best of our knowledge, the CardiAMP Cell Therapy System is the first cardiac cell-based therapy with an accepted pivotal trial that is to be regulated by the FDA Center for Biologics Evaluation and Research, or CBER, via the pre-market approval, or PMA, pathway requiring a single pivotal trial. The CardiAMP Cell Therapy System for the treatment of chronic myocardial ischemia is also to be regulated in the same fashion. All other cardiac cell-based therapies in clinical trials are believed to be regulated by the same agency, but as biologics which generally require two separate pivotal trials. There is no guarantee that the FDA will grant us regulatory clearance or approval to market the CardiAMP Cell Therapy System on the basis of a single pivotal trial, or that the FDA will continue to allow us to develop the CardiAMP Cell Therapy System via the PMA pathway. Two well-controlled pivotal studies could be necessary to provide FDA assurance of safety or effectiveness.

FDA acceptance of a Phase III pivotal trial is not a guarantee of an approval of a product candidate or any permissible claims about the product candidate. Failure to successfully complete our ongoing Phase III trial of CardiAMP in heart failure would significantly impair our financial results. Such a failure could (i) delay or prevent the CardiAMP Cell Therapy System from obtaining regulatory approval, (ii) require us to perform another clinical trial, which will be expensive, may not be successful and will significantly delay our ability to commercialize the CardiAMP Cell Therapy System and (iii) impair our ability to convince hospitals and physicians of the benefits of our CardiAMP Cell Therapy System product. Furthermore, even if we are granted regulatory clearances or approvals, they may include significant limitations on the indicated uses for CardiAMP, which may limit the market for this product.

Our CardiAMP and CardiALLO cell therapy system therapeutic candidates are based on novel technology, which makes it difficult to accurately and reliably predict the time and cost of product development and subsequently obtaining regulatory approval. At the moment, no cell-based therapies have been approved in the United States for a cardiac indication.

The success of our business depends on our ability to develop and commercialize our therapeutic candidates, including CardiAMP. We have concentrated our product research and development efforts on our CardiAMP therapeutic candidate, a novel type of cell-based therapy. Our future success depends on the successful development of this therapeutic approach. There can be no assurance that any development problems we experience in the future related to our therapeutic candidates and products will not cause significant delays or unanticipated costs, or that such development problems can be solved. We may be unable to maintain and further develop sustainable, reproducible and scalable manufacturing processes, or transfer these processes to collaborators, which may prevent us from completing our clinical studies or commercializing our products on a timely or profitable basis, if at all.

In addition, the clinical study requirements of the FDA, the European Medicines Agency, or EMA, and other regulatory agencies and the criteria these regulators use to determine the safety and efficacy of a product candidate vary substantially according to the type, complexity, novelty, intended use and market of the potential product candidates. The regulatory approval process for novel product candidates such as our CardiAMP and CardiALLO Cell Therapy Systems may be more expensive and take longer than other, better known or extensively studied pharmaceutical or other product candidates to develop. In addition, adverse developments in clinical trials of cell-based products or therapies conducted by others may cause the FDA or other regulatory bodies to change the requirements for approval of any of our therapeutic candidates. At the moment, no other cell-based therapies have been approved in the United States for a cardiac indication, which makes it difficult to determine how long it will take or how much it will cost to obtain regulatory approvals for our therapeutic candidates in either the United States or elsewhere.

Regulatory requirements governing cell-based therapy products have changed frequently and may continue to change in the future. For example, the FDA established the Office of Cellular, Tissue and Gene Therapies within CBER to consolidate the review of gene therapy and related products, and the Cellular, Tissue and Gene Therapies Advisory Committee to advise CBER on its review. These regulatory authorities and advisory groups and the new requirements or guidelines they promulgate may lengthen the regulatory review process, require us to perform additional studies, increase our development costs, lead to changes in regulatory positions and interpretations, delay or prevent approval and commercialization of our product candidates or lead to significant post-approval limitations or restrictions. As we advance our product candidates, we will be required to consult with the FDA and other regulatory authorities, and our products could be reviewed by the FDA's advisory committee. We also must comply with applicable requirements, and if we fail to do so, we may be required to delay or discontinue development of our product candidates.

We will require substantial additional financing to achieve our goals, and our failure to obtain this necessary capital when needed could force us to delay, limit, reduce or terminate our product development or commercialization efforts.

Our operations have consumed substantial amounts of cash since inception. We expect to continue to incur significant expenses and operating losses for the foreseeable future in connection with our planned research, development and product commercialization efforts, including our planned clinical trials for our CardiAMP and CardiALLO Cell Therapy System therapeutic candidates. In addition, we will require additional financing to achieve our goals and our failure to do so could adversely affect our commercialization efforts. We anticipate that our expenses will increase substantially if and as we:

- continue the research and clinical development of our CardiAMP and CardiALLO Cell Therapy System therapeutic candidates;
- initiate and advance our CardiAMP and CardiALLO Cell Therapy System therapeutic candidates into larger and more expensive clinical studies, including the ongoing Phase III pivotal trial for our CardiAMP Cell Therapy System therapeutic candidate in heart failure and our recently approved Phase III pivotal trial for our CardiAMP Cell Therapy System therapeutic candidate in chronic myocardial ischemia;
- seek to identify, assess, acquire, and/or develop other product candidates and technologies;
- seek regulatory and marketing approvals in multiple jurisdictions for our therapeutic candidates that successfully complete clinical studies;
- build and maintain a sales, marketing and distribution infrastructure to commercialize any products for which we may obtain marketing approval, or otherwise establish collaborations with third parties for the development and commercialization of our therapeutic candidates;

- further develop and implement our manufacturing processes and expand our manufacturing capabilities and resources for commercial production;

- seek coverage and reimbursement from third-party payors, including government and private payors for future products;

- seek to maintain, protect and expand our intellectual property portfolio; and

- seek to attract and retain skilled personnel.

If we were to experience any delays or encounter issues with any of the above, including clinical holds, failed studies, inconclusive or complex results, safety or efficacy issues, or other regulatory challenges that require longer follow-up of existing studies, additional major studies, or additional supportive studies in order to pursue marketing approval, it could further increase the costs associated with the above. Further, the net operating losses we incur may fluctuate significantly from quarter to quarter and year to year, such that a period-to-period comparison of our results of operations may not be a good indication of our future performance.

We may encounter substantial delays in our clinical studies.

We cannot guarantee that any preclinical testing or clinical trials will be conducted as planned or completed on schedule, if at all. As a result, we may not achieve the expected clinical milestones outlined in this Report. A failure can occur at any stage of testing. Events that may prevent successful or timely commencement, enrollment or completion of clinical development include:

- delays in raising, or inability to raise, sufficient capital to fund the planned trials;
- delays in reaching a consensus with regulatory agencies on trial design;
- changes in trial design;
- inability to identify, recruit and train suitable clinical investigators;
- inability to add new clinical trial sites;
- delays in reaching agreement on acceptable terms for the performance of the trials with prospective clinical research organizations, or CROs, and clinical trial sites;
- delays in obtaining required Institutional Review Board, or IRB, approval at each clinical trial site;
- delays in recruiting suitable clinical sites and patients (*i.e.*, subjects) to participate in clinical trials;
- imposition of a clinical hold by regulatory agencies for any reason, including negative clinical results, safety concerns or as a result of an inspection of manufacturing or clinical operations or trial sites;
- failure by us, CROs or other third parties to adhere to clinical trial requirements;
- failure to perform in accordance with the FDA's current Good Clinical Practices, or GCP, or applicable regulatory guidelines in other countries;
- delays in the testing, validation, manufacturing and delivery to the clinical sites;

- delays caused by patients not completing participation in a trial or not returning for post-treatment follow-up;
- delays caused by clinical trial sites not completing a trial;
- failure to demonstrate adequate efficacy;
- occurrence of serious adverse events in clinical trials that are associated with the therapeutic candidates or products that are viewed to outweigh its potential benefits;
- changes in regulatory requirements and guidance that require amending or submitting new clinical protocols; or
- disagreements between us and the FDA or other regulatory agencies interpreting the data from our clinical trials.

Delays, including those caused by the above factors, can be costly and could negatively affect our ability to complete clinical trials for our therapeutic candidates. If we are not able to successfully complete clinical trials or are not able to do so in a timely and cost-effective manner, we will not be able to obtain regulatory approval and/or will not be able to commercialize our therapeutic candidates or products, which would have an adverse effect on our business. Clinical trial delays could also shorten any periods during which we may have the exclusive right to commercialize our therapeutic candidates or products or allow our competitors to bring products to market before we do, which could impair our ability to successfully commercialize our therapeutic candidates or products and may harm our business and results of operations.

We may find it difficult to enroll patients in our clinical trials, which could delay or prevent development of our therapeutic candidates.

Identifying and qualifying patients to participate in clinical trials of our therapeutic candidates is critical to our success. The timing of our clinical trials depends on the speed at which we can recruit patients to participate in testing our therapeutic candidates as well as completion of required follow-up periods. In general, if patients are unwilling to participate in our cell-based therapy trials because of negative publicity from adverse events in the biotechnology or cell-based industries or for other reasons, including competitive clinical trials for similar patient populations, the timeline for recruiting patients, conducting trials and obtaining regulatory approval for our therapeutic candidates may be delayed. These delays could result in increased costs, delays in advancing our product development, delays in testing the effectiveness of our therapeutic candidates or termination of the clinical trials altogether.

Patient enrollment and completion of clinical trials are affected by factors including:

- size of the patient population;
- severity of the disease under investigation;
- design of the trial protocol;
- eligibility criteria for the particular trial;
- perceived risks and benefits of the product candidate being tested;
- proximity and availability of clinical trial sites for prospective patients;
- availability of competing therapies and clinical trials;
- efforts to facilitate timely enrollment in clinical trials;
- patient referral practices of physicians;
- ability to monitor patients adequately during and after treatment; and

- the degree of treatment effect in event-driven trials.

Once enrolled, patients may choose to discontinue their participation at any time during the trial, for any reason. Participants also may be terminated from the study at the initiative of the investigator, for example if they experience serious adverse clinical events or do not follow the study directions. If we are unable to maintain an adequate number of patients in our clinical trials, we may be required to delay or terminate an ongoing clinical trial, which would have an adverse effect on our business.

We depend on our license and distribution agreement with Biomet Biologics, LLC, and if we fail to comply with our obligations under this agreement, or if our rights under this agreement are otherwise reduced or terminated, we could lose intellectual property rights that are important to our business.

In October 2012, we entered into a license and distribution agreement with Biomet Biologics, LLC under which we obtained an exclusive, nontransferable, worldwide distribution right, patent license and trademark license to Biomet Biologic, LLC's point of care cell processing platform. Under the terms of the agreement, we are obligated to pay Biomet Biologics, LLC a royalty based on the price of the disposables in the CardiAMP cell processing platform. A breach or termination of this agreement would materially adversely affect the clinical development or commercialization strategy of our CardiAMP therapeutic candidate as currently planned. A reduction or elimination of our rights under this agreement may result in our having to negotiate new or reinstated arrangements on less favorable terms, or our not having sufficient intellectual property rights to operate our business as currently planned. The occurrence of such events could materially harm our business and financial condition.

We rely on third parties to conduct some or all aspects of our product manufacturing, diagnostic protocol development, research, and preclinical and clinical testing, and these third parties may not perform satisfactorily.

We do not currently, and do not expect to in the future, independently conduct all aspects of our product manufacturing, anticipated companion diagnostic testing, protocol development, research and monitoring and management of our ongoing preclinical and clinical programs. We currently rely, and expect to continue to rely, on third parties with respect to these items, and control only certain aspects of their activities.

Any of these third parties may terminate their engagements with us at any time. If we need to enter into alternative arrangements, our commercialization activities or our therapeutic candidate or companion diagnostic development activities may be delayed or suspended. Our reliance on these third parties for research and development activities, including the conduct of any IDE and IND-enabling studies, reduces our control over these activities but does not relieve us of our responsibility to ensure compliance with all required legal, regulatory and scientific standards and any applicable trial protocols. For example, for therapeutic candidates that we develop and commercialize on our own, we will remain responsible for ensuring that each of our IDE and IND-enabling studies and clinical trials are conducted in accordance with the trial plan and protocols.

If these third parties do not successfully carry out their contractual duties, meet expected deadlines or conduct our studies in accordance with regulatory requirements or our stated study plans and protocols, we may be delayed in completing, or unable to complete, the preclinical studies and clinical trials required to support future IDE and IND submissions and approval of our therapeutic candidates.

Reliance on third-party manufacturers entails exposure to risks to which we would not be subject if we manufactured the therapeutic candidates or companion diagnostic ourselves, including:

- we may be unable to negotiate manufacturing agreements with third parties under commercially reasonable terms;
- reduced control over the manufacturing process for our therapeutic candidates and companion diagnostic as a result of using third-party manufacturers for many aspects of manufacturing activities;
- termination or nonrenewal of manufacturing agreements with third parties in a manner or at a time that may be costly or damaging to us or result in delays in the development or commercialization of our therapeutic candidates or companion diagnostic; and
- disruptions to the operations of our third-party manufacturers or suppliers caused by conditions unrelated to our business or operations, including the bankruptcy of the manufacturer or supplier.

Any of these events could lead to delays in the development of our therapeutic candidates, including delays in our clinical trials, or failure to obtain regulatory approval for our therapeutic candidates, or it could impact our ability to successfully commercialize our current therapeutic candidates, companion diagnostic or any future products. Some of these events could be the basis for FDA or other regulatory action, including injunction, recall, seizure or total or partial suspension of production.

We rely on third parties to conduct, supervise and monitor our clinical trials. If these third parties do not successfully carry out their contractual duties or meet expected deadlines, we may not be able to obtain regulatory approval for or commercialize our product candidates and our business could be substantially harmed.

We rely on CROs and clinical trial sites to ensure our clinical trials are conducted properly and on time. While we will have agreements governing their activities, we will have limited influence over their actual performance. We will control only certain aspects of our CROs' activities. Nevertheless, we will be responsible for ensuring that each of our clinical trials is conducted in accordance with the applicable protocol, legal, regulatory and scientific standards, and our reliance on the CROs does not relieve us of our regulatory responsibilities.

We and our CROs are required to comply with the FDA's GCPs for conducting, recording and reporting the results of clinical trials to assure that the data and reported results are credible and accurate and that the rights, integrity and confidentiality of clinical trial participants are protected. The FDA, the Competent Authorities of the Member States of the EEA, and comparable foreign regulatory authorities, enforce these GCPs through periodic inspections of trial sponsors, principal investigators and clinical trial sites. If we or our CROs fail to comply with applicable GCPs, the clinical data generated in our future clinical trials may be deemed unreliable and the FDA, the EMA, or other foreign regulatory authorities may require us to perform additional clinical trials before approving any marketing applications. Upon inspection, the FDA may determine that our clinical trials did not comply with GCPs. In addition, our future clinical trials will require a sufficient number of test subjects to evaluate the safety and effectiveness of our therapeutic candidates. Accordingly, if our CROs fail to comply with these regulations or fail to recruit a sufficient number of patients, we may be required to repeat such clinical trials, which would delay the regulatory approval process.

Our CROs are not our employees, and we are therefore unable to directly monitor whether or not they devote sufficient time and resources to our clinical and nonclinical programs. These CROs may also have relationships with other commercial entities, including our competitors, for whom they may also be conducting clinical trials or other product development activities that could harm our competitive position. If our CROs do not successfully carry out their contractual duties or obligations, fail to meet expected deadlines, or if the quality or accuracy of the clinical data they obtain is compromised due to the failure to adhere to our clinical protocols or regulatory requirements, or for any other reasons, our clinical trials may be extended, delayed or terminated, and we may not be able to obtain regulatory approval for, or successfully commercialize, our therapeutic candidates. If any such event were to occur, our financial results and the commercial prospects for our therapeutic candidates would be harmed, our costs could increase, and our ability to generate revenues could be delayed.

If any of our relationships with these third-party CROs terminate, we may not be able to enter into arrangements with alternative CROs or to do so on commercially reasonable terms. Further, switching or adding additional CROs involves additional costs and requires management time and focus. In addition, there is a natural transition period when a new CRO commences work. As a result, delays occur, which could materially impact our ability to meet our desired clinical development timelines. Though we carefully manage our relationships with our CROs, there can be no assurance that we will not encounter challenges or delays in the future or that these delays or challenges will not have a material adverse impact on our business, financial condition and prospects.

We may also rely on other third parties to store and distribute our products for the clinical trials that we conduct. Any performance failure on the part of our distributors could delay clinical development or marketing approval of our therapeutic candidates or commercialization of our products, if approved, producing additional losses and depriving us of potential product revenue.

We depend on third party vendors to manufacture some of our components and sub-assemblies, which could make us vulnerable to supply shortages and price fluctuations that could harm our business.

We currently manufacture some of our components and sub-assemblies internally and rely on third party vendors for other components and sub-assemblies used in our products and therapeutic candidates. Our reliance on third party vendors subjects us to a number of risks that could impact our ability to manufacture our products and therapeutic candidates and harm our business, including:

- interruption of supply resulting from modifications to, or discontinuation of, a supplier's operations;
- delays in product shipments resulting from uncorrected defects, reliability issues or a supplier's failure to consistently produce quality components;

- price fluctuations due to a lack of long-term supply arrangements with our suppliers for key components;

- inability to obtain adequate supply in a timely manner or on commercially reasonable terms;

- difficulty identifying and qualifying alternative suppliers for components in a timely manner;

- inability of the manufacturer or supplier to comply with Quality System Regulations, or QSRs, enforced by the FDA and state regulatory authorities;

- inability to control the quality of products manufactured by third parties;

- production delays related to the evaluation and testing of products from alternative suppliers and corresponding regulatory qualifications; and

- delays in delivery by our suppliers due to changes in demand from us or their other customers.

Any significant delay or interruption in the supply of components or sub-assemblies, or our inability to obtain substitute components, sub-assemblies or materials from alternate sources at acceptable prices in a timely manner, could impair our ability to meet the demand of our customers and harm our business.

Our future commercial success depends upon attaining significant market acceptance of our therapeutic candidates, if approved, among physicians, patients and healthcare payors.

Even when product development is successful and regulatory approval has been obtained, our ability to generate significant revenue depends on the acceptance of our products by physicians, payors and patients. Many potential market participants have limited knowledge of, or experience with, cell-based products and therapies, so gaining market acceptance and overcoming any safety or efficacy concerns may be more challenging than for more traditional therapies. Our efforts to educate the medical community and third-party payors on the benefits of our therapeutic candidates may require significant resources and may never be successful. Such efforts to educate the marketplace may require more resources than are required by conventional therapies marketed by our competitors. We cannot assure you that our products will achieve the expected market acceptance and revenue if and when they obtain the requisite regulatory approvals. Alternatively, even if we obtain regulatory approval, that approval may be for indications or patient populations that are not as broad as intended or desired or may require labeling that includes significant use or distribution restrictions or safety warnings. The market acceptance of each of our therapeutic candidates will depend on a number of factors, including:

- the efficacy and safety of the therapeutic candidate, as demonstrated in clinical trials;
- the clinical indications for which the product is approved and the label approved by regulatory authorities for use with the product, including any warnings that may be required on the label;
- acceptance by physicians and patients of the product as a safe and effective treatment;
- the cost, safety and efficacy of treatment in relation to alternative treatments;
- the continued projected growth of markets for our various indications;
- relative convenience and ease of administration;
- the prevalence and severity of adverse side effects; and
- the effectiveness of our sales and marketing efforts.

Market acceptance is critical to our ability to generate significant revenue. Any therapeutic candidate, if approved and commercialized, may be accepted in only limited capacities or not at all. If any approved products are not accepted by the market to the extent that we expect, we may not be able to generate significant revenue and our business would

suffer.

If we fail to attract and keep senior management and key scientific personnel, we may be unable to successfully develop our therapeutic candidates, conduct our clinical trials and commercialize our therapeutic candidates.

We are highly dependent on the members of our executive team, the loss of whose services may adversely impact the achievement of our objectives. Any of our executive officers could leave our employment at any time, as all of our employees are "at will" employees. Recruiting and retaining other qualified employees, consultants and advisors for our business, including scientific and technical personnel, will also be critical to our success.

Recruiting and retaining qualified scientific, clinical, manufacturing, sales and marketing personnel will also be critical to our success. We may not be able to attract and retain these personnel on acceptable terms given the competition among numerous pharmaceutical and biotechnology companies for similar personnel. We also experience competition for the hiring of scientific and clinical personnel from universities and research institutions. In addition, we rely on consultants and advisors, including scientific and clinical advisors, to assist us in formulating our research and development and commercialization strategy. Our consultants and advisors may be employed by employers other than us and may have commitments under consulting or advisory contracts with other entities that may limit their availability to us.

We will need to expand our organization and we may experience difficulties in managing this growth, which could disrupt our operations.

As of December 31, 2017, we had 24 full-time employees. As we mature and expand our research and development and other pre-commercialization activities, we expect to expand our full-time employee base and to hire more consultants and contractors. In addition, we currently plan to commercialize the CardiAMP Cell Therapy System, if approved, using an internal sales force to selected cardiologists, interventional cardiologists and third-party payors in the United States. Our management may need to divert a disproportionate amount of its attention away from our day-to-day activities and devote a substantial amount of time to managing these growth activities. We may not be able to effectively manage the expansion of our operations, which may result in weaknesses in our infrastructure, operational mistakes, loss of business opportunities, loss of employees and reduced productivity among remaining employees. Our expected growth could require significant capital expenditures and may divert financial resources from other projects, such as the development of additional product candidates. If our management is unable to effectively manage our growth, our expenses may increase more than expected, our ability to generate and/or grow revenues could be reduced, and we may not be able to implement our business strategy. Our future financial performance and our ability to commercialize product candidates and compete effectively will depend, in part, on our ability to effectively manage any future growth.

We face substantial competition, which may result in others discovering, developing or commercializing products before, or more successfully, than we do.

Our industry is highly competitive and subject to rapid change. The industry continues to expand and evolve as an increasing number of competitors and potential competitors enter the market. Some of the pharmaceutical, biotechnology and medical device companies we expect to potentially compete with include Astra Zeneca, Capricor Therapeutics, Caladrius Biosciences, Celixr, CellProthera, Cesca Therapeutics, Celyad, Juventas Therapeutics, Mesoblast, Tenaya Therapeutics, Vericel Corp, and Uniqure, among others. Many of our competitors, potentially including the aforementioned, have significantly greater development, financial, manufacturing, marketing, technical and human resources than we do. Large pharmaceutical and medical device companies, in particular, have extensive experience in clinical testing, obtaining regulatory approvals, recruiting patients and in manufacturing pharmaceutical and medical device products. Recent and potential future merger and acquisition activity in the biotechnology and pharmaceutical industries may result in even more resources being concentrated among a smaller number of our competitors. Established companies may also invest heavily to accelerate discovery and development of novel products that could make our therapeutic candidates obsolete. As a result of all of these factors, our competitors may succeed in obtaining patent protection and/or FDA approval or discovering, developing and commercializing our therapeutic candidates or competitors to our therapeutic candidates before we do. Specialized, smaller or early-stage companies may also prove to be significant competitors, particularly those with a focus and expertise in the stem cell industry and/or those with collaboration arrangements and other third party payors. In addition, any new product that competes with an approved product must demonstrate compelling advantages in efficacy, convenience, tolerability and safety in order to overcome price competition and to be commercially successful. If we are not able to compete effectively against potential competitors, our business will not grow and our financial condition and results of operations will suffer.

Even if we obtain regulatory approval for a product candidate, including our CardiAMP and CardiALLO Cell Therapy System therapeutic candidates, these products or therapies, along with our other regulated products, will be subject to ongoing regulatory scrutiny.

Even if we obtain regulatory approval or clearance in a jurisdiction, regulatory authorities may still impose significant restrictions on the indicated uses or marketing of our therapeutic candidates, or impose ongoing requirements for potentially costly post-approval studies or post-market surveillance. For example, once a product receives regulatory approval or clearance for sale, we are obligated to monitor and report adverse events and any failure of a product to meet the specifications in the applicable regulatory approval or clearance. We must also submit new or supplemental applications and obtain FDA approval or clearance for certain changes to the approved or cleared product, product labeling or manufacturing process. Advertising and promotional materials must comply with FDA rules and are subject to FDA review, in addition to other potentially applicable federal and state laws.

In addition, product manufacturers and their facilities are subject to payment of user fees and continual review and periodic inspections by the FDA and other regulatory authorities for compliance with good manufacturing practices or QSRs and adherence to commitments made in the applicable regulatory approval. If we or a regulatory agency discovers previously unknown problems with a product such as adverse events of unanticipated severity or frequency, or problems with the facility where the product is manufactured, a regulatory agency may impose restrictions relative to that product or the manufacturing facility, including requiring recall or withdrawal of the product from the market or suspension of manufacturing.

If we fail to comply with applicable regulatory requirements following approval of any of our therapeutic candidates, a regulatory agency may impose the following:

- restrictions on the marketing or manufacturing of our products, withdrawal of our products from the market, or voluntary or mandatory product recalls;
- costly regulatory inspections;
- fines, warning letters, or holds on clinical trials;

- refusal by the FDA to approve pending applications or supplements to approved applications filed by us or our collaborators, or suspension or revocation of applicable regulatory approvals;

- product seizure or detention, or refusal to permit the import or export of products; and

- injunctions or the imposition of civil or criminal penalties by FDA or other regulatory bodies.

Any government investigation of alleged violations of law could require us to expend significant time and resources in response and could generate negative publicity. The occurrence of any event or penalty described above may inhibit our ability to commercialize our therapeutic candidates and generate revenues.

Our ability to compete is highly dependent on demonstrating the benefits of CardiAMP to physicians, hospitals and patients.

In order to generate sales, we must be able to clearly demonstrate that CardiAMP is both a more effective treatment system and less costly than alternative products and treatments offered by our competitors. If we are unable to convince physicians that CardiAMP leads to significant improvement in functional capacity, improved quality of life and reduced hospitalization, our business will suffer.

We may fail to demonstrate safety and efficacy to the satisfaction of applicable regulatory agencies.

We have not obtained regulatory approval for either our CardiAMP or CardiALLO Cell Therapy System therapeutic candidates. We must conduct extensive testing of our therapeutic candidates to demonstrate their safety and efficacy, including human clinical trials and, if applicable, preclinical animal testing, before we can obtain regulatory approval to market and sell them. Conducting such testing is a lengthy, time-consuming, and expensive process and there is a high rate of failure. Our current and completed preclinical and clinical results for our therapeutic candidates are not necessarily predictive of the results of our ongoing or future clinical trials. Promising results in preclinical studies of a therapeutic candidate may not be predictive of similar results in humans during clinical trials, and successful results from early human clinical trials of a therapeutic candidate may not be replicated in later and larger human clinical trials or in clinical trials for different indications. If the results of our ongoing or future clinical trials are negative or inconclusive with respect to the efficacy of our therapeutic candidates or if we or they do not meet the clinical endpoints with statistical significance or if there are safety concerns or adverse events associated with our therapeutic candidates, we may be prevented or delayed in obtaining marketing approval for our therapeutic candidates.

If we fail to obtain and maintain necessary regulatory clearances or approvals for our therapeutic candidates or products, or if clearances or approvals for our therapeutic candidates or products in additional indications are delayed or not issued, our commercial operations would be harmed.

We are required to timely file various reports with the FDA, require that we report to the regulatory authorities if our therapeutic candidates or products may have caused or contributed to a death or serious injury or malfunctioned in a way that would likely cause or contribute to a death or serious injury if the malfunction were to recur. If these reports are not filed timely, regulators may impose sanctions and sales may suffer, and we may be subject to product liability or regulatory enforcement actions, all of which could harm our business.

If we initiate a correction or removal to reduce a risk to health posed, we would be required to submit a publicly available Correction and Removal report to the FDA and in many cases, similar reports to other regulatory agencies. This report could be classified by the FDA as a product recall which could lead to increased scrutiny by the FDA, other international regulatory agencies and our customers regarding the quality and safety of our therapeutic candidates or products. Furthermore, the submission of these reports has been and could be used by competitors against us in competitive situations and cause customers to delay purchase decisions or cancel orders and would harm our reputation.

The FDA and the Federal Trade Commission, or FTC, also regulate the advertising and promotion of our therapeutic candidates or products to ensure that the claims we make are consistent with our regulatory approvals, that there are adequate and reasonable data to substantiate the claims and that our promotional labeling and advertising is neither false nor misleading in any respect. If the FDA or FTC determines that any of our advertising or promotional claims are misleading, not substantiated or not permissible, we may be subject to enforcement actions, including warning letters, and we may be required to revise our promotional claims and make other corrections or restitutions.

FDA and state authorities have broad enforcement powers. Our failure to comply with applicable regulatory requirements could result in enforcement action by FDA or state agencies, which may include any of the following sanctions:

- adverse publicity, warning letters, fines, injunctions, consent decrees and civil penalties;
- repair, replacement, refunds, recall or seizure of our products;
- operating restrictions, partial suspension or total shutdown of production;
- refusing our requests for premarket approval of new products, new intended uses or modifications to existing products;
- withdrawing premarket approvals that have already been granted; and
- criminal prosecution.

If any of these events were to occur, our business and financial condition would be harmed.

Serious adverse events or other safety risks could require us to abandon development and preclude, delay or limit approval of our therapeutic candidates or products, or limit the scope of any approved indication or market acceptance.

Participants in clinical trials of our investigational cell-based therapies and products may experience adverse reactions or other undesirable side effects. While some of these can be anticipated, others may be unexpected. We cannot predict the frequency, duration, or severity of adverse reactions or undesirable side effects that may occur during clinical investigation. If any of our therapeutic candidates or products, prior to or after any approval for commercial sale, cause adverse events or are associated with other safety risks, a number of potentially significant negative consequences could result, including:

- regulatory authorities may suspend (*e.g.*, through a clinical hold) or terminate clinical trials;

- regulatory authorities may deny regulatory approval of our therapeutic candidates or products;

- regulatory authorities may restrict the indications or patient populations for which a therapeutic candidate or products is approved;

- regulatory authorities may require certain labeling statements, such as warnings or contraindications or limitations on the indications for use, and/or impose restrictions on distribution in the form of a Risk Evaluation and Mitigation Strategy, or REMS, in connection with approval, if any;

- regulatory authorities may withdraw their approval, require more onerous labeling statements or impose a more restrictive REMS than any therapeutic candidate or product that is approved;

- we may be required to change the way the therapy or therapeutic candidate or product is administered or conduct additional clinical trials;

- patient recruitment into our clinical trials may suffer;

- we could be required to provide compensation to subjects for their injuries, *e.g.*, if we are sued and found to be liable or if required by the laws of the relevant jurisdiction or by the policies of the clinical site; or

- our reputation may suffer.

There can be no assurance that adverse events associated with our therapeutic candidates or products will not be observed, even where no prior adverse events have occurred. We may voluntarily suspend or terminate our clinical trials if at any time we believe that they present an unacceptable risk to participants or if preliminary data demonstrate that our therapeutic candidates or products are unlikely to receive regulatory approval or are unlikely to be successfully commercialized. Regulatory agencies, IRBs or data safety monitoring boards may at any time recommend the temporary or permanent discontinuation of our clinical trials or request that we cease using investigators in the clinical trials if they believe that the clinical trials are not being conducted in accordance with applicable regulatory requirements, or that they present an unacceptable safety risk to participants. If we elect or are forced to suspend or terminate a clinical trial for any reason this would have an adverse effect on our business.

Our therapeutic candidates are intended to treat patients who are extremely ill, and patient deaths that occur in our clinical trials could negatively impact our business even if they are not shown to be related to our therapeutic candidates.

Generally, patients remain at high risk following their treatment with our CardiAMP and CardiALLO therapeutic candidates. As a result, it is likely that we will observe severe adverse outcomes during our clinical trials for these therapeutic candidates, including patient death. If a significant number of study subject deaths were to occur, regardless of whether such deaths are attributable to our therapeutic candidates, our ability to obtain regulatory approval for the applicable therapeutic candidate may be adversely impacted and our business could be materially harmed.

If we or our suppliers fail to comply with the FDA's QSRs, our manufacturing operations could be delayed or shut down and product sales could suffer.

Our manufacturing processes and those of our third party suppliers are required to comply with the FDA's QSRs, which covers the procedures and documentation of the design, testing, production, control, quality assurance, labeling, packaging, storage and shipping. We are also subject to similar state requirements and licenses. In addition, we must engage in extensive record keeping and reporting and must make available our manufacturing facilities and records for periodic unannounced inspections by governmental agencies, including the FDA, state authorities and comparable agencies in other countries. If we fail a Quality System inspection, our operations could be disrupted and our manufacturing interrupted. Failure to take adequate corrective action in response to an adverse Quality System inspection could result in, among other things, a shut-down of our manufacturing operations, significant fines, suspension of marketing clearances and approvals, seizures or recalls, operating restrictions and criminal prosecutions, any of which would cause our business to suffer. Furthermore, our key component suppliers may not currently be or may not continue to be in compliance with applicable regulatory requirements, which may result in manufacturing delays and cause our revenues to decline.

We have registered with the FDA as a medical device manufacturer and have obtained a manufacturing license from the California Department of Health Services, or CDHS. The FDA has broad post-market and regulatory enforcement powers. We are subject to unannounced inspections by the FDA and the Food and Drug Branch of CDHS to determine our compliance with the QSR and other regulations, and these inspections may include the manufacturing facilities of our suppliers. If the FDA or CDHS inspect our facility and discover compliance problems, we may have to shut down our facility and cease manufacturing until we can take the appropriate remedial steps to correct the audit findings. Taking corrective action may be expensive, time consuming and a distraction for management and if we experience a shutdown or delay at our manufacturing facility we may be unable to produce our products, which may have an adverse impact on our business.

The requirements to obtain regulatory approval of the FDA and regulators in other jurisdictions can be costly, time-consuming, and unpredictable. If we are unable to obtain timely regulatory approval for our therapeutic candidates, our business may be substantially harmed.

The regulatory approval process is expensive and the time and resources required to obtain approval from the FDA or other regulatory authorities in other jurisdictions to sell any therapeutic candidate or product is uncertain and approval may take years. Whether regulatory approval will be granted is unpredictable and depends upon numerous factors, including the discretion of the regulatory authorities. For example, governing legislation, approval policies, regulations, regulatory policies, or the type and amount of preclinical and clinical data necessary to gain approval may change during the course of a therapeutic candidate's clinical development and may vary among jurisdictions. It is possible that none of our existing or future therapeutic candidates will ever obtain regulatory approval, even if we expend substantial time and resources seeking such approval.

Further, regulatory requirements governing cell-based therapy products in particular have changed frequently and may continue to change in the future. For example, in November 2014, Japan's parliament enacted new legislation to promote the safe and accelerated development of treatments using stem cells. The new Pharmaceuticals, Medical Devices and Other Therapeutic Products Act, or PMD Act, establishes a framework for expedited approval in Japan for regenerative medical products. As this is a new regulation, it is not clear yet what impact it will have on the operation of our business. Any regulatory review committees and advisory groups and any contemplated new guidelines may lengthen the regulatory review process, require us to perform additional studies, increase our development costs, lead to changes in regulatory positions and interpretations, delay or prevent approval and commercialization of our therapeutic candidates or products or lead to significant post-approval limitations or restrictions. As we advance our therapeutic candidates or products, we will be required to consult with these regulatory and advisory groups, and comply with applicable guidelines. If we fail to do so, we may be required to delay or discontinue development of our therapeutic candidates or products. Delay or failure to obtain, or unexpected costs in obtaining, the regulatory approval necessary to bring a therapeutic candidate or product to market could decrease our ability to generate sufficient revenue to maintain our business.

Our therapeutic candidates could fail to receive regulatory approval for many reasons, including the following:

- we may be unable to successfully complete our ongoing and future clinical trials of therapeutic candidates;
- we may be unable to demonstrate to the satisfaction of the FDA or other regulatory authorities that a therapeutic candidate is safe, pure, and potent for any or all of a therapeutic candidate's proposed indications;
- we may be unable to demonstrate that a therapeutic candidate's benefits outweigh the risk associated with the therapeutic candidate;
- the FDA or other regulatory authorities may disagree with the design or implementation of our clinical trials;
- the results of clinical trials may not meet the level of statistical significance required by the FDA or other regulatory authorities for approval;
- the FDA or other regulatory authorities may disagree with our interpretation of data from preclinical studies or clinical trials;
- a decision by the FDA, other regulatory authorities or us to suspend or terminate a clinical trial at any time;
- the data collected from clinical trials of our therapeutic candidates may be inconclusive or may not be sufficient to obtain regulatory approval in the United States or elsewhere;
- the inability to obtain sufficient quantities of the therapeutic candidates for use in clinical trials;
- our third party manufacturers of supplies needed for manufacturing therapeutic candidates may fail to satisfy FDA or other regulatory requirements and may not pass inspections that may be required by FDA or other regulatory authorities;
- the failure to comply with applicable regulatory requirements following approval of any of our therapeutic candidates may result in the refusal by the FDA or similar foreign regulatory agency to approve a pending PMA or a biologics license application, or BLA, or supplement to a PMA or BLA submitted by us for other indications or new therapeutic candidates or products; and
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the approval policies or regulations of the FDA or other regulatory authorities outside of the United States may significantly change in a manner rendering our clinical data insufficient for approval.

We may gain regulatory approval for any of our therapeutic candidates in some but not all of the territories available and any future approvals may be for some but not all of the target indications, limiting their commercial potential. Regulatory requirements and timing of product approvals vary from country to country and some jurisdictions may require additional testing beyond what is required to obtain FDA approval. Approval by the FDA does not ensure approval by regulatory authorities in other countries or jurisdictions, and approval by one foreign regulatory authority does not ensure approval by regulatory authorities in other countries or by the FDA. The foreign regulatory approval process may include all of the risks associated with obtaining FDA approval. In addition, regulatory approval does not specify pricing or reimbursement which may not match our expectations based on the results of our clinical data.

Even if we obtain and maintain approval for our therapeutic candidates or products from the FDA, we may never obtain approval for our therapeutic candidates or products outside of the United States, which would limit our market opportunities and adversely affect our business.

Approval in the United States by the FDA does not ensure approval by regulatory authorities in other countries or jurisdictions, and approval by one regulatory authority does not ensure approval by regulatory authorities in other foreign countries or by the FDA. Sales of our therapeutic candidates or products, if approved, outside of the United States will be subject to foreign regulatory requirements governing clinical trials and marketing approval.

Even if the FDA grants marketing approval, comparable regulatory authorities of foreign countries must also approve the manufacturing and marketing in those countries. Approval procedures vary among jurisdictions and can involve requirements and administrative review periods different from, and greater than, those in the United States, including additional preclinical studies or clinical trials. In many countries outside the United States, a therapeutic candidate or product must be approved for reimbursement before it can be approved for sale in that country. In some cases, the price that we intend to charge, if approved, is also subject to approval. While we may decide to submit a request to the EMA for approval of our therapeutic candidates, including CardiAMP, as Advanced Therapeutic Medicinal Products, or ATMPs, in Europe, obtaining such approval is a lengthy and expensive process and the EMA has its own procedures for approval. Even if a therapeutic candidate or product is approved, the FDA or the EMA, as the case may be, may limit the indications for which it may be marketed, require extensive warnings on the product labeling or require expensive and time-consuming clinical trials or reporting as conditions of approval. Regulatory authorities in countries outside of the United States and Europe also have requirements for approval of therapeutic candidates or products with which we must comply prior to marketing in those countries. Obtaining foreign regulatory approvals and compliance with foreign regulatory requirements could result in significant delays, difficulties and costs for us and could delay or prevent the introduction in certain countries. Further, clinical trials conducted in one country may not be accepted by regulatory authorities in other countries and regulatory approval in one country does not ensure approval in any other country, while a failure or delay in obtaining regulatory approval in one country may have a negative effect on the regulatory approval process in others. Also, regulatory approval may be withdrawn. If we fail to comply with the regulatory requirements in international markets and/or receive applicable marketing approvals, our target market will be reduced and our ability to realize the full market potential of our therapeutic candidates or products will be harmed and our business will be adversely affected.

We may face competition from biosimilars due to changes in the regulatory environment.

We may face competition for the CardiALLO Cell Therapy System from biosimilars due to the changing regulatory environment. In the United States, the Biologics Price Competition and Innovation Act of 2009 created an abbreviated approval pathway for biological products that are demonstrated to be “highly similar,” or biosimilar to, or “interchangeable” with an FDA-approved innovator (original) biological product. This new pathway could allow competitors to reference data from innovator biological products already approved after 12 years from the time of approval. In Europe, a competitor may reference data from biological products already approved, but will not be able to get on the market until 10 years after the time of approval. This 10-year period will be extended to 11 years if, during the first eight of those 10 years, the marketing authorization holder obtains an approval for one or more new therapeutic indications that bring significant clinical benefits compared with existing therapies. In addition, companies may be developing biosimilars in other countries that could compete with CardiALLO, if approved. Additionally, the FDA may approve our competitors’ products through a PMA pathway, similar to CardiAMP. If competitors are able to obtain marketing approval for biosimilars referencing CardiALLO, if approved, it may become subject to competition from such biosimilars with the attendant competitive pressure and consequences.

If we fail to comply with environmental, health and safety laws and regulations, we could become subject to fines or penalties or incur costs that could have a material adverse effect on the success of our business.

We are subject to numerous environmental, health and safety laws and regulations, including those governing laboratory procedures and the handling, use, storage, treatment and disposal of hazardous materials and wastes. Our operations may involve the use of hazardous and flammable materials, including chemicals and biological materials. Our operations may also produce hazardous waste products. We generally contract with third parties for the disposal of these materials and wastes. We cannot eliminate the risk of contamination or injury from these materials, which could cause an interruption of our commercialization efforts, research and development efforts and business operations, environmental damage resulting in costly clean-up and liabilities under applicable laws and regulations governing the use, storage, handling and disposal of these materials and specified waste products. Although we believe that the safety procedures utilized by our third-party manufacturers for handling and disposing of these materials generally comply with the standards prescribed by these laws and regulations, we cannot guarantee that this is the case or eliminate the risk of accidental contamination or injury from these materials. In such an event, we may be held liable for any resulting damages and such liability could exceed our resources and state or federal or other applicable authorities may curtail our use of certain materials and/or interrupt our business operations. Furthermore, environmental laws and regulations are complex, change frequently and have tended to become more stringent. We cannot predict the impact of such changes and cannot be certain of our future compliance. In addition, we may incur substantial costs in order to comply with current or future environmental, health and safety laws and regulations. These current or future laws and regulations may impair our research, development or production efforts. Failure to comply with these laws and regulations also may result in substantial fines, penalties or other sanctions. We do not currently carry biological or hazardous waste insurance coverage.

Although we maintain workers' compensation insurance to cover us for costs and expenses we may incur due to injuries to our employees resulting from the use of hazardous materials or other work-related injuries, this insurance may not provide adequate coverage against potential liabilities.

We are subject to various federal and state fraud and abuse laws, including, without limitation, the federal Anti-Kickback Statute and the federal False Claims Act.

Even though we do not and will not control referrals of healthcare services or bill directly to Medicare, Medicaid or other third party payors, certain federal and state healthcare laws and regulations pertaining to fraud and abuse will be applicable to our business. Healthcare fraud and abuse regulations are complex and can be subject to varying interpretations as to whether or not a statute has been violated. The laws that may affect our ability to operate include:

- the federal Anti-Kickback Statute which prohibits, among other things, the knowing and willful payment of remuneration to induce or reward patient referrals or the generation of business involving any item or service which may be payable by the federal health care programs (*e.g.*, drugs, supplies, or health care services for Medicare or Medicaid patients);

- the federal False Claims Act which prohibits, among other things, individuals or entities from knowingly presenting, or causing to be presented, claims for payment for government funds (*e.g.*, payment from Medicare or Medicaid) or knowingly making, using, or causing to be made or used a false record or statement material to a false or fraudulent claim for government funds;

- the federal Health Insurance Portability and Accountability Act of 1996, or HIPAA, as amended by the Health Information Technology for Economic and Clinical Health Act, or HITECH, and its implementing regulations, imposes certain requirements relating to the privacy, security and transmission of individually identifiable health information. Among other things, HIPAA imposes civil and criminal liability for the wrongful access or disclosure of protected health information;

- the federal Physician Payments Sunshine Act, created under Section 6002 of the Patient Protection and Affordable Care Act, as amended, the ACA, requires certain manufacturers of drugs, devices, biologics and medical supplies for which payment is available under Medicare, Medicaid or the Children's Health Insurance Program (with certain exceptions) to report information related to certain payments or other transfers of value made or distributed to physicians and teaching hospitals, or to entities or individuals at the request of, or designated on behalf of, those physicians and teaching hospitals and to report annually certain ownership and investment interests held by physicians and their immediate family members;

- the federal Food, Drug and Cosmetic Act which prohibits, among other things, the adulteration or misbranding of drugs and devices;

- the U.S. Foreign Corrupt Practices Act which prohibits corrupt payments, gifts or transfers of value to non-U.S. officials; and

- non-U.S. and U.S. state law equivalents of each of the above federal laws, such as anti-kickback and false claims laws which may apply to items or services reimbursed by any third-party payor, including commercial insurers.

The federal fraud and abuse laws have been interpreted to apply to arrangements between medical device and pharmaceutical manufacturers and a variety of health care professional. Although the federal Anti-Kickback Statute has several statutory exemptions and regulatory safe harbors protecting certain common activities from prosecution, all elements of the potentially applicable exemption or safe harbor must be met in order for the arrangement to be protected, and prosecutors have interpreted the federal healthcare fraud statutes to attack a wide range of conduct by medical device and pharmaceutical companies. In addition, most states have statutes or regulations similar to the federal anti-kickback and federal false claims laws, which apply to items and services covered by Medicaid and other state programs, or, in several states, apply regardless of the payor. Administrative, civil and criminal sanctions may be imposed under these federal and state laws.

Further, the ACA, among other things, amended the intent standard under the Anti-Kickback Statute such that a person or entity no longer needs to have actual knowledge of the statute or specific intent to violate it in order to have committed a violation. In addition, the ACA makes clear that a claim including items or services resulting from a violation of the federal Anti-Kickback Statute constitutes a false or fraudulent claim under the federal False Claims Act. Any violations of these laws, or any action against us for violation of these laws, even if we successfully defend against it, could result in a material adverse effect on our reputation, business, results of operations and financial condition.

Efforts to ensure that our business arrangements will comply with applicable healthcare laws may involve substantial costs. It is possible that governmental and enforcement authorities will conclude that our business practices do not comply with current or future statutes, regulations or case law interpreting applicable fraud and abuse or other healthcare laws and regulations. If any such actions are instituted against us, and we are not successful in defending ourselves or asserting our rights, those actions could have a significant impact on our business, including the imposition of civil, criminal and administrative penalties, damages, disgorgement, monetary fines, possible exclusion from participation in Medicare, Medicaid and other federal healthcare programs, contractual damages, reputational harm, diminished profits and future earnings, and curtailment of our operations, any of which could harm our ability to operate our business and our results of operations. In addition, the clearance or approval and commercialization of any of our products outside the United States will also likely subject us to foreign equivalents of the healthcare laws mentioned above, among other foreign laws.

A failure to adequately protect private health information could result in severe harm to our reputation and subject us to significant liabilities, each of which could have a material adverse effect on our business.

Throughout the clinical trial process, we may obtain the private health information of our trial subjects. There are a number of state, federal and international laws protecting the privacy and security of health information and personal data. As part of the American Recovery and Reinvestment Act of 2009, or ARRA, Congress amended the privacy and security provisions of HIPAA. HIPAA imposes limitations on the use and disclosure of an individual's healthcare information by healthcare providers conducting certain electronic transactions, healthcare clearinghouses, and health insurance plans, collectively referred to as covered entities. The HIPAA amendments also impose compliance obligations and corresponding penalties for non-compliance on certain individuals and entities that provide services to or perform certain functions on behalf of healthcare providers and other covered entities involving the use or disclosure of individually identifiable health information, collectively referred to as business associates. ARRA also made significant increases in the penalties for improper use or disclosure of an individual's health information under HIPAA and extended enforcement authority to state attorneys general. The amendments also create notification requirements to federal regulators, and in some cases local and national media, for individuals whose health information has been inappropriately accessed or disclosed. Notification is not required under HIPAA if the health information that is improperly used or disclosed is deemed secured in accordance with certain encryption or other standards developed by the U.S. Department of Health and Human Services, or HHS. Most states have laws requiring notification of affected individuals and state regulators in the event of a breach of personal information, which is a broader class of information than the health information protected by HIPAA. Many state laws impose significant data security requirements, such as encryption or mandatory contractual terms to ensure ongoing protection of personal information. Activities outside of the United States implicate local and national data protection standards, impose additional compliance requirements and generate additional risks of enforcement for noncompliance. The European Union's Data Protection Directive, Canada's Personal Information Protection and Electronic Documents Act and other data protection, privacy and similar national, state/provincial and local laws may also restrict the access, use and disclosure of patient health information abroad. We may be required to expend significant capital and other resources to ensure ongoing compliance with applicable privacy and data security laws, to protect against security breaches and hackers or to alleviate problems caused by such breaches.

A recall of any of our commercialized products, or the discovery of serious safety issues, could have a significant negative impact on us.

The FDA and other relevant regulatory agencies have the authority to require or request the recall in the event of material deficiencies or defects in design or manufacture or in the event an unacceptable risk to health. Manufacturers may, under their own initiative, also initiate a recall. A government-mandated or voluntary recall could occur as a result of an unacceptable risk to health, component failures, manufacturing errors, design or labeling defects or other deficiencies and issues. Recalls would divert managerial and financial resources and have an adverse effect on our reputation, financial condition and operating results.

Further, under the FDA's reporting regulations, we are required to report to the FDA any event that reasonably suggests that our products may have caused or contributed to a death or serious injury or in which our product malfunctioned and, if the malfunction of the same or similar product marketed by us were to recur, would likely cause or contribute to death or serious injury. The FDA also requires reporting of serious, life-threatening, unexpected and other adverse experiences and the submission of periodic safety reports and other information. Malfunctions or other adverse event reports may result in a voluntary or involuntary recall and other adverse actions, which could divert managerial and financial resources, impair our ability to manufacture in a cost-effective and timely manner and have an adverse effect on our reputation, financial condition and operating results. Similar reporting requirements exist in Europe and other jurisdictions.

Any adverse event involving our products could result in future voluntary corrective actions, such as recalls or customer notifications, or regulatory agency action, which could include inspection, mandatory recall or other enforcement action. Any corrective action, whether voluntary or involuntary, will require the dedication of our time and capital, distract management from operating our business and may harm our reputation and financial results. For example, in 2014 we notified the FDA that we were going to initiate a voluntary recall of our Morph AccessPro product based on a manufacturing observation, which was completed to the FDA's satisfaction in the same year, and in 2017 we updated our instructions for use for the Helix and Morph catheter products to provide guidance on known potential risks. There can be no guarantee that we will not experience similar product recalls or changes in the future with these products or our other products or therapeutic candidates, if approved.

Modifications to our products may require reclassifications, new regulatory approvals or clearances, or may require us to cease marketing or recall the modified products until new CE marking is obtained.

Currently there are six Morph product family model numbers approved for commercial use in the United States via a 510(k) clearance and three in Europe under CE Mark. A modification to these products could lead to a reclassification and could result in further requirements (including additional clinical trials) to maintain each respective clearance or approval. If we fail to comply with such further requirements we may be required to cease marketing or to recall the modified product until we obtain clearance or approval, and we may be subject to significant regulatory fines or penalties.

The financial performance of our enabling and delivery products may be adversely affected by medical device tax provisions in the healthcare reform laws in the United States.

The Patient Protection and Affordable Care Act, as amended by the Health Care and Education Reconciliation Act of 2010, or collectively, the Affordable Care Act, imposes, among other things, an annual excise tax of 2.3% on any entity that manufactures or imports medical devices offered for sale in the United States beginning with tax year 2013. Under these provisions, the Congressional Research Service predicts that the total cost to the medical device industry may be up to $20 billion over the next decade. On December 18, 2015, President Obama signed into law the Consolidated Appropriations Act, 2016 (H.R. 2029), which includes a two-year moratorium on the medical device excise tax. It amended section 4191 of the Internal Revenue Code to exempt medical device sales during the period of January 1, 2016 to December 31, 2017. On January 22, 2018, President Trump signed legislation that suspended the medical device excise tax through December 31, 2021. Absent further legislative action, the tax will be automatically reinstated for medical device sales starting on January 1, 2022. The financial impact this tax may have on our business is unclear and there can be no assurance that our business will not be materially adversely affected by it.

We work with outside scientists and their institutions in developing therapeutic candidates and products. These scientists may have other commitments or conflicts of interest, which could limit our access to their expertise.

We work with scientific advisors and collaborators at academic research institutions in connection with our development programs. These scientific advisors serve as our link to the specific pools of trial participants we are targeting in that these advisors may:

- identify individuals as potential candidates for study;
- obtain their consent to participate in our research;
- perform medical examinations and gather medical histories;
- conduct the initial analysis of suitability of the individuals to participate in our research based on the foregoing; and
- collect data and biological samples from trial participants periodically in accordance with our study protocols.

These scientists and collaborators are not our employees, rather they serve as either independent contractors or the primary investigators under research collaboration agreements that we have with their sponsoring academic or research institution. Such scientists and collaborators may have other commitments that would limit their availability to us. Although our scientific advisors generally agree not to do competing work, if an actual or potential conflict of interest between their work for us and their work for another entity arises, we may lose their services. It is also possible that some of our valuable proprietary knowledge may become publicly known through these scientific advisors if they breach their confidentiality agreements with us, which would cause competitive harm to our business.

The use, misuse or off-label use of our products or therapies, if approved, may result in injuries that lead to product liability suits, which could be costly to our business.

We are not permitted to make claims about the use of our marketed products and will not be permitted to make claims about the use of our therapeutic candidates, if approved, outside of their approved indications. Further, we are not and will not be able to proactively discuss or provide information on off-label uses of such products, with very specific and limited exceptions. However, we cannot prevent a physician from using our products or therapeutic candidates, if approved, for off-label applications. Off-label use of our products or therapies, if approved, is more likely to result in complications that have serious consequences. Product liability claims are especially prevalent in our industry and could harm our reputation, divert management's attention from our core business, be expensive to defend and may result in sizable damage awards against us. Although we maintain product liability insurance, the amount or breadth of our coverage may not be adequate for the claims that may be made against us. In addition, failure to follow FDA rules and guidelines relating to promotion and advertising can result in, among other things, the FDA's refusal to approve a product or therapeutic candidate, the suspension or withdrawal of an approved product or therapy from the market, product recalls, fines, disgorgement of money, operating restrictions, injunctions or criminal prosecutions.

Our employees, principal investigators, consultants and collaboration partners may engage in misconduct or other improper activities, including noncompliance with laws and regulatory standards and requirements and insider trading.

We are exposed to the risk of employee fraud or other misconduct. Misconduct by employees could include failures to comply with FDA regulations, to provide accurate information to the FDA, to comply with manufacturing standards we have established, to comply with federal and state healthcare fraud and abuse laws and regulations, to report financial information or data accurately or to disclose unauthorized activities to us. In particular, sales, marketing and business arrangements in the healthcare industry are subject to extensive laws and regulations intended to prevent fraud, kickbacks, self-dealing and other abusive practices. These laws and regulations restrict or prohibit a wide range of activity relating to pricing, discounting, marketing and promotion, sales commissions, customer incentive programs and other business arrangements. Employee misconduct could also involve the improper use of information obtained in the course of clinical trials, which could result in regulatory sanctions and serious harm to our reputation, or a breach of insider trading laws. It is not always possible to identify and deter employee misconduct, and the precautions we take to detect and prevent this activity may not be effective in controlling unknown or unmanaged risks or losses or in protecting us from governmental investigations or other actions or lawsuits stemming from a failure to be in compliance with such laws or regulations. If any such actions are instituted against us, and we are not successful in defending ourselves or asserting our rights, those actions could have a significant impact on our business, including the imposition of significant fines or other sanctions.

If we are unable to establish sales and marketing capabilities or enter into agreements with third parties to market and sell our therapeutic candidates, if approved, we may be unable to generate any revenues.

We currently have a limited organization for the sales, marketing and distribution of products and the cost of establishing and maintaining such an organization may exceed the cost-effectiveness of doing so. In order to market any products that may be approved, including CardiAMP and CardiALLO Cell Therapy Systems, we must build our sales, distribution, marketing, managerial and other non-technical capabilities or make arrangements with third parties to perform these services. We have limited prior experience in the marketing, sale or distribution of approved products and there are significant risks involved in building and managing a sales organization, including our ability to hire, retain, and incentivize qualified individuals, generate sufficient sales leads, provide adequate training to sales and marketing personnel, and effectively manage a geographically dispersed sales and marketing team. Any failure or delay in the development of our internal sales, marketing and distribution capabilities would adversely impact the commercialization of our therapeutic candidates.

Our strategy is to obtain FDA approval and market the CardiAMP Cell Therapy System for potential heart failure and chronic myocardial ischemia indications using a dedicated direct sales model focused on selected cardiologists and interventional cardiologists. We may in the future, choose to align ourselves with collaborators as part of our commercialization strategy, particularly outside of the United States, and our future collaboration partners, if any, may not dedicate sufficient resources to the commercialization of our therapeutic candidates or companion diagnostic or may otherwise fail in their commercialization due to factors beyond our control. If we are unable to establish effective collaborations to enable the sale of our therapeutic candidates and companion diagnostic to healthcare professionals and in geographical regions, including the United States, that will not be covered by our own marketing and sales force, or if our potential future collaboration partners do not successfully commercialize our therapeutic candidates or companion diagnostic, our ability to generate revenues from product sales, including sales of CardiAMP and CardiALLO Cell Therapy Systems, will be adversely affected.

Building an internal sales force involves many challenges, including:

- recruiting and retaining talented people;
- training employees that we recruit;
- setting the appropriate system of incentives;
- managing additional headcount; and
- integrating a new business unit into an existing corporate architecture.

If we are unable to build our own sales force or negotiate a strategic partnership for the commercialization of CardiAMP or CardiALLO Cell Therapy Systems in the United States, we may be forced to delay the potential commercialization of these therapies or reduce the scope of our sales and marketing activities for CardiAMP or CardiALLO Cell Therapy Systems. To fund commercialization activities we will need to obtain additional capital, which may not be available to us on acceptable terms, or at all. If we do not have sufficient funds, we will not be able to bring CardiAMP or CardiALLO Cell Therapy Systems to market or generate product revenue.

If we are unable to establish adequate sales, marketing and distribution capabilities, whether independently or with third parties, we may not be able to generate sufficient product revenue and may not become profitable. We will be competing with many companies that currently have extensive and well-funded marketing and sales operations. Without an internal team or the support of a third party to perform marketing and sales functions, we may be unable to compete successfully against these more established companies.

In addition, there are risks involved with both establishing our own sales and marketing capabilities and entering into arrangements with third parties to perform these services. For example, recruiting and training a sales force is expensive and time-consuming and could delay any launch. If the commercial launch of a therapeutic candidate for which we recruit a sales force and establish marketing capabilities is delayed or does not occur for any reason, we would have prematurely or unnecessarily incurred these commercialization expenses. This may be costly, and our investment would be lost if we cannot retain or reposition our sales and marketing personnel.

We have limited experience manufacturing our therapeutic candidates or products in commercial quantities, which could harm our business.

Because we have only limited experience in manufacturing therapeutic candidates or products in commercial quantities, we may encounter production delays or shortfalls. Such production delays or shortfalls may be caused by many factors, including the following:

- we intend to significantly expand our manufacturing capacity, and our production processes may have to change to accommodate this growth;
- key components and sub-assemblies of our products and therapeutic candidates are currently provided by a single supplier or limited number of suppliers, and we do not maintain large inventory levels of these components and sub-assemblies; if we experience a shortage in any of these components or sub-assemblies, we would need to identify and qualify new supply sources, which could increase our expenses and result in manufacturing delays;
- we may experience a delay in completing validation and verification testing for new controlled-environment rooms at our manufacturing facilities;
- we have limited experience in complying with FDA's QSRs, which applies to the manufacture of our products and therapeutic candidates; and
- to increase our manufacturing output significantly, we will have to attract and retain qualified employees, who are in short supply, for our manufacturing operations.

If we are unable to keep up with demand for our products, our revenues could be impaired, market acceptance for our products could be harmed and our customers might instead purchase our competitors' products. Our inability to successfully manufacture our products would materially harm our business.

If we fail to obtain and sustain an adequate level of reimbursement for our products by third-party payors, sales and profitability would be adversely affected.

Our ability to commercialize any therapeutic candidates or products successfully will depend, in part, on the extent to which coverage and reimbursement for our therapeutic candidates or products and related treatments will be available from government healthcare programs, private health insurers, managed care plans, and other organizations. Additionally, even if there is a commercially viable market, if the level of third-party reimbursement is below our expectations, our revenue and profitability could be materially and adversely affected.

Third-party payors, such as government programs, including Medicare in the United States, or private healthcare insurers, carefully review and increasingly question the coverage of, and challenge the prices charged for medical products and services, and many third-party payors limit coverage of or reimbursement for newly approved therapies or products. Reimbursement rates and coverage from private health insurance companies vary depending on the company, the insurance plan and other factors. As a result, the coverage determination process will require us to provide scientific and clinical support for the use of our therapeutic candidates to each private health insurance company separately, with no assurance that adequate coverage and reimbursement will be obtained.

A current trend in the U.S. healthcare industry as well as in other countries around the world is toward cost containment, including a number of legislative and regulatory changes to the health care system that could impact our ability to sell our approved therapies or products profitably. In particular, the Medicare Prescription Drug, Improvement, and Modernization Act of 2003 revised the payment methodology for many products under Medicare in the United States, which has resulted in lower rates of reimbursement. In 2010, the Affordable Care Act was enacted. This expansion in the government's role in the U.S. healthcare industry may further lower rates of reimbursement.

Other legislative changes have been proposed and adopted in the United States since the Affordable Care Act was enacted. On August 2, 2011, the Budget Control Act of 2011, among other things, created measures for spending reductions by Congress. A Joint Select Committee on Deficit Reduction, tasked with recommending a targeted deficit reduction of at least $1.2 trillion for the years 2012 through 2021, was unable to reach required goals, thereby triggering the legislation's automatic reduction to several government programs. This includes aggregate reductions of Medicare payments to providers up to 2% per fiscal year. On January 2, 2013, President Obama signed into law the American Taxpayer Relief Act of 2012, or the ATRA, which delayed for another two months the budget cuts mandated by these sequestration provisions of the Budget Control Act of 2011. On March 1, 2013, the President signed an executive order implementing sequestration, and on April 1, 2013, the 2% Medicare payment reductions went into effect. The ATRA also, among other things, reduced Medicare payments to several providers, including hospitals, imaging centers and cancer treatment centers, and increased the statute of limitations period for the government to recover overpayments to providers from three to five years.

In Europe, the European Commission has submitted a Proposal for a Regulation of the European Parliament and the Council on medical devices, amending Directive 2001/83/EC, Regulation (EC) No 178/2002 and Regulation (EC) No 1223/2009, to replace, inter alia, Directive 93/42/EEC and to amend regulations regarding medical devices in the European Union, which could result in changes in the regulatory requirements for medical devices in Europe.

Large public and private payors, managed care organizations, group purchasing organizations and similar organizations are exerting increasing influence on decisions regarding the use of, and reimbursement levels for, particular treatments. In particular, third-party payors may limit the covered indications. Cost-control initiatives could decrease the price we might establish, which could result in revenue and profitability being lower than anticipated.

There may be significant delays in obtaining coverage and reimbursement for newly approved therapies or products, and coverage may be more limited than the purposes for which the therapy or product is approved by the FDA or other regulatory authorities. Moreover, eligibility for coverage and reimbursement does not imply that a therapy or product will be paid for in all cases or at a rate that covers our costs, including research, development, manufacture, sale and distribution expenses. Interim reimbursement levels, if applicable, may also be insufficient to cover our and any partner’s costs and may not be made permanent. Our inability to promptly obtain coverage and profitable payment rates from both government-funded and private payors for any approved therapies or products that we develop could have a material adverse effect on our operating results, our ability to raise capital needed to commercialize therapies or products and our overall financial condition.

Furthermore, reimbursement systems in international markets vary significantly by country and by region, and reimbursement approvals must be obtained on a country-by-country basis. In many countries, therapies or products cannot be commercially launched until reimbursement is approved and the negotiation process in some countries can exceed 12 months. In addition, pricing and reimbursement decisions in certain countries can be affected by decisions taken in other countries, which can lead to mandatory price reductions and/or additional reimbursement restrictions across a number of other countries, which may thereby adversely affect our sales and profitability. In the event that countries impose prices which are not sufficient to allow us to generate a profit, this would adversely affect sales and profitability.

Price controls may be imposed in foreign markets, which may adversely affect our future profitability.

In some countries, particularly European Union member states, Japan, Australia and Canada, the pricing of therapies and products is subject to governmental control. In these countries, pricing negotiations with governmental authorities can take considerable time after receipt of marketing approval for a therapy or product. In addition, there can be considerable pressure by governments and other stakeholders on prices and reimbursement levels, including as part of cost containment measures. Political, economic and regulatory developments may further complicate pricing negotiations, and pricing negotiations may continue after reimbursement has been obtained. Reference pricing used by various European Union member states and parallel distribution, or arbitrage between low-priced and high-priced member states, can further reduce prices. In some countries, we or our partners may be required to conduct a clinical trial or other studies that compare the cost-effectiveness of our therapeutic candidates to other available therapies in order to obtain or maintain reimbursement or pricing approval. Publication of discounts by third-party payors or authorities may lead to further pressure on the prices or reimbursement levels within the country of publication and other countries. If reimbursement of our therapies or products is unavailable or limited in scope or amount, or if pricing is set at unsatisfactory levels, our business, revenues or profitability could be adversely affected.

If the market opportunities for our therapeutic candidates or products are smaller than we believe they are, our revenues may be adversely affected and our business may suffer.

It is very difficult to estimate the future commercial potential of the CardiAMP Cell Therapy System, the CardiALLO Cell Therapy System, and our commercialized products due to factors such as safety and efficacy compared to other available treatments, changing standards of care, third-party payor reimbursement standards, patient and physician preferences, and the availability of competitive alternatives that may emerge. We believe that approximately 70% of the NYHA Class II and Class III ischemic systolic heart failure patients in the United States will be eligible for CardiAMP due to a sufficient CardiAMP potency assay score. However, if considerably less than approximately 70% of NYHA Class II and Class III ischemic heart failure patients are eligible for CardiAMP due to an insufficient CardiAMP potency assay score, it would significantly and negatively impact our business, financial condition and results of operations.

If product liability lawsuits are brought against us, we may incur substantial liabilities and may be required to limit commercialization of our therapeutic candidates or products.

We face an inherent risk of product liability as a result of the human clinical use of our therapeutic candidates and products and will face an even greater risk if we continue to commercialize our therapeutic candidates and products. For example, we may be sued if any therapy or product we develop allegedly causes injury or is found to be otherwise unsuitable during product testing, manufacturing, marketing or sale. Any such product liability claims may include allegations of defects in manufacturing, defects in design, a failure to warn of inherent dangers, negligence, strict liability, and a breach of warranties. Claims could also be asserted under state consumer protection acts. If we cannot

successfully defend ourselves against product liability claims, we may incur substantial liabilities or be required to limit commercialization. Even a successful defense would require significant financial and management resources. Regardless of the merits or eventual outcome, liability claims may result in:

- decreased demand, even if such products or therapies are approved;
- injury to our reputation;
- withdrawal of clinical trial participants;
- costs to defend the related litigations;
- a diversion of management's time and our resources;
- substantial monetary awards to trial participants or patients;
- recalls, withdrawals, or labeling, marketing or promotional restrictions;
- increased cost of liability insurance;

- loss of revenue;

- the inability to receive regulatory approvals or commercialize our approved products or therapies; and

- a decline in our share price.

Although we maintain product liability insurance with coverage that we believe is consistent with industry norms for companies at our stage of development, the amount or breadth of our coverage may not be adequate for the claims that may be made against us. Failure to obtain and retain sufficient product liability insurance at an acceptable cost to protect against potential product liability claims could prevent or inhibit the commercialization of products or therapies we develop. Additionally, our insurance policies have various exclusions, and we may be subject to a product liability claim for which we have no coverage or reduced coverage. Any claim that may be brought against us could result in a court judgment or settlement in an amount that is not covered, in whole or in part, by our insurance or that is in excess of the limits of our insurance coverage. We will have to pay any amounts awarded by a court or negotiated in a settlement that exceed our coverage limitations or that are not covered by our insurance, and we may not have, or be able to obtain, sufficient capital to pay such amounts.

Our business and operations would suffer in the event of system failures.

Despite the implementation of security measures, our internal computer systems and those of our current and any future CROs and other contractors, consultants and potential collaborators are vulnerable to damage from computer viruses, unauthorized access, natural disasters, terrorism, war and telecommunication and electrical failures. For example, our systems have been impacted by computer viruses in the past, and while we have not experienced any material system failure, accident or security breach that has resulted in lasting impacts to date, if such an event were to occur and cause interruptions in our operations, it could result in a material disruption of our development programs and our business operations. For example, the loss of clinical trial data from completed or future clinical trials could result in delays in our regulatory approval efforts and significantly increase our costs to recover or reproduce the data. Likewise, we rely on third parties for manufacturing our therapeutic candidates and conducting clinical trials, and similar events relating to their computer systems could also have a material adverse effect on our business. To the extent that any disruption or security breach were to result in a loss of, or damage to, our data or applications, or inappropriate disclosure of confidential or proprietary information, we could incur liability and the further development and commercialization of our therapeutic candidates could be delayed.

Interruptions in supply or inventory loss may adversely affect our operating results and financial condition.

Our therapeutic candidates and products are manufactured and distributed using technically complex processes requiring specialized facilities, highly specific raw materials and other production constraints. The complexity of these

processes, as well as strict company and government standards for manufacture and storage, subjects us to production risks. While batches released for use in clinical trials or for commercialization undergo sample testing, some defects may only be identified following release. In addition, process deviations or unanticipated effects of approved process changes may result in these intermediate products not complying with stability requirements or specifications. The investigation and remediation of any identified problems can cause production delays, substantial expense, lost sales and delays of new product or therapy launches. Any supply interruption or the loss thereof could hinder our ability to timely distribute our approved products and satisfy demand. Any unforeseen storage failure or loss in supply could delay our clinical trials and, if our therapeutic candidates are approved, result in a loss of our market share and negatively affect our revenues and operations.

We or the third parties upon whom we depend may be adversely affected by earthquakes or other natural disasters and our business continuity and disaster recovery plans may