

Cytosorbents Corp
Form 10-K
March 03, 2017

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, 2016

or

TRANSITION REPORT PURSUANT TO SECTION 13 or 15(d) OF THE SECURITIES EXCHANGE ACT OF 1934

Commission file number 001-36792

CYTOSORBENTS CORPORATION

(Exact name of registrant as specified in its charter)

Delaware

(State or other jurisdiction of incorporation or organization)

98-0373793

(I.R.S. Employer Identification No.)

7 Deer Park Drive, Suite K

Monmouth Junction, New Jersey 08852

(Address of principal executive offices) (Zip Code)

Registrant's telephone number, including area code **(732) 329-8885**

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

Title of each class:	Name of each exchange on which registered:
Common Stock, \$0.001 par value	NASDAQ Stock Market LLC

Securities registered pursuant to Section 12(g) of the Act: None

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

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

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 (§232.405 of this chapter) 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 (§229.405 of this chapter) is not contained herein, and will not be contained, to the best of registrant's knowledge, in definitive proxy or

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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.

Large Accelerated Filer

Accelerated Filer

Non-accelerated Filer (do not check if a smaller reporting company) Smaller reporting company

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 common stock of the registrant held by non-affiliates as of June 30, 2016 was approximately \$102,000,000. As of February 28, 2017 there were outstanding 25,523,967 shares of common stock.

Documents incorporated by reference:

Portions of the CytoSorbents Corporation definitive proxy statement to be filed pursuant to Regulation 14A within 120 days after the end of the registrant’s fiscal year are incorporated by reference into Part III of this Form 10-K and certain documents are incorporated by reference into Part IV of this Form 10-K.

CYTOSORBENTS CORPORATION

ANNUAL REPORT ON FORM 10-K

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CAUTIONARY NOTE REGARDING FORWARD-LOOKING STATEMENTS

This Annual Report on Form 10-K, or this Report, contains “forward-looking statements” within the meaning of Section 27A of the Securities Act, and Section 21E of the Exchange Act. Forward-looking statements discuss matters that are not historical facts. Because they discuss future events or conditions, forward-looking statements may include words such as “anticipate,” “believe,” “estimate,” “intend,” “could,” “should,” “would,” “may,” “seek,” “plan,” “might,” “will,” “expect,” “project,” “forecast,” “potential,” “continue,” negatives thereof or similar expressions. These forward-looking statements are found at various places throughout this Report and include information concerning possible or assumed future results of our operations; business strategies; future cash flows; financing plans; plans and objectives of management; any other statements regarding future operations, future cash needs, business plans and future financial results, and any other statements that are not historical facts. Unless otherwise indicated, the terms “CytoSorbents,” “Company,” “we,” “us” and “our” refer to CytoSorbents Corporation.

From time to time, forward-looking statements also are included in our other periodic reports on Forms 10-Q and 8-K, in our press releases, in our presentations, on our website and in other materials released to the public. Any or all of the forward-looking statements included in this Report and in any other reports or public statements made by us are not guarantees of future performance and may turn out to be inaccurate. These forward-looking statements represent our intentions, plans, expectations, assumptions and beliefs about future events and are subject to risks, uncertainties and other factors. Many of those factors are outside of our control and could cause actual results to differ materially from the results expressed or implied by those forward-looking statements. In light of these risks, uncertainties and assumptions, the events described in the forward-looking statements might not occur or might occur to a different extent or at a different time than we have described. You are cautioned not to place undue reliance on these forward-looking statements, which speak only as of the date of the applicable Report or public statement. All subsequent written and oral forward-looking statements concerning other matters addressed in this Report or public statement and attributable to us or any person acting on our behalf are expressly qualified in their entirety by the cautionary statements contained or referred to in this Report.

Except to the extent required by law, we undertake no obligation to update or revise any forward-looking statements, whether as a result of new information, future events, a change in events, conditions, circumstances or assumptions underlying such statements, or otherwise. For discussion of factors that we believe could cause our actual results to differ materially from expected and historical results see “Item 1A — Risk Factors” below.

TRADEMARKS

This Report includes our trademarks and trade names, such as CytoSorb®, BetaSorb™, HemoDefend™, and VetResQ™, which are protected under applicable intellectual property laws and are the property of CytoSorbents Corporation and its subsidiaries. This Report also contains the trademarks, trade names and service marks of other companies, which

are the property of their respective owners. Solely for convenience, trademarks, trade names and service marks referred to in this Report may appear without the TM, ®, SM symbols, but such references are not intended to indicate, in any way, that we will not assert, to the fullest extent under applicable law, our rights or the rights of the applicable licensor to these trademarks, trade names and service marks. We do not intend our use or display of other parties' trademarks, trade names or service marks to imply, and such use or display should not be construed to imply, a relationship with, or endorsement or sponsorship of us by, these other parties.

PART I

Item 1. Business.

Overview

We are a leader in critical care immunotherapy, investigating and commercializing our CytoSorb blood purification technology to reduce deadly uncontrolled inflammation in hospitalized patients around the world, with the goal of preventing or treating multiple organ failure in life-threatening illnesses and cardiac surgery. Organ failure is the cause of nearly half of all deaths in the intensive care unit (“ICU”), with little to improve clinical outcome. CytoSorb, our flagship product, is approved in the European Union (“EU”) as a safe and effective extracorporeal cytokine filter and is designed to reduce the “cytokine storm” that could otherwise cause massive inflammation, organ failure and death in common critical illnesses such as sepsis, burn injury, trauma, lung injury, and pancreatitis. These are conditions where the mortality is extremely high, yet no effective treatments exist. In addition, CytoSorb can be used in other inflammatory conditions such as cardiac surgery, autoimmune disease flares, and potentially for cancer, cytokine release syndrome in cancer immunotherapy, and cancer cachexia, a common syndrome that affects cancer patients, where cytokines play a major role in the cause of inflammation. CytoSorb has been used globally in more than 20,000 human treatments to date, with more than 16,000 in critical illnesses and more than 4,000 in cardiac surgery. Our purification technologies are based on biocompatible, highly porous polymer beads that can actively remove toxic substances from blood and other bodily fluids by pore capture and surface adsorption. We have numerous products under development based upon this unique blood purification technology, protected by 32 issued U.S. patents and multiple applications pending, including HemoDefend, ContrastSorb, DrugSorb, and others.

In March 2011, CytoSorb, as an extracorporeal cytokine filter indicated for use in clinical situations where cytokines are elevated, was “CE marked” in the EU, allowing for commercial marketing. The CE mark demonstrates that a conformity assessment has been carried out and the product complies with the Medical Devices Directive. The goal of CytoSorb is to prevent or treat organ failure by reducing cytokine storm and the potentially deadly systemic inflammatory response syndrome (“SIRS”) in diseases such as sepsis, trauma, burn injury, acute respiratory distress syndrome, pancreatitis, liver failure, and many others. Organ failure is the leading cause of death in the ICU, and remains a major unmet medical need, with little more than supportive care therapy (e.g., mechanical ventilation, dialysis, vasopressors, fluid support, etc.) as treatment options. By potentially preventing or treating organ failure, CytoSorb may improve clinical outcome, including survival, while reducing the need for costly ICU treatment, thereby potentially saving significant healthcare costs.

Our CE Mark enables CytoSorb to be sold throughout the European Union and member states of the European Economic Area. In addition, many countries outside the EU accept the CE Mark for medical devices, but may also require registration with or without additional clinical studies. The broad indication for which CytoSorb is CE marked

allows it to be used “on-label” in diseases where cytokines are elevated including, but not limited to, critical illnesses such as those mentioned above, autoimmune disease flares, cancer cachexia, and many other conditions where cytokine-induced inflammation plays a detrimental role.

Cytokines are small proteins that normally stimulate and regulate the immune response. However, in certain diseases, particularly life-threatening conditions commonly seen in the ICU, such as sepsis and infection, trauma, acute respiratory distress syndrome (“ARDS”), severe burn injury, liver failure, and acute pancreatitis, cytokines are often produced in vast excess – a condition often called cytokine storm. Left unchecked, this cytokine storm can lead to a severe maladaptive SIRS that can then cause cell death, multiple organ dysfunction syndrome, and multiple organ failure. Failure of vital organs such as the heart, lungs, and kidneys, accounts for nearly half of all deaths in the ICU, despite the wide availability of supportive care therapies, or “life support”, such as dialysis, mechanical ventilation, extracorporeal membrane oxygenation, and vasopressors. By replacing the function of failed organs, these supportive care therapies can initially help to keep patients alive, but do not help patients recover faster, and in many cases can increase the risk of dangerous complications. Unlike these supportive care therapies, the goal of the CytoSorb cytokine filter is to proactively prevent or treat organ failure by reducing cytokine storm and reducing the maladaptive SIRS response. In doing so, CytoSorb targets the reduction in the severity of patient illness and the need for intensive care, while potentially improving clinical outcome and saving healthcare costs.

As part of the CE Mark process, we completed our randomized, controlled, European Sepsis Trial amongst 14 trial sites in Germany in 2011, with enrollment of 100 patients with sepsis and respiratory failure. The trial established that CytoSorb was sufficiently safe in this critically-ill population to support the CE mark. In the European Sepsis Trial, the treatment was well-tolerated with no serious device related adverse events reported. Although the trial was not powered to demonstrate significant reduction in other clinical endpoints such as mortality, these were also included as secondary and exploratory endpoints in the trial.

The first 22 patients in the study represented a sepsis pilot study. In the next 31 patients, a compromise of the manual randomization schedule at two trial sites led to an imbalance in the severity of illness between the control and treatment patient groups of the study. After a thorough review, the Scientific Advisory Board and the independent Data Safety Monitoring Board both recommended that due to this enrollment bias, these 31 patients should only be used for safety evaluation purposes and that new patients should be enrolled into the trial using electronic web-based randomization to randomly assign patients into either the control or treatment arms.

Excluding four patients that withdrew, the remaining 43 evaluable patients enrolled under electronic randomization (of which 25 were in the control group and 18 were in the treatment group) were relatively balanced in terms of the severity of illness in treatment and control patients, confirming the findings of the Scientific Advisory Board and the Data Safety Monitoring Board. An independent Contract Research Organization, RCRI, Inc., (Minneapolis, MN), analyzed 41 of these 43 evaluable patients in the European Sepsis Trial and showed on a statistically significant basis ($p < 0.05$), the ability of CytoSorb to reduce circulating levels of key cytokines from whole blood in treated patients on the average of 30% to 50% over the seven day treatment period. Additionally, post-hoc subgroup analyses of the clinical outcome data from patients enrolled under electronic randomization demonstrated statistically significant reduction in mortality in patients at high risk of death in sepsis, specifically in patients with:

· Very high cytokine levels ($IL-6 \geq 1,000$ pg/mL and/or $IL-1ra \geq 16,000$ pg/mL) where 28-day mortality was 0% treated as compared to 63% control, $p=0.03$, $n=14$; and

· Age ≥ 65 (14-day mortality: 0% treated as compared to 36% control, $p=0.04$, $n=21$).

We plan to conduct larger, prospective studies in septic patients in the future to confirm these findings. According to a recent study by the U.S. Centers for Disease Control and Prevention (“CDC”), those older than age 65 account for approximately two-thirds of patients hospitalized in the U.S. for sepsis, and were responsible for the doubling in the incidence of sepsis over the past decade. Without effective therapies to treat sepsis, the incidence of sepsis and sepsis-related deaths are expected to continue to increase significantly over the course of the next decade, particularly as the baby boomer generation, which began turning 65 in 2011, continues to get older.

In addition to CE marking, we also achieved ISO 13485:2003 Full Quality Systems certification, an internationally recognized quality standard designed to ensure that medical device manufacturers have the necessary comprehensive management systems in place to safely design, develop, manufacture and distribute medical devices in the EU. We manufacture CytoSorb at our manufacturing facilities in New Jersey for commercial sales abroad and for additional clinical studies. In September 2016, we were granted a two-year renewal for the CytoSorb CE Mark. In June 2016, we successfully completed an ISO 13485:2003 annual surveillance audit maintaining our good standing with our Notified Body. We also established a reimbursement path for CytoSorb in Germany and Austria.

From September 2011 through June 2012, we began a controlled market release of CytoSorb in select geographic territories in Germany. The purpose of this program was to prepare for commercialization of CytoSorb in Germany in terms of manufacturing, reimbursement, logistics, infrastructure, marketing, contacts, and other key issues.

In late June 2012, following the establishment of our European subsidiary, CytoSorbents Europe GmbH, a wholly-owned operating subsidiary of CytoSorbents Corporation, we began the commercial launch of CytoSorb in Germany with the hiring of Dr. Christian Steiner as Vice President of Sales and Marketing and three additional sales

representatives who joined us and completed their sales training during the third quarter of 2012. The fourth quarter of 2012 represented the first quarter of direct sales with the full sales team in place. During this period, we expanded our direct sales efforts to include both Austria and Switzerland.

In March 2016, we established CytoSorbents Switzerland GmbH, a wholly-owned subsidiary of CytoSorbents Europe GmbH, our wholly-owned subsidiary, to conduct marketing and direct sales in Switzerland. This indirect subsidiary began operations during the second quarter of 2016.

Fiscal year 2013 represented the first full year of CytoSorb commercialization. We focused our direct sales efforts in Germany, Austria and Switzerland with four sales representatives. The focus of the team was to encourage acceptance and usage by key opinion leaders (“KOLs”) throughout these countries. By the end of 2015, we had hundreds of KOLs in critical care, cardiac surgery, and blood purification who are either using CytoSorb or planning to use CytoSorb in the near future. We believe our relationships with KOLs will be essential to drive adoption and recurrent usage of CytoSorb, facilitate purchases by hospital administration, arrange reimbursement, and generate data for papers and presentations. In addition, we now currently have more than 55 investigator initiated studies being planned in Germany, Austria, and the United Kingdom in multiple applications including sepsis, cardiac surgery, lung injury, trauma, pancreatitis, liver failure, kidney failure, and others, with many already enrolling patients and some completed. These studies are being supported by our European Director of Scientific Affairs. As of February 1, 2017, we have increased our sales force to include 13 direct sales people, one contract sales person, and 12 sales and distributor support staff.

We have complemented our direct sales efforts with sales to distributors and/or corporate partners. In 2013, we reached agreement with distributors in the United Kingdom, Ireland, the Netherlands, Russia and Turkey. In April 2014, we announced distribution of CytoSorb in the Middle East, including Saudi Arabia, the United Arab Emirates, Kuwait, Qatar, Bahrain, and Oman (the Gulf Cooperative Council (“GCC”)) and Yemen, Iraq, and Jordan through an exclusive agreement with TechnoOrbits. In December 2014, we entered into an exclusive agreement with Smart Medical Solutions S.R.L., to distribute CytoSorb for critical care applications in Romania and the neighboring Republic of Moldova. In 2015, we announced exclusive distribution agreements with Aferetica SRL to distribute CytoSorb in Italy, AlphaMedix Ltd. to distribute CytoSorb in Israel, TekMed Pty Ltd. to distribute CytoSorb in Australia and New Zealand, and Hoang Long Pharma to distribute CytoSorb in Vietnam. In June 2016, we announced an exclusive distribution agreement with Palex Medical SA to distribute CytoSorb in Spain and Portugal. In September 2016, we announced an exclusive agreement with Armaghan Salamat Kish Group (Arsak) to distribute CytoSorb in Iran. In October 2016, we announced an exclusive agreement with Foxx Medical Chile SpA to distribute CytoSorb in Chile.

We have been expanding our strategic partnerships by number and scope. In September 2013, we entered into a strategic partnership with Biocon Ltd., India’s largest biotech company, with an initial distribution agreement for India and select emerging markets, under which Biocon has the exclusive commercialization rights for CytoSorb initially focused on sepsis. In October 2014, the Biocon partnership was expanded to include all critical care applications and cardiac surgery. In addition, Biocon committed to higher annual minimum purchases of CytoSorb to maintain distribution exclusivity and committed to conduct and publish results from multiple investigator initiated studies and patient case studies.

In December 2014, we entered into a multi-country strategic partnership with Fresenius Medical Care AG & Co KGaA (“Fresenius”) to commercialize the CytoSorb therapy. Under the terms of this agreement, Fresenius has exclusive rights to distribute CytoSorb for critical care applications in France, Poland, Sweden, Denmark, Norway, and Finland. The partnership will allow Fresenius to offer an innovative and easy way to use blood purification therapy for removing cytokines in patients that are treated in the ICU. To promote the success of CytoSorb, Fresenius will also engage in the ongoing clinical development of the product. This includes the support and publication of a number of small case series and patient case reports as well as the potential for future larger, clinical collaborations. In January 2017, the Fresenius partnership was expanded. The terms of the revised three-year agreement extend Fresenius’ exclusive distributorship of CytoSorb for all critical care applications in their existing territories through 2019 and include guaranteed minimum quarterly orders and payments, evaluable every one and a half years. In addition, we have entered into a new comprehensive co-marketing agreement with Fresenius. Under the terms of the agreement, CytoSorbents and Fresenius will jointly market CytoSorb and Fresenius’ CytoSorb compatible blood tubing sets to Fresenius’ critical care customer base in all countries where CytoSorb is being actively commercialized. CytoSorb will continue to be sold by our direct sales force or through our international network of distributors and partners, while Fresenius will sell all ancillary products to their customers. Fresenius will also provide a written endorsement of CytoSorb for use with their multiFiltrate and multiFiltratePRO acute care dialysis machines that can be used by us and our distribution partners to promote CytoSorb worldwide. Training and preparation for this co-marketing program is ongoing and it is expected co-marketing activity will commence during the second half of 2017.

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In September 2016, we entered into a multi-country strategic partnership with Terumo Cardiovascular Group to commercialize CytoSorb for cardiac surgery applications. Under the terms of the agreement, Terumo has exclusive rights to distribute the CytoSorb cardiopulmonary bypass (CPB”) procedure pack for intra-operative use during cardiac surgery in France, Sweden, Denmark, Norway, Finland and Iceland. Terumo launched the product in these six countries in December 2016.

Overall, we have established either direct sales or distribution (via distributors or strategic partners) of CytoSorb in 42 countries worldwide. Registration of CytoSorb is typically required in each of these countries prior to active commercialization. With CE Mark approval, this can be typically achieved within several months in EU countries. Outside of the EU, the process is more variable and can take several months to more than a year due to different requirements for documentation and clinical data. Variability in the timing of registration affects the initiation of active commercialization in these countries, which affects the timing of expected CytoSorb sales. We actively support all of our distributors and strategic partners in the product registration process. We cannot generally predict the timing of these registrations, and there can be no guarantee that we will ultimately achieve registration in countries where we have established distribution. For example, in August 2014 we announced exclusive distribution of CytoSorb in Taiwan with Hemoscien Corporation. However, in March 2015, due to the complexity we encountered with Taiwanese product registration, we elected to terminate our agreement with Hemoscien. Outside of the EU, CytoSorb is actively being commercialized in Turkey, India, Australia, New Zealand, Russia, South Africa, Serbia, Norway, Vietnam, Chile, Iceland and Saudi Arabia. We cannot guarantee that we will generate meaningful sales in the countries where we have established registration, due to other factors such as market adoption and reimbursement. We are currently actively evaluating other potential distributor and strategic partner networks in other major countries that accept CE Mark approval.

The market focus for CytoSorb is the prevention or treatment of organ failure in life-threatening conditions, including commonly seen illnesses in the ICU such as infection and sepsis, trauma, burn injury, ARDS, and others. Severe sepsis and septic shock, a potentially life-threatening systemic inflammatory response to a serious infection, accounts for approximately 10% to 20% of all ICU admissions and is one of the largest target markets for CytoSorb. Sepsis is a major unmet medical need with no approved products in the U.S. or Europe to treat it. As with other critical care illnesses, multiple organ failure is the primary cause of death in sepsis. When used with standard of care therapy, that includes antibiotics, the goal of CytoSorb in sepsis is to reduce excessive levels of cytokines and other inflammatory toxins, to help reduce the SIRS response and either prevent or treat organ failure.

In addition to the sepsis indication, we intend to conduct or support additional clinical studies in sepsis, cardiac surgery, and other critical care diseases where CytoSorb could be used, such as ARDS, trauma, severe burn injury, acute pancreatitis, and in other acute conditions that may benefit by the reduction of cytokines in the bloodstream. Some examples include the prevention of post-operative complications of cardiac surgery (cardiopulmonary bypass surgery) and damage to organs donated for transplant prior to organ harvest. We intend to generate additional clinical data to expand the scope of clinical experience for marketing purposes, to increase the number of treated patients, and to support potential future publications.

We have completed a single arm, dose ranging trial in Germany amongst several clinical trial sites to evaluate the safety and efficacy of CytoSorb when used 24 hours per day for seven days, each day with a new device and are conducting final statistical analysis of the data. Patients are being stratified for age, cytokine levels, and co-morbid illnesses in this matched pairs analysis. These additional dosing data are intended to help clinicians with additional treatment options for CytoSorb, help support the positive clinical data from our first European Sepsis Trial, and help shape the trial protocol for a pivotal sepsis study.

In addition to the dosing study, we plan to use data generated and published in the more than 55 investigator initiated studies and trials sponsored by us currently planned, enrolling or completed in Germany, Austria, Switzerland, the Netherlands, Hungary, the United Kingdom, India, and the U.S. Approximately 20 of these studies are currently enrolling patients and some have been completed. These trials, which are funded and supported by well-known university hospitals and KOLs, are the equivalent of Phase 2 clinical studies. They will provide invaluable information regarding the success of the device in the treatment of sepsis, cardio-pulmonary bypass surgery, trauma, and many other indications, and if successful, will be integral in helping to drive additional usage and adoption of CytoSorb.

In addition to sepsis and other critical care applications, cardiac surgery is emerging as an important potential application for CytoSorb in the European market. There are approximately one million cardiac surgery procedures performed annually in the U.S. and EU including, for example, coronary artery bypass graft surgery, valve replacement surgery, heart and lung transplant, congenital heart defect repair, aortic reconstruction, and left ventricular assist device (“LVAD”) implantation. Cardiac surgery can result in inflammation and the production of high levels of inflammatory cytokines, as activation of complement, and cause hemolysis, leading to the release of toxic plasma free hemoglobin. These can lead to post-operative complications such as respiratory failure and acute kidney injury. CytoSorb has a unique competitive advantage as the only cytokine and free hemoglobin removal technology that can be used during the operative procedure and can be easily installed in a bypass circuit in a heart-lung machine without the need for an additional pump. Direct cytokine and hemoglobin removal with CytoSorb enables it to replace the existing market for leukoreduction filters in cardiac surgery that attempt to indirectly reduce cytokines by capturing cytokine-producing leukocytes – an inefficient and suboptimal approach.

In February 2015, the U.S. Food and Drug Administration (“FDA”) approved our Investigational Device Exemption (“IDE”) application to commence a planned U.S. cardiac surgery feasibility study called REFRESH I (REduction of FREe Hemoglobin) amongst 20 patients and three U.S. clinical sites. The FDA subsequently approved an amendment to the protocol, expanding the trial to be a 40 patient randomized controlled study (20 treatment, 20 control) in eight clinical centers. REFRESH I represents the first part of a larger clinical trial strategy intended to support the approval of CytoSorb in the U.S. for intra-operative use during cardiac surgery.

The REFRESH I study is designed to evaluate the safety of CytoSorb when used intra-operatively in a heart-lung machine to reduce plasma free hemoglobin and cytokines in patients undergoing complex cardiac surgery. The length, complexity and invasiveness of these procedures cause hemolysis and inflammation, leading to high levels of plasma free hemoglobin, cytokines, activated complement, and other substances. These inflammatory mediators directly correlate with the incidence of serious post-operative complications such as kidney injury and failure. The goal of CytoSorb is to actively remove these inflammatory and toxic substances as they are being generated during the surgery and reduce complications. As of December 31, 2016, enrollment was complete with 46 patients. A total of 38 patients were evaluable and completed all aspects of the study.

The primary safety and efficacy endpoints of the study were the assessment of serious device related adverse events and the change in plasma free hemoglobin levels, respectively. On October 5, 2016, we announced positive top-line safety data. In addition, following a detailed review of all reported adverse events in a total of 46 enrolled patients, the independent Data Safety Monitoring Board (“DSMB”) found no safety concerns related to the CytoSorb device, achieving the primary safety endpoint of the trial and fulfilling a key requisite to move forward with a larger, definitive pivotal study. In addition, the therapy was well-tolerated and technically feasible, implementing easily into the cardiopulmonary bypass circuit without the need for an additional external blood pump. This study represents the first randomized controlled trial demonstrating the safety of intra-operative CytoSorb use in patients undergoing high risk cardiac operations.

Investigators of the REFRESH I trial have submitted an abstract with data, including free hemoglobin data, from the REFRESH I trial to the American Association of Thoracic Surgery conference to be held in late April 2017, and a manuscript is being prepared for journal submission. In parallel, the Company plans to meet with the FDA to discuss the results of REFRESH I in anticipation of filing an IDE application to initiate a pivotal REFRESH 2 trial in 2017.

Even though we have obtained CE Mark approval, no guarantee or assurance can be given that our CytoSorb product will work as intended or that we will be able to obtain FDA approval to sell CytoSorb in the U.S. or approval in any other country or jurisdiction. Because of the limited studies we have conducted, we are subject to substantial risk that our technology will have little or no effect on the treatment of any indications that we have targeted.

We have been successful in obtaining technology development contracts from agencies in the U.S. Department of Defense, including the Defense Advanced Research Projects Agency (“DARPA”), the U.S. Army, and the U.S. Air Force, as well as the National Institutes of Health. See the section entitled “Government Research Grants” of this Item 1 of this Report for information regarding the specific grants.

In January 2017, we launched VetResQ™ for the United States veterinary market. The FDA has been notified of the launch and we have provided the FDA with the related instructions for use and a marketing brochure. VetResQ is a broad spectrum blood purification adsorber designed to help treat deadly inflammation and toxic injury in animals with critical illnesses such as septic shock, toxic shock syndrome, severe systemic inflammation, toxin-mediated diseases, pancreatitis, trauma, liver failure, and drug intoxication. Based upon cumulative studies, VetResQ is capable of reducing a broad range of excessive inflammatory mediators and toxins that could otherwise cause direct tissue injury or serious systemic inflammation that can rapidly lead to instability, organ failure, and death. VetResQ is manufactured in the United States for the treatment of cats, dogs, horses, and animals of comparable size. VetResQ is compatible with standard hemodialysis, continuous renal replacement therapy (“CRRT”), and hemoperfusion blood pumps. VetResQ is available only for veterinary animal usage and is not for human use. We do not expect VetResQ to be significant source of revenue for us in the near term.

In addition to CytoSorb and VetResQ, we are developing other products utilizing our adsorbent polymer technology that have not yet received regulatory approval including HemoDefend, CytoSorb-XL, ContrastSorb, DrugSorb, BetaSorb, and others. The HemoDefend technology platform is a development-stage blood purification system that can remove contaminants in transfused blood products, with the goal of reducing potentially fatal transfusion reactions and improving the quality of blood. CytoSorb-XL is a development-stage, next-generation product to CytoSorb, adding endotoxin removal capability to cytokine, exotoxin, and other inflammatory mediator removal. ContrastSorb is designed to remove intravenous radiocontrast (IV contrast), that is administered during interventional radiology procedures, for example, coronary angiograms for heart disease, and computed tomography (CT scans) or computer axial tomography imaging (CAT scans) that can cause kidney failure in high risk patients, for example, those with pre-existing kidney disease, diabetes, hypertension, congestive heart failure, and who are of old age. DrugSorb is designed to remove toxic drugs from blood, such as in drug overdose. The BetaSorb filter was designed for use with renal replacement therapy in end-stage renal disease patients, to remove mid-molecular weight toxins that are not adequately removed by hemodialysis or hemofiltration. BetaSorb is not the current focus of our near-term commercialization plans. With the exception of HemoDefend, all of these products are known medically as hemoperfusion devices. During hemoperfusion, blood is removed from the body via a catheter or other blood access device, perfused through a filter medium where toxic compounds are removed, and returned to the body. Hemoperfusion, along with hemodialysis and hemofiltration, are the three major forms of blood purification.

HemoDefend is a development-stage blood purification technology platform designed to safeguard and protect the blood supply. Continued development of the product is being supported through a \$1.5 Phase II SBIR contract funded by the National Heart, Lung and Blood Institute (NHLBI) – a division of the National Institutes of Health (“NIH”), and U.S. Special Operations Command (USSOCOM). We seek to license the HemoDefend platform and have not yet received regulatory approval in any markets. HemoDefend consists of a mixture of proprietary porous polymer beads that target the removal of contaminants that can cause transfusion reactions or cause disease in patients receiving the tens of millions of transfused blood products administered worldwide each year. These contaminants include, for example, foreign antibodies, antigens, cytokines, free hemoglobin, bioactive lipids, toxins, drugs, and other inflammatory mediators that either were from the donor or accumulated during blood storage. The goal of the HemoDefend technology is to reduce these contaminants in transfused blood products to reduce transfusion reactions, to keep new blood fresh, and to improve the quality and safety of blood.

The HemoDefend beads are intended to be used in multiple configurations, including as a common in-line filter between the blood bag and the patient as well as a patent-pending “Beads in a Bag” treatment configuration, where the beads are placed directly into a blood storage bag. Once blood is put into this bag, the beads begin to automatically remove contaminants from the blood, and are designed to continue purifying blood throughout the entire blood storage period. The use of neutrally buoyant beads eliminates the need for mixing and is compatible with current blood storage conditions. Integrated filters in the bag prevent beads from leaving the bag during the transfusion process. The base polymer meets ISO 10993 standards for biocompatibility, hemocompatibility, genotoxicity, cytotoxicity, acute sensitivity and complement activation and can therefore directly contact blood for extended periods of time. In addition, the beads are inert and stable at a wide range of temperatures, and do not contain any antibodies, biologics, ligands, or drugs. Because of this, the beads have a very long shelf life that is consistent with blood storage bag manufacturing standards. No special equipment or handling is required, making it well-suited for mainstream and military applications, as well as for use in less developed countries that are not well-equipped to test and process blood products.

CytoSorb-XL is a development-stage, porous polymer bead technology that combines lipopolysaccharide endotoxin removal with the robust cytokine, toxin, and inflammatory mediator reduction achieved by CytoSorb. CytoSorb-XL and its novel endotoxin binding chemistry is the subject of a broad composition of matter patent application, intended to protect the technology worldwide for the next two decades. In a head-to-head comparison with the leading endotoxin adsorber, Toraymyxin (Toray, Japan), CytoSorb-XL matched the level of endotoxin reduction in an *in vitro* plasma recirculation system on a comparable volume basis. CytoSorb-XL is expected to replace stand-alone endotoxin specific filters by offering superior performance in the removal of not just endotoxin, but a much broader array of inflammatory mediators that drive uncontrolled deadly inflammation, organ failure, and death in sepsis. The expected market for CytoSorb-XL is similar in size and scope as for CytoSorb.

ContrastSorb is a development-stage blood purification technology that is being optimized for the removal of IV contrast from blood in order to prevent contrast-induced nephropathy (“CIN”). CIN is the acute loss of renal function within the first 48 hours following IV contrast administration. An estimated 65 million CT scans are performed worldwide with IV contrast each year to enhance the images and make it easier to identify anatomic structures. IV contrast is also administered during vascular interventional radiology procedures and angiography of blood vessels in the brain, heart, limbs, and other parts of the body to diagnose and treat atherosclerosis (narrowing of blood vessels due to cholesterol deposits), vascular injury, aneurysms, etc. For example, an estimated 10 million coronary angiograms are performed worldwide each year to diagnose and treat coronary artery disease by placing coronary stents, performing balloon angioplasty, or atherectomy (removal of plaque in arteries). The reported risk of CIN in patients undergoing contrast enhanced CT scans has been reported to be 2% to 13%. For coronary intervention, the risk has been estimated to be as high as 20% to 30% in high risk patients with pre-existing renal insufficiency, long-term diabetes, hypertension, congestive heart failure, and older age. The use of low osmolar IV contrast, hydration of patients pre-procedure, orally administration of N-acetylcysteine, and other agents to prevent CIN have demonstrated modest benefit in some clinical studies, but in many cases, the results across studies have been equivocal and inconsistent. In high risk patients, the direct removal of IV contrast from the blood with ContrastSorb to prevent CIN represents a potentially more effective alternative.

DrugSorb is a development-stage blood purification technology that is capable of removing a wide variety of drugs and chemicals from blood, as a potential treatment for drug overdose, drug toxicity, toxic chemical exposure, use in high-dose regional chemotherapy, and other applications. It has demonstrated extremely high single pass removal efficiency of a number of different drugs that exceeds the extraction capability of hemodialysis or other filtration technologies. It is similar in action to activated charcoal hemoperfusion cartridges that have been available for many years, but has the advantage of having inherent biocompatibility and hemocompatibility without coatings, and can be easily customized for specific agents.

Our BetaSorb device is intended to remove beta₂-microglobulin and other mid-molecular weight toxins from the blood of patients suffering from chronic kidney failure who rely on long term dialysis therapy to sustain their life. Standard high-flux hemodialysis is very effective in removing small uremic toxins, but much less effective in removing these mid-molecular weight toxins that functional kidneys normally remove. BetaSorb utilizes an adsorbent polymer packed into a similarly shaped and constructed cartridge as utilized for our CytoSorb product, although the polymers used in the two devices are physically different, with one optimized for short-term critical care use and the other specifically designed for the needs of long-term chronic usage. The BetaSorb device also incorporates industry standard connectors at either end of the device, which connect directly into the extra-corporeal circuit (bloodlines) in series with a dialyzer. To date, we have manufactured the BetaSorb device on a limited basis for testing purposes, including for use in clinical studies.

We initially identified end stage renal disease as the target market for our polymer-based adsorbent technology. However, during the development of BetaSorb, we identified several applications for our adsorbent technology in the treatment of critical care patients. As a result, we shifted our priorities to pursue critical care applications (such as for the treatment of sepsis) for our technology given that the potential for usage of BetaSorb in chronic conditions such as end stage renal disease is anticipated to have a longer and more complex regulatory pathway. We may pursue our

BetaSorb product in the future after the commercialization of the CytoSorb device. At such time as we determine to proceed with our proposed BetaSorb product, if ever, we will need to conduct additional clinical studies using the BetaSorb device and obtain separate regulatory approval in Europe and/or the U.S.

We have conducted clinical studies using our BetaSorb device in patients with chronic kidney failure, which have provided valuable data that underpin the development of the critical care applications for our technology. The BetaSorb device has been used in a total of four human pilot studies, involving 20 patients, in the U.S. and Europe. The studies included approximately 345 treatments, with some patients using the device for up to 24 weeks (in multiple treatment sessions lasting up to four hours, three times per week) in connection with the application of our products to patients suffering from chronic kidney failure.

Corporate History

We were originally organized as a Delaware limited liability company in August 1997 as Advanced Renal Technologies, LLC. We changed our name to RenalTech International, LLC in November 1998, and to MedaSorb Technologies, LLC in October 2003. In December 2005, MedaSorb Technologies, LLC converted from a limited liability company to a corporation. CytoSorbents Corporation was incorporated in Nevada on April 25, 2002 as Gilder Enterprises, Inc., and was originally engaged in the business of installing and operating computer networks that provided high-speed access to the Internet. On June 30, 2006, we disposed of our original business, and pursuant to an Agreement and Plan of Merger, acquired all of the stock of MedaSorb Technologies, Inc., a Delaware corporation, in a merger, and the business of MedaSorb Technologies, Inc. became our business. Following the merger, in July 2006, we changed our name to MedaSorb Technologies Corporation. In November 2008, we changed the name of our operating subsidiary from MedaSorb Technologies, Inc. to CytoSorbents, Inc. In May 2010, we finalized the name change of MedaSorb Technologies Corporation to CytoSorbents Corporation. On October 28, 2014, we changed the name of our operating subsidiary from CytoSorbents, Inc. to CytoSorbents Medical, Inc.

On December 3, 2014, we effected a twenty-five-for-one (25:1) reverse split of our common stock. As a result of this reverse stock split, shares of our common stock outstanding were reduced by approximately 96%. Based on the 582,097,092 shares of common stock outstanding as of December 3, 2014, the total number of shares of common stock outstanding after the reverse stock split, including accounting for fractional shares which were rounded up to the next whole number, were 23,284,040 shares. Accordingly, all share, option and warrant information included in this Annual Report has been retroactively adjusted to reflect the reduced number of shares resulting from this action. Immediately after the reverse stock split, pursuant to an Agreement and Plan of Merger dated December 3, 2014, we changed our state of incorporation from the State of Nevada to the State of Delaware, whereby we merged with and into our recently formed, wholly-owned Delaware subsidiary. At the effective time of the merger, (i) we merged with and into our Delaware subsidiary, (ii) our separate corporate existence in Nevada ceased to exist, (iii) the Delaware subsidiary became the surviving corporation, (iv) the certificate of incorporation, as amended and restated, and the bylaws of the Delaware subsidiary became our certificate of incorporation and bylaws, and (v) each share of our common stock outstanding immediately prior to the effective time was converted into one fully-paid and non-assessable share of our common stock as a Delaware corporation. The reverse stock split, the merger and the Agreement and Plan of Merger were approved by our Board of Directors and stockholders representing a majority of our then-outstanding common stock. All references to “us”, “we”, or the Company, on or after December 3, 2014, refer to CytoSorbents Corporation, a Delaware corporation.

Our executive offices are located at 7 Deer Park Drive, Suite K, Monmouth Junction, New Jersey 08852, and our telephone number is (732) 329-8885. Our website address is <http://cytosorbents.com>. We have included our website address as an inactive textual reference only. We make available free of charge through our website our Annual Reports on Form 10-K, our Quarterly Reports on Form 10-Q, our Current Reports on Form 8-K and amendments to those reports filed or furnished pursuant to Section 13(a) or 15(d) of the Exchange Act as soon as reasonably practicable after we electronically file such material, or furnish it to the SEC. We also similarly make available, free of charge on our website, the reports filed with the SEC by our executive officers, directors and 10% stockholders pursuant to Section 16 under the Exchange Act as soon as reasonably practicable after copies of those filings are

provided to us by those persons. We are not including the information contained at <http://cytosorbents.com>, or at any other website address, as part of, or incorporating it by reference into, this Annual Report on Form 10-K.

We have been engaged in research and development since our inception and have raised approximately \$98 million from investors. These proceeds have been used to fund the development of multiple product applications and to conduct clinical studies, to establish in-house manufacturing capacity to meet commercial and clinical testing needs, expand our intellectual property through additional patents, and to develop extensive proprietary know-how with regard to our products. For the years ended December 31, 2016, 2015 and 2014, our research and development expenses amounted to approximately \$4,783,000, \$3,871,000 and \$2,432,000, respectively. There are no customer-sponsored research activities relating to the development of new products.

We have raised funds through various means including convertible note offerings and equity transactions. Our most significant financing transactions are discussed below.

Shelf Registration

On July 29, 2015, our registration statement on Form S-3 (Registration No. 333-205806), as filed with the SEC on July 23, 2015 (Shelf Registration Statement), was declared effective using a “shelf” registration process. Under this shelf registration statement, we may issue, in one or more offerings, any combination of common stock, preferred stock, senior or subordinated debt securities, warrants, or units, up to a total dollar amount of \$100 million.

Principal Terms of the November 4, 2015 Controlled Equity Offering

On November 4, 2015, we entered into a Controlled Equity OfferingSM Sales Agreement (“Sales Agreement”) with Cantor Fitzgerald and Co. (“Cantor”), as agent, pursuant to which we may offer to sell, from time to time through Cantor, shares of our common stock, having an aggregate offering price of up to \$25,000,000 (“Shares”). Any Shares offered and sold will be issued pursuant to our Shelf Registration Statement, as supplemented by a prospectus supplement dated November 4, 2015, which we filed with the SEC pursuant to Rule 424(b)(5) under the Securities Act.

Under the Sales Agreement, Cantor may sell Shares by any method permitted by law and deemed to be an “at the market offering” as defined in Rule 415 promulgated under the Securities Act of 1933, as amended (“Securities Act”), including sales made directly on The NASDAQ Capital Market, on any existing trading market for our common stock or to or through a market maker. In addition, under the Sales Agreement, Cantor may sell the Shares by any other method permitted by law, including in privately negotiated transactions. We may instruct Cantor not to sell Shares if the sales cannot be effected at or above the price designated by us from time to time.

We are not obligated to make any sales of Shares under the Sales Agreement, and if we elects to make any sales, we can set a minimum sales price for the Shares. The offering of Shares pursuant to the Sales Agreement will terminate upon the earlier of (i) the sale of all the shares subject to the Sales Agreement, or (ii) the termination of the Sales Agreement by Cantor or by us, as permitted therein. In the fourth quarter of 2015, we sold 28,880 shares at an average selling price of \$8.02 per share, generating net proceeds of approximately \$225,000 under the Sales Agreement. There were no sales of any shares in 2016 under the Sales Agreement.

We pay a commission rate of 3.0% of the aggregate gross proceeds from each sale of shares under the Sales Agreement, and have agreed to provide Cantor with customary indemnification and contribution rights. We have also reimbursed Cantor \$50,000 for certain specified expenses in connection with entering into the Sales Agreement.

We intend to use the net proceeds raised through “at the market” sales for research and development activities, which include the funding of additional clinical studies and costs of obtaining regulatory approvals in countries not covered by the CE Mark, capital expenditures and other costs necessary to expand production capacity, support of various sales and marketing efforts, product development and general working capital purposes.

Research and Development

We have been engaged in research and development since inception. Since 2012, we have been awarded an aggregate of approximately \$8.3 million in grants and contracts from DARPA (\$3.8M over 5 years), the U.S. Army (\$100,000 Phase I SBIR; \$50,000 Phase I option, \$803K Phase II SBIR, \$443K Phase II enhancement), the National Heart, Lung and Blood Institute and USSOCOM (\$203,000 Phase I SBIR; \$1.5 million Phase II SBIR), Phase I Universal Plasma (\$150K), Mycotoxin Phase I and Phase I option (\$150K), Mycotoxin Phase II (\$1M) and Peritoneal dialysis/mesh packing for hyperkalemia Phase I SBIR (\$150K) to further develop our technologies for sepsis, trauma and burn injury, and blood transfusions, respectively. Payments are based on achieving certain technology milestones.

Technology, Products and Applications

For approximately the past half-century, the field of blood purification has been focused on hemodialysis, a mature, well accepted medical technique primarily used to sustain the lives of patients with permanent or temporary loss of kidney function. It is widely understood by the medical community that dialysis has inherent limitations in that its ability to remove toxic substances from blood drops precipitously as the size of toxins increases. Our hemocompatible adsorbent technology is expected to address this shortcoming by removing toxins and toxic compounds largely untouched by dialysis technology.

Our polymer adsorbent technology can remove drugs, bioactive lipids, inflammatory mediators such as cytokines, free hemoglobin, toxins, and immunoglobulin from blood and physiologic fluids depending on the polymer construct. It is believed that the technology may have many applications in the treatment of common, chronic and acute healthcare conditions including, but not limited to, the adjunctive treatment and/or prevention of sepsis; the treatment of other critical care illnesses such as severe burn injury, trauma, acute respiratory distress syndrome and pancreatitis; the prevention of post-operative complications of cardiopulmonary bypass surgery; the treatment of cancer cachexia; the treatment of cytokine release syndrome in cancer immunotherapy, the prevention of damage to organs donated by brain-dead donors prior to organ harvest; the prevention of transfusion reactions caused by contaminants in transfused blood products; the prevention of contrast induced nephropathy, the treatment of drug overdose, and the treatment of chronic kidney failure. These applications vary by cause and complexity as well as by severity but share a common characteristic i.e. high concentrations of inflammatory mediators and toxins in the circulating blood.

Our flagship product, CytoSorb, animal-targeted VetResQ, and other product candidates under development, including CytoSorb XL, BetaSorb, ContrastSorb, and DrugSorb, consist of a cartridge containing adsorbent, porous polymer beads, although the polymers used in these devices are physically different. The cartridges incorporate industry standard connectors at either end of the device, which connect directly to the extracorporeal circuit (bloodlines) in series with a dialyzer as a standalone device. The extra-corporeal circuit consists of plastic blood tubing, our blood filtration cartridges containing adsorbent polymer beads, pressure monitoring gauges, and a blood pump to maintain blood flow. The patient's blood is accessed through a catheter inserted into his or her veins. The catheter is connected to the extra-corporeal circuit and the blood pump draws blood from the patient, pumps it through the cartridge and returns it back to the patient in a closed loop system. All of these devices are expected to be compatible with standard blood pumps or hemodialysis machines used commonly in hospitals and will therefore not require hospitals to purchase additional expensive equipment, and will require minimal training.

The polymer beads designed for the HemoDefend platform are intended to be used in multiple configurations, including a point-of-transfusion in-line filter between the blood bag and the patient, as well as a patent-pending "Beads in a Bag" configuration, where the beads are placed directly into a blood storage bag.

Markets

We are a critical care focused immunotherapy company. Immunotherapy is the ability to control the immune response to fight disease. Critical care medicine includes the treatment of patients with serious or life-threatening conditions who require comprehensive care in the ICU, with highly-skilled physicians and nurses and advanced technologies to support critical organ function to keep patients alive. Examples of such conditions include severe sepsis and septic shock, severe burn injury, trauma, acute respiratory distress syndrome and severe acute pancreatitis. In the U.S., an estimated \$110 billion or 0.7% of the U.S. gross domestic product is spent annually on critical care medicine. In most larger hospitals, critical care treatment accounts for up to 20% of a hospital's overall budget and often results in financial losses for the hospital.

In many critical care illnesses, the mortality is often higher than 30%. A major cause of death is multiple organ failure, where vital organs such as the lungs, kidneys, heart and liver are damaged and no longer function properly. Such patients are kept alive with supportive care therapy, or “life support”, such as mechanical ventilation, dialysis and vasopressor treatment, that is designed to keep the patient from dying while using careful patient management to tip the balance towards gradual recovery over time. Unfortunately, most supportive care therapies only help to keep patients alive by supporting organ function but do not help reverse the underlying causes of organ failure and do not help patients recover more quickly. Because of this, the treatment course is often poorly defined and highly variable, leading to lengthy ICU stays, a higher risk of adverse outcomes from hospital acquired infections, medical errors, and other factors, as well as exorbitant costs. There is an urgent need for more effective “active” therapies that can help to reverse or prevent organ failure. Our main product, CytoSorb, is a unique cytokine filter designed to try to address this void, by reducing “cytokine storm” and working to reduce the subsequent deadly inflammation that can lead to organ failure and death. Together the total addressable market to address these numerous critical care applications in the U.S. and EU with CytoSorb is estimated at \$10 billion to \$15 billion.

Sepsis

Sepsis is characterized by a systemic inflammatory response triggered by a severe infection. It is commonly seen in the ICU, accounting for approximately 10% to 20% of all ICU admissions. However, there are currently no approved products that are available to treat sepsis in the U.S. or EU. Each year, there are more than one million and 1.5 million new cases of severe sepsis or septic shock in the U.S. and Europe, respectively. Based on the reported incidence of sepsis in a number of developed countries, the worldwide incidence is estimated to be 18 million cases per year. The Global Sepsis Alliance estimates there are more than 30 million cases per year with approximately 10 million deaths. According to the CDC, the incidence of serious infection and sepsis has doubled in the U.S. in the past 10 years. The main driver of sepsis incidence is the aging demographic, specifically patients who are older than age 65 who are more prone to infection and now account for two-thirds of patients hospitalized for sepsis and the majority of sepsis deaths. Other factors contributing to the increase in sepsis incidence include the spread of antibiotic resistant bacteria like methicillin-resistant *Staphylococcus aureus* (“MRSA”), an increase in co-morbid conditions like HIV, cancer and diabetes that increases the risk of infection, an increasing use of implantable devices like artificial hips and knees that are prone to colonization by bacteria, and the appearance of new highly virulent or contagious strains of common pathogens such as H1N1 influenza.

There are generally three categories of sepsis, including mild to moderate sepsis, severe sepsis and septic shock. Mild to moderate sepsis typically occurs with an infection that is responsive to antibiotics or antiviral medication. An example is a patient with self-limiting influenza or a treatable community acquired pneumonia. Mortality is generally very low. Severe sepsis is sepsis with evidence of organ dysfunction. An example is a patient who develops respiratory failure due to a severe pneumonia and requires mechanical ventilation in the ICU. Severe sepsis has a mortality rate of approximately 25% to 35%. Septic shock, or severe sepsis with low blood pressure that is not responsive to fluid resuscitation, is the most serious form of sepsis with an expected mortality in excess of 40% to 50%.

In sepsis, there are two major problems: the infection and the body’s immune response to the infection. Antibiotics are main therapy used to treat the triggering infection, and although antibiotic resistance is growing, the infection is often eventually controlled. However, it is the body’s immune response to this infection that frequently leads to the most devastating damage. Recently, the 3rd International Consensus Definition Task Force defined sepsis as “life-threatening organ dysfunction due to a dysregulated host response to infection.” The body’s immune system normally produces large amounts of inflammatory mediators called cytokines to help stimulate and regulate the immune response during an infection. In severe infection, however, many people suffer from a massive, unregulated overproduction of cytokines, often termed “cytokine storm” that can kill cells and damage organs, leading to multiple organ dysfunction syndrome and multiple organ failure, and in many cases death. Until recently, there have been no available therapies in the U.S. or EU that can control the aberrant immune response and cytokine storm. Our CytoSorb device is a first-in-class, clinically-proven broad-spectrum extracorporeal cytokine filter currently approved for sale in the E.U. The goal of CytoSorb is to prevent or treat organ failure by reducing cytokine storm and controlling a “run-away” immune response, while antibiotics work to control the actual infection. CytoSorb has been evaluated in the randomized, controlled European Sepsis Trial in 100 patients in Germany with predominantly septic shock and acute respiratory distress syndrome or acute lung injury. The therapy was safe in more than 300 human treatments and

generally well-tolerated. CytoSorb demonstrated the ability to reduce a broad range of cytokines from the blood of critically ill patients. In a post-hoc analysis, this was associated with improvements in clinical outcome in two high-risk patient populations – those with very high cytokine levels and patients 65 years of age and older. We have completed a follow-up Dosing study at several clinical trial sites in Germany, supporting the safety of continuous treatment, exchanging a new device daily for up to 7 days.

The only treatment that had been approved to treat sepsis in the U.S. or EU was Xigris from Eli Lilly. Because of concerns of cost, limited efficacy, and potentially dangerous side effects including the increased risk of fatal bleeding events such as intracranial bleeding for those at risk, and also because of problems with reimbursement, worldwide sales of Xigris decreased from \$160M in 2009 to \$104M in 2010. In October 2011, following its PROWESS SHOCK trial that demonstrated no benefit in mortality in septic shock patients, Lilly voluntarily withdrew Xigris from all markets worldwide, and is no longer available as a treatment.

Development of most other experimental therapies has been discontinued, including Eritoran from Eisai, CytoFab from BTG/Astra Zeneca, Talactoferrin from Agennix, and others.

Spectral Medical, Inc. is collaborating with Toray on the EUPHRATES trial, combining an endotoxin assay with extracorporeal endotoxin removal by Toraymyxin, a polymyxin-B immobilized polystyrene fiber cartridge. The study began in June 2010 and completed enrollment in June 2016. Endotoxemia is a result of Gram negative sepsis, which only accounts for 45% of cases of sepsis. It is a potent stimulator of cytokine storm. However, all anti-endotoxin strategies have failed pivotal studies to date, believed to be the result of intervening too late in the sepsis cascade. The original trial was designed as a randomized control trial in 360 patients with septic shock and high endotoxin levels (≥ 0.60 EAA units) as confirmed by Spectral's Endotoxin Activity Assay ("EAA"). In a second interim analysis finalized in April 2014, following the enrollment of 184 patients with 28-day follow-up, the DSMB recommended that the trial continue. However, the expected trial size was increased to 650 patients and the exclusion criteria was modified to only accept sicker patients with a multiple organ dysfunction syndrome score greater than 9. In September 2015, Spectral reported that the composite mortality in the new subgroup had risen to ~50%, from ~30% previously. New statistical analysis on patients in the new subgroup, and comparable patients in a European treatment registry, led to a sample size recalculation of 446 evaluable patients. Spectral announced in June 2016 that they had completed enrollment for the EUPHRATES trial. In October 2016, Spectral announced top-line results that the trial did not meet the main goal of absolute reduction in 28 day all-cause mortality, but reiterated safety of treatment and potential benefit in the sickest group of patients (multiple organ dysfunction score > 9). There have now been several large scale studies failing to demonstrate the beneficial effect of Toraymyxin on 28-day mortality in sepsis.

Few therapies are currently under development. In April 2015, Leading Biosciences began a 260 patient randomized, controlled Phase 2 clinical SSAIL trial in septic shock patients using its investigational orally administered drug, LB1148, also known as tranexemic acid. Tranexemic acid is a serine protease inhibitor, designed to inhibit digestive enzymes and preserve and promote healing of the intestine's mucosal barrier, with the goal of preventing the escape of potent digestive enzymes into the blood, which could exacerbate sepsis. Leading Biosciences expects completion of the trial in December 2016.

Currently, there are two late stage trials ongoing. The first of which was initiated in November 2012 and was an 800 patient Phase III randomized controlled SCARLET study began for Reomodulin (ART 123, Artisan/Asahi Kasei), a recombinant human thrombomodulin, for the treatment of septic patients with coagulopathy. In mid-2013, following an interim analysis of safety data, the DSMB recommended that the trial continue. The primary completion date of the trial was expected to be March 2015, however based on a February 2017 business update, this trial still appears to be enrolling patients. Reomodulin has been approved in Japan since 2009 for the treatment of disseminated intravascular coagulation, a late complication of sepsis, at a cost of \$5,800 per treatment. Although it has other activity, it works primarily by a similar anticoagulant mechanism to Xigris. Because of this, it has only demonstrated a limited mortality benefit in earlier studies (~9%: 34.6% control as compared to 26% treatment), similar to that seen in Xigris' initial PROWESS Trial (~6%: 31% control as compared to 25% treatment) and is unlikely to have greater benefit in larger scale studies.

The second study is being conducted by Atox Bio, a development stage company in clinical studies with peptide therapeutics that are designed to prevent superactivation of the immune response by certain toxins such as toxic shock syndrome toxin. It is currently focused on necrotizing soft tissue infections. The investigational peptide, AB103, is being evaluated in the ACCUTE Trial, a Phase 3 randomized controlled trial in 60 investigative sites in the U.S in 290 patients with necrotizing soft tissue infections. Primary outcomes include 28-day survival, amputation, and reduction in the modified sequential organ failure assessment score. The estimated study completion date is January 2018.

Severe sepsis and septic shock patients are among the most expensive patients to treat in a hospital. Because of this, we believe that cost savings to hospitals and/or clinical efficacy, rather than the cost of treatment itself, will be the determining factor in the adoption of CytoSorb in the treatment of sepsis. CytoSorb is approved in the EU and is being sold directly in Germany, Austria, Switzerland, Belgium and Luxembourg with our own direct sales force. We recently announced the achievement of a permanent, dedicated reimbursement procedure code for CytoSorb therapy in Germany, providing for specific and enhanced reimbursement in the largest medical device market in Europe. We have established strategic partnerships with Fresenius Medical Care, the world's largest dialysis company, for exclusive distribution of CytoSorb for critical care applications in France, Poland, Denmark, Sweden, Norway, and Finland, and Biocon Ltd, India's largest biotechnology company, for exclusive distribution of CytoSorb in India and other select emerging markets. We have ongoing discussions with potential corporate partners and independent distributors to market CytoSorb in other select EU countries and in other countries outside the EU that accept CE Mark approval. We have established direct sales or distribution of CytoSorb in 42 countries worldwide.

We estimate that the market potential in Europe for our products is larger than that in the U.S. For example, in the U.S. and Europe, there are an estimated one million and 1.5 million new cases, respectively, of severe sepsis and septic shock annually. In Germany alone, according to the German Sepsis Society, there are approximately 154,000 cases of severe sepsis each year. Germany is the largest medical device market in Europe and the third largest in the world.

Sepsis patients are treated in the ICU for 12 to 18 days on average and for a total of 20 to 25 days in the hospital. A typical severe sepsis or septic shock patient in the U.S. costs approximately \$45,000 to \$60,000 to treat without using CytoSorb. CytoSorb therapy for sepsis typically costs in the range of \$1,000 to \$5,000, depending on the number of treatments. The goal of therapy is to not only improve clinical outcomes, but to also reduce the severity of illness and reduce the need for costly ICU care (estimated at approximately \$4,300 per day in the ICU). The cost of CytoSorb therapy represents a fraction of what is currently spent on the treatment of patients with sepsis and would be cost-effective if it decreased ICU stay by one to two days. Based upon this price point, the total addressable market for CytoSorb for the treatment of sepsis in the U.S. and EU is approximately \$6 billion to \$8 billion.

Cardiac Surgery

There are approximately 500,000 cardiopulmonary bypass and cardiac surgery procedures performed annually in the U.S., 500,000 in the EU, and approximately 1.5 million procedures worldwide. These include relatively common procedures including coronary artery bypass graft surgery, valve replacement surgery, heart and lung transplant, aortic reconstruction, congenital heart defect repair, and LVAD for the treatment of heart failure. Cardiac surgery can result in inflammation and the production of high levels of inflammatory cytokines, activation of complement, as well as hemolysis, causing the release of free hemoglobin. These can lead to post-operative complications including infection, pulmonary, renal, and neurological dysfunction. Complications lead to longer ICU recovery times and hospital stays, increased morbidity and mortality, and higher costs. An average coronary artery bypass graft procedure already costs approximately \$36,000 in the U.S. without complications. According to the National Foundation for Transplants, a heart and lung transplant and first year expenses costs \$1.2 million in the U.S. The use of CytoSorb to reduce cytokines and other inflammatory mediators during and after the surgical procedure may prevent or mitigate these post-operative complications. During the procedure, the CytoSorb filter can be incorporated in a bypass circuit in the heart-lung machine without the need for a separate pump, a unique competitive advantage over other technologies. After the surgery, CytoSorb can be used similarly to dialysis on patients that develop a severe post-operative inflammatory response. Direct cytokine and hemoglobin removal with CytoSorb enables it to replace the existing market for leukoreduction filters in cardiac surgery that attempt to indirectly reduce cytokines by capturing cytokine-producing leukocytes – an inefficient and suboptimal approach. Modified ultrafiltration is sometimes used after termination of cardiopulmonary bypass in cardiac surgery to remove excess fluid and inflammatory substances, but has had mixed benefit. The peri-procedural total addressable market for CytoSorb in the U.S. and EU in cardiothoracic surgery procedures is estimated to be \$500 million to \$1 billion.

Acute Respiratory Distress Syndrome

Acute lung injury (“ALI”) and ARDS are two of the most serious conditions on the continuum of respiratory failure when both lungs are compromised by inflammation and fluid infiltration, severely compromising the lung’s ability to both oxygenate the blood and rid the blood of carbon dioxide produced by the body. There are an estimated 165,000 cases of acute respiratory distress syndrome in the U.S. each year, with more cases in the EU. Patients with ALI and ARDS typically require mechanical ventilation, and sometimes extracorporeal membrane oxygenation therapy, to help achieve adequate oxygenation of the blood. Patients on mechanical ventilation are at high risk of ongoing ventilator-induced lung injury, oxygen toxicity, barotrauma, ventilator-acquired pneumonias, and other hospital acquired infections, and outcome is significantly dependent on the presence of other organ dysfunction as well as co-morbid conditions such as pre-existing lung disease (e.g., emphysema or chronic obstructive pulmonary disease) and age. Because of this, mortality is typically greater than 30%, even with modern medicine and ventilation techniques. ALI and ARDS can be precipitated by a number of conditions including pneumonia and other infections, burn and smoke inhalation injury, aspiration, reperfusion injury and shock. Cytokine injury plays a major role in the vascular compromise and cell-mediated damage to the lung through tight junction disruption of respiratory endothelium, leading to capillary leak syndrome, and other factors. Reduction of cytokine levels may either prevent or mitigate lung injury, enabling patients to wean from mechanical ventilation faster, potentially reducing numerous sequelae such as infection, pneumothoraces, and respiratory muscle deconditioning, and allow faster ICU discharge, thereby potentially saving costs. CytoSorb treatment of patients with either ALI or ARDS in the setting of sepsis was the subject of our European Sepsis Trial where in a post-hoc analysis in patients with very high cytokine levels, we observed faster ventilator weaning in CytoSorb treated patients that showed a statistical trend to benefit. Future, prospectively defined, larger studies are required to confirm these findings. Although a number of therapies have been tried such as corticosteroids, nitric oxide, surfactant therapy, and others, there are currently no approved treatments for ARDS. Only low tidal volume ventilation has been demonstrated to improve mortality (31.0 as compared to 39.8% control) in this patient population. However, even with this intervention, mortality is still unacceptably high. The total addressable market for CytoSorb to treat ARDS and ALI in the EU is estimated to be between \$500 million to \$1.25 billion, and between \$1 billion to \$2 billion in the U.S. and EU.

Severe Burn Injury

In the U.S., there are approximately 2.4 million burn injuries per year, with 650,000 treated by medical professionals and approximately 75,000 requiring hospitalization. Aggressive modern management of burn injury, including debridement, skin grafts, anti-microbial dressings and mechanical ventilation for smoke and chemical inhalation injury has led to significant improvements in survival of burn injury to approximately 95% on average in leading burns centers. However, there remains a need for better therapies to reduce the mortality in those patients with large burns and inhalation injury as well as to reduce complications of burn injury and hospital length of stay for all patients. According to National Burn Repository Data, the average hospital stay for burn patients is directly correlated with the percent total body surface area (“TBSA”) burned. Every 1% increase of TBSA burned equates to approximately 1 additional day in the hospital. A single patient with more than 30% TBSA burned who survives, is hospitalized for an average of 30 days and costs approximately \$200,000 to treat. Major causes of death following severe burn and smoke inhalation injury are multiple organ failure (hemodynamic shock, respiratory failure, acute renal failure) and

sepsis, particularly in patients with greater than 30% TBSA burns. Specifically, burns and inhalation injury lead to severe systemic and localized lung inflammation, loss of fluid, and cytokine overproduction. This “cytokine storm” causes numerous problems, including: hypovolemic shock and inadequate oxygen and blood flow to critical organs, acute respiratory distress syndrome preventing adequate oxygenation of blood, capillary leakage resulting in tissue edema and intravascular depletion, hypermetabolism leading to massive protein degradation and catabolism and yielding increased risk of infection, impaired healing, severe weakness and delayed recovery, immune dysfunction causing a higher risk of secondary infections (wound infections, pneumonia) and sepsis, and direct apoptosis and cell-mediated killing of cells, leading to organ damage. Up to a third of severe hospitalized burn patients develop multiple organ failure and sepsis that can often lead to complicated, extended hospital courses, or death. Broad reduction of cytokine storm has not been previously feasible and represents a novel approach to limiting or reversing organ failure, potentially enabling more rapid mechanical ventilation weaning, prevention of shock, reversal of the hypermetabolic state encouraging faster healing and patient recovery, reducing hospital costs, and potentially improving survival. The total addressable market in the EU for CytoSorb to address burn and smoke inhalation injury is estimated at \$150 million to \$350 million and \$300 million to \$600 million in the U.S and EU.

Trauma

According to the National Center for Health Statistics, in the U.S., there are more than 31 million visits to hospital emergency rooms, with 1.9 million hospitalizations, and 167,000 deaths every year due to injury. The leading causes of injury are trauma from motor vehicle accidents, being struck by an object or other person, and falls. Trauma is a well-known trigger of the immune response and a surge of cytokine production or cytokine storm. In trauma, cytokine storm contributes to a systemic inflammatory response syndrome and a cascade of events that cause cell death, organ damage, organ failure and often death. Cytokine storm exacerbates physical trauma in many ways. For instance, trauma can cause hypovolemic shock due to blood loss, while cytokine storm causes capillary leak and intravascular volume loss, and triggers nitric oxide production that causes cardiac depression and peripheral dilation. Shock can lead to a lack of oxygenated blood flow to vital organs, causing organ injury. Severe systemic inflammation and cytokine storm can lead to acute lung injury and acute respiratory distress syndrome as is often seen in ischemia and reperfusion injury following severe bleeding injuries. Penetrating wound injury from bullets, shrapnel and knives, can lead to infection and sepsis, another significant cause of organ failure in trauma. Complicating matters is the breakdown of damaged skeletal muscle, or rhabdomyolysis, from blunt trauma that can lead to a massive release of myoglobin into the blood that can crystallize in the kidneys, leading to acute kidney injury and renal failure. Renal failure in trauma is associated with a significant increase in expected mortality. Cytokine and myoglobin reduction by CytoSorb and related technologies may have benefit in trauma, potentially improving clinical outcome. The total addressable market for CytoSorb for the treatment of trauma is estimated to be \$1.5 billion to \$2.0 billion in the U.S. and the EU.

Severe Acute Pancreatitis

Acute pancreatitis is the inflammation of the pancreas that results in the local release of digestive enzymes and chemicals that cause severe inflammation, necrosis and hemorrhage of the pancreas and local tissues. Approximately 210,000 people in the U.S. are hospitalized each year with acute pancreatitis with roughly 20% requiring ICU care. It is caused most frequently by a blockage of the pancreatic duct or biliary duct with gallstones, cancer, hyperlipidemia, or from excessive alcohol use. Severe acute pancreatitis is characterized by severe pain, inflammation, and edema in the abdominal cavity, as well as progressive systemic inflammation, generalized edema, and multiple organ failure that is correlated with high levels of cytokines and digestive enzymes in the blood. Little can be done to treat severe acute pancreatitis today, except for pancreatic duct decompression with endoscopic techniques, supportive care therapy, pain control, enteral tube feeding, and fluid support. ICU stay is frequently measured in weeks and although overall ICU mortality is approximately 10%, patients with multiple organ failure have a much higher risk of death. CytoSorb may potentially benefit overall outcomes in episodes of acute pancreatitis by removing a diverse set of toxins from blood. The total addressable market for CytoSorb for the treatment of severe acute pancreatitis in the U.S. and EU is estimated to be between \$400 million to \$600 million.

Cancer Cachexia and Cancer Immunotherapy

Cancer cachexia is a progressive wasting syndrome characterized by rapid weight loss, anorexia, and physical debilitation that significantly contributes to death in the majority of cancer patients. Cancer cachexia is a systemic inflammatory condition, driven by excessive pro-inflammatory cytokines and other factors, that cripples the patient's physical and immunologic reserve to fight cancer. Despite afflicting millions of patients worldwide each year, there are no effective approved treatments for cancer cachexia, with only symptomatic treatments available. CytoSorb blood purification may stop or reverse cancer cachexia through broad reduction of cytokines and other inflammatory mediators, when treated over time. For example, CytoSorb efficiently removes TNF-alpha (originally called "cachectin" or "cachexin" when first isolated in cancer cachexia patients) and other major pro-inflammatory cytokines including IL-1, IL-6, and gamma interferon that can cause cachexia. This broad immunotherapy approach may lead to improved clinical outcomes while reducing patient suffering.

In February 2014, we announced a research collaboration with researchers at the University of Pennsylvania School of Veterinary Medicine to evaluate the use of CytoSorb as a treatment for cancer cachexia in animals. Demonstrating the potential benefit of CytoSorb therapy in animals may provide the data to begin evaluating the therapy in human cancer patients in the U.S. and Europe. CytoSorb is approved in the EU with a broad indication for use, allowing it to be used in any clinical situation where cytokines are elevated, including the potential treatment today of cancer related issues such as cancer cachexia. Because of this, any positive data from this collaboration could potentially be translated to human studies relatively quickly.

The collaboration will also explore the use of CytoSorb as a primary immunotherapy to treat cancer, or in synergy with more traditional chemotherapy or immunotherapy agents. Cancer cells have evolved ways to proliferate while confusing and evading the immune response. Many of these mechanisms rely on immunologic messages relayed by cytokines and other soluble factors that CytoSorb has the potential to remove. In doing so, CytoSorb may help to restore the ability of the immune system to attack cancer cells.

CytoSorb may also represent a rescue or salvage therapy in activated T-cell cancer immunotherapy, where cytokine release syndrome (i.e. cytokine storm) is common, and can lead to organ failure and death in certain patients.

The total addressable market for CytoSorb for the treatment of cancer cachexia and cancer in the U.S. and EU is estimated to be in excess of \$4 billion.

Brain-Dead Organ Donors

There are in excess of 6,000 brain dead organ donors each year in the United States; worldwide, the number of these organ donors is estimated to be at least double the U.S. brain dead organ donor population. There is a severe shortage of donor organs. Currently, there are more than 100,000 individuals on transplant waiting lists in the United States. Cytokine storm is common in these organ donors, resulting in reduced viability of potential donor organs. The potential use of CytoSorb hemoperfusion to control cytokine storm in brain dead organ donors could increase the number of viable organs harvested from the donor pool and improve the survival of transplanted organs. A proof-of-concept pilot study using our technology in human brain dead donors has been published. In addition, CytoSorb treatment in a porcine animal model of brain death demonstrated a reduction in cytokines as well as a preservation of cardiac function compared to untreated controls.

Blood Transfusions

The HemoDefend platform is a development-stage technology designed to be a practical, low cost, and effective way to safeguard the quality and safety of the blood supply. In the U.S. alone, 15 million packed red blood cell ("pRBC") transfusions and another 15 million transfusions of other blood products (e.g., platelet, plasma, and cryoprecipitate) are administered each year with an average of 10% of all U.S. hospital admissions requiring a blood transfusion. The sheer volume of transfusions, not just in the U.S., but worldwide, complicates an already difficult task of maintaining a safe and reliable blood supply. Trauma, invasive operative procedures, critical care illnesses, supportive care in cancer, military usage, and inherited blood disorders are just some of the drivers of the use of transfused blood. In war, hemorrhage from trauma is a leading cause of preventable death, accounting for an estimated 30% to 40% of all fatalities. For example, in Operation Iraqi Freedom, due to a high rate of penetrating wound injuries, up to 8% of admissions required massive transfusions, defined as 10 units of blood or more in the first 24 hours. There is a clear need for a stable and safe source of blood products. However, blood shortages are common and exacerbated by the finite lifespan of blood. According to the Red Cross, pRBC units have a refrigerated life span of 42 days. However, many medical experts believe there is an increased risk of infection and transfusion reactions once stored blood ages beyond two weeks. Transfusion-related acute lung injury is the leading cause of non-hemolytic transfusion-related morbidity and mortality, with an incidence of 1 in 2,000-5,000 transfusions and a mortality rate of up to 10%. Fatal cases of transfusion-related acute lung injury have been most closely related to anti-HLA or anti-granulocyte antibodies found in a donor's transfused blood. Other early transfusion reactions such as transfusion-associated dyspnea, fever and allergic reactions occur in 3% to 5% of all transfusions and can vary in severity depending on the patient's condition. These are caused by cytokines, bioactive lipids, free hemoglobin, toxins, foreign antigens, certain drugs, and a number of other inflammatory mediators that accumulate in transfused blood products during storage. Leukoreduction can remove the majority of white cells that can produce new cytokines but cannot eliminate those cytokines already in blood, and cannot otherwise remove other causative agents such as free hemoglobin and

antibodies. Automated washing of pRBC is effective but is impractical due to the time, cost, and logistics of washing each unit of blood. The HemoDefend platform is a potentially superior alternative to purify blood transfusion products to these methods. The total addressable market for HemoDefend is more than \$500 million for pRBCs alone.

Radiocontrast Removal

ContrastSorb is a development-stage blood purification technology that is being optimized for the removal of IV contrast from blood in order to prevent CIN. Contrast-induced nephropathy is the acute loss of renal function within the first 48 hours following IV contrast administration. IV contrast is widely administered to patients undergoing CT scans, to enhance the images and make it easier to identify anatomic structures. IV contrast is also administered during vascular interventional radiology procedures and angiography of blood vessels in the brain, heart, limbs, and other parts of the body to diagnose and treat atherosclerosis (narrowing of blood vessels due to cholesterol deposits), vascular injury, aneurysms, etc. For example, an estimated 10 million coronary angiograms are performed worldwide each year to diagnose and treat coronary artery disease by placing coronary stents, performing balloon angioplasty, or atherectomy (removal of plaque in arteries). Overall, there are an estimated 80 million doses of IV contrast administered worldwide each year, split between approximately 65 million contrast-enhanced CT scans, 10 million coronary angiograms, and 5 million conventional angiograms. There are an estimated 30 million doses administered each year in the U.S. alone. The reported risk of CIN in patients undergoing contrast enhanced CT scans has been reported to be 2% to 13%. For coronary intervention, the risk has been estimated to be as high as 20% to 30% in high risk patients with pre-existing renal insufficiency, long-term diabetes, hypertension, congestive heart failure, and older age. The use of low osmolar IV contrast, hydration of patients pre-procedure, orally administration of N-acetylcysteine, and other agents to prevent CIN have demonstrated modest benefit in some clinical studies, but in many cases, the results across studies have been equivocal and inconsistent. In high risk patients, the direct removal of IV contrast from the blood with ContrastSorb to prevent CIN represents a potentially more effective alternative. The worldwide market opportunity for ContrastSorb in this high risk group is approximately \$1 billion to \$2 billion.

Drug Removal

DrugSorb is a development-stage blood purification technology that is capable of removing a wide variety of drugs and chemicals from blood, as a potential treatment for drug overdose, drug toxicity, toxic chemical exposure, use in high-dose regional chemotherapy, and other applications. It has demonstrated extremely high single pass removal efficiency of a number of different drugs that exceeds the extraction capability of hemodialysis or other filtration technologies. It is similar in action to activated charcoal hemoperfusion cartridges that have been available for many years, but has the advantage of having inherent biocompatibility and hemocompatibility without coatings, and can be easily customized for specific agents.

Chronic Kidney Failure

The National Kidney Foundation estimates that more than 20 million Americans have chronic kidney disease. Left untreated, chronic kidney disease can ultimately lead to chronic kidney failure, which requires a kidney transplant or chronic dialysis (generally three times per week) to sustain life. There are approximately 400,000 patients in the U.S. currently receiving chronic dialysis and more than 3.0 million worldwide. Approximately 66% of patients with chronic kidney disease are treated with hemodialysis. One of the problems with standard high-flux dialysis is the limited ability to remove certain mid-molecular weight toxins such as β_2 -microglobulin. Over time, β_2 -microglobulin can accumulate and cause amyloidosis in joints and elsewhere in the musculoskeletal system, leading to pain and disability. Our BetaSorb device has been designed to remove these mid-molecular weight toxins when used in conjunction with standard dialysis. Standard dialysis care typically involves three sessions per week, averaging approximately 150 sessions per year.

Products

The polymer adsorbent technology used in our products can remove middle molecular weight toxins, such as cytokines, from blood and physiologic fluids. All of the potential applications described below (i.e., the adjunctive treatment and/or prevention of sepsis; the adjunctive treatment and/or prevention of other critical care conditions such as acute respiratory distress syndrome, burn injury, trauma and pancreatitis; the prevention of damage to organs donated by brain-dead donors prior to organ harvest; the prevention of post-operative complications of cardiopulmonary bypass surgery; the prevention of kidney injury from IV contrast; and the treatment of chronic kidney failure) share in common high concentrations of toxins in the circulating blood. However, because of the limited studies we have conducted to date, we are subject to substantial risk that our technology will have little or no effect on the treatment of any of these indications. In 2011, we completed our European Sepsis Trial of our CytoSorb device. The study was a randomized, open label, controlled clinical study in fourteen (14) sites in Germany of one hundred (100) critically ill patients with predominantly septic shock and respiratory failure. The trial successfully demonstrated the ability of CytoSorb to reduce levels of key cytokines from whole blood in treated patients, and that

treatment was safe in these critically-ill patients with multiple organ failure. We completed the CytoSorb technical file review with our Notified Body and CytoSorb subsequently received EU regulatory approval under the CE Mark as an extracorporeal cytokine filter indicated for use in any clinical situation where cytokines are elevated. Given sufficient and timely financial resources, we intend to continue to commercialize in Europe and conduct additional clinical studies of our products. However, there can be no assurance that we will ever obtain regulatory approval for any other device, or that the CytoSorb device will be able to generate significant sales.

We manufacture the CytoSorb device at our facility located in Monmouth Junction, New Jersey. We purchase our raw materials from multiple vendors located primarily in the United States. We believe that our risk of an interruption in the supply of our raw materials is minimal due to the use of multiple vendors and the availability of alternate vendors. We do not have contractual minimum finished goods inventory requirements, however our practice is to maintain a minimum inventory level sufficient to provide a supply of products for the next two months.

The CytoSorb Device (Critical Care)

APPLICATION: Adjunctive Therapy in the Treatment of Sepsis

Sepsis is a potentially life threatening disease defined as a systemic inflammatory response in the presence of a known or suspected infection. Sepsis is mediated by high levels of inflammatory mediators such as cytokines, which are released into the blood stream as part of the body's immune response to severe infection or injury. Excessive concentrations of these mediators cause severe inflammation and damage healthy tissues, which can lead to organ dysfunction and failure. Organ failure is the leading cause of death in the ICU. Sepsis is very expensive to treat and has a high mortality rate.

Potential Benefits: To the extent our adsorbent blood purification technology is able to prevent or reduce the accumulation of cytokines, toxins, or other inflammatory mediators in the circulating blood, we believe our products may be able to prevent or mitigate severe inflammation, organ dysfunction and failure in sepsis patients. Therapeutic goals as an adjunctive therapy include improved clinical outcome, reduced ICU and total hospitalization time, and reduced hospital costs.

Background and Rationale: We believe that the effective treatment of sepsis is the most valuable potential application for our technology. Severe sepsis (sepsis with organ dysfunction) and septic shock (severe sepsis with persistent hypotension despite fluid resuscitation) carries mortality rates of between 20% and 80%. Death can occur within hours or days, depending on many variables, including cause, severity, patient age and co-morbidities. There are approximately 1.6 million new cases of sepsis in the U.S. each year; and based on estimates by the Global Sepsis Alliance, the worldwide incidence is estimated to be 30 million cases annually. The incidence of sepsis is also rising due to:

- 1) an aging population;
- 2) increased incidence of antibiotic resistance;
- 3) increase in co-morbid conditions like cancer and diabetes; and
- 4) increased use of indwelling medical devices that are susceptible to infection.

In the U.S. alone, treatment of sepsis costs nearly \$20 billion annually. According to the CDC, sepsis is a top ten cause of death in the U.S. The incidence of sepsis is believed to be under-reported as the primary infection (i.e., pneumonia, pyelonephritis, etc.) is often cited as the cause of death.

An effective treatment for sepsis has been elusive. Pharmaceutical companies have been trying to develop drug therapies to treat the condition. With the exception of Xigris® from Eli Lilly, no other products have been approved in either the U.S. or Europe for the treatment of sepsis. In 2011, after completing a follow up study required by the FDA, it was subsequently determined that Xigris® does not have a statistically significant mortality benefit, and Eli Lilly has withdrawn Xigris® from all markets worldwide.

Many medical professionals believe that blood purification for the treatment of sepsis holds tremendous promise. Studies using dialysis and hemofiltration technology have been encouraging, but have only had limited benefit to sepsis patients. The reason for this appears to be rooted in a primary limitation of dialysis technology itself: the inability of standard dialysis to effectively and efficiently remove significant quantities of larger toxins such as cytokines from circulating blood. CytoSorb has demonstrated the ability to safely reduce key cytokines in the blood of septic patients with multiple organ failure in our European Sepsis Trial.

The ability of CytoSorb to interact safely with blood (hemocompatibility) has been demonstrated through ISO 10993 testing, which includes testing for hemocompatibility, biocompatibility, cytotoxicity, genotoxicity, acute sensitivity and complement activation. CytoSorb use has been considered safe and well-tolerated in more than 20,000 human treatments to date.

CytoSorb has been designed to achieve broad-spectrum removal of both pro- and anti-inflammatory cytokines, preventing or reducing the accumulation of high concentrations in the bloodstream. It also removes a wide range of inflammatory mediators such as activated complement, bacterial toxins, myoglobin, free hemoglobin, bilirubin, and many others. This approach is intended to modulate the immune response without causing damage to the immune system. For this reason, researchers have referred to the approach reflected in our technology as “immunomodulatory” therapy.

Projected Timeline: In 2011, the CytoSorb filter received EU regulatory approval under the CE Mark as an extracorporeal cytokine filter to be used in clinical situations where cytokines are elevated. Our manufacturing facility has also achieved ISO 13485:2003 Full Quality Systems certification, an internationally recognized quality standard designed to ensure that medical device manufacturers have the necessary comprehensive management systems in place to safely design, develop, manufacture and distribute medical devices in the EU. We are currently manufacturing our CytoSorb device for commercial sale in the EU. We are currently selling CytoSorb in Germany, Austria, and Switzerland with a direct sales force. Based on its CE Mark approval, CytoSorb can also be sold throughout all 28 countries of the EU and countries outside the EU that will accept European regulatory approval with registration. Overall, we have established either direct sales or distribution (via distributors or strategic partners) of CytoSorb in 42 countries worldwide. Registration of CytoSorb is typically required in each of these countries prior to active commercialization. With CE Mark approval, this can be typically achieved within several months in EU countries. Outside of the EU, the process is more variable and can take months to more than a year due to different requirements for documentation and clinical data. Variability in the timing of registration affects the initiation of active commercialization in these countries, which affects the timing of expected CytoSorb sales. We actively support all of our distributors and strategic partners in the product registration process. Outside of the EU, CytoSorb is actively being commercialized in Turkey, India, Australia, New Zealand, Russia and Saudi Arabia and other countries. We cannot generally predict the timing of these registrations, and there can be no guarantee that we will ultimately achieve registration in countries where we have established distribution. We also cannot guarantee that we will generate meaningful sales in the countries where we have established registration, due to other factors such as market adoption and reimbursement. We are currently actively evaluating other potential distributor and strategic partner networks in other major countries that accept CE Mark approval. With sufficient resources and continued positive clinical data, assuming availability of adequate and timely funding, and continued positive results from our clinical studies, we intend to continue our commercialization plans for our product worldwide as well as to pursue U.S. clinical trials to seek FDA regulatory approval for CytoSorb in the U.S. by 2020.

APPLICATION: Adjunctive Therapy in Other Critical Care Applications

Potential Benefits: Cytokine-mediated organ damage and immune suppression can increase the risk of death and infection in patients with commonly seen critical care illnesses such as acute respiratory distress syndrome, severe burn injury, trauma and pancreatitis. By reducing both pro- and anti-inflammatory cytokines, CytoSorb has the potential to reduce the systemic inflammatory response and:

- prevent or mitigate multiple organ dysfunction syndrome (“MODS”) and/or multiple organ failure (“MOF”);
- prevent or reduce secondary infections;
- reduce the need for expensive life-sparing supportive care therapies such as mechanical ventilation; and
- reduce the need for ICU care, freeing expensive critical care resources, and reducing hospital costs and costs to the healthcare system.

Background and Rationale: A shared feature of many life-threatening conditions seen in the ICU is severe inflammation (either sepsis or systemic inflammatory response syndrome) due to an over-reactive immune system and high levels of cytokines that can cause or contribute to organ dysfunction, organ failure and patient death. Examples of such conditions include severe burn injury, trauma, acute respiratory distress syndrome and severe acute pancreatitis. MODS and MOF are common causes of death in these illnesses and mortality is directly correlated with the number of organs involved. There are currently few active therapies to prevent or treat MODS or MOF. If CytoSorb can reduce direct or indirect cytokine injury of organs, it may mitigate MODS or MOF, improve overall patient outcome and reduce costs of treatment. In addition, secondary infection, such as ventilator-acquired pneumonia, urinary tract infections, or catheter-related line infections, are another major cause of morbidity and mortality in all patients treated in the ICU that increase with longer ICU stay. Prolonged illness, malnutrition, age, multiple interventional procedures, and exposure to antibiotic resistant pathogens are just some of the many risk factors for functional immune suppression and infection. In sepsis and SIRS, the overexpression of pro-inflammatory cytokines can also cause a depletion of immune effector cells through apoptosis and other means, and anti-inflammatory cytokines can cause profound immune suppression, both major risk factors for infection.

Projected Timeline: The EU CE Mark approval for CytoSorb as an extracorporeal cytokine filter and its broad approved indication to be used in any clinical situation where cytokines are elevated, allows it to be used “on label” in critical care applications such as acute respiratory distress syndrome, severe burn injury, trauma, liver failure, and pancreatitis, and in other conditions where cytokine storm, sepsis and/or SIRS plays a prominent role in disease pathology. Our goal is to stimulate investigator-initiated clinical studies with our device for these applications. Currently, we have more than 55 investigator initiated or company-sponsored studies being planned, enrolling, or completed. We have been moving forward in parallel with a program to further understand the potential benefit of CytoSorb hemoperfusion in these conditions through additional investigational animal studies and potential human pilot studies in the U.S. funded either directly by us, through grants, or through third-parties. Commencement of these and other formal studies is contingent upon adequate funding and, in the case of U.S. human studies, FDA IDE approval of the respective human trial protocols.

APPLICATION: Prevention and treatment of post-operative complications of cardiopulmonary bypass surgery

Potential Benefits: If CytoSorb is able to prevent or reduce high levels of cytokines, free hemoglobins, and other inflammatory mediators from accumulating in the blood system during and following cardiac surgery, we anticipate that post-operative complications of cardiopulmonary bypass surgery may be able to be prevented or mitigated. The primary goals for this application are to:

- reduce ventilator and oxygen therapy requirements;
- reduce post-operative complications such as ARDS, acute kidney injury, post-perfusion syndrome, and the SIRS;
- reduce length of stay in hospital ICUs; and
- reduce the total cost of patient care.

Background and Rationale: Due to the highly invasive nature of cardiopulmonary bypass surgery, high levels of cytokines are produced by the body, triggering severe inflammation. In addition, hemolysis of red blood cells frequently occurs, resulting in the release of free hemoglobin into the bloodstream. These inflammatory mediators can lead to post-operative complications. CytoSorb is the only cytokine reduction technology approved in the EU that can be used intraoperatively in a bypass circuit in a heart-lung machine during cardiopulmonary bypass without the need for another machine. If our products are able to prevent or reduce the accumulation of cytokines or free hemoglobin in a patient’s blood stream, we may be able to prevent or mitigate post-operative complications caused by an excessive or protracted inflammatory response to the surgery. Intra-operative use of CytoSorb on high risk cardiac surgery patients, where the risk of post-operative complications is the highest, is expected to be the main initial target market. The use of CytoSorb in the post-operative period to treat post-operative SIRS is another application of the technology.

Projected Timeline: We commissioned the University of Pittsburgh to conduct a study to characterize the production of cytokines as a function of the surgical timeline for cardiopulmonary bypass surgery. An observational study of 32 patients was completed, and information was obtained with respect to the onset and duration of cytokine release.

Cardiac surgeons and cardiac perfusionists in Germany and Austria have now used CytoSorb successfully intra-operatively and post-operatively on more than 1,000 cardiac surgery patients. This application is also the subject of many planned and enrolling investigator-initiated studies in Germany and Austria.

In February 2015, the FDA approved our IDE application to commence a planned U.S. cardiac surgery feasibility study called REFRESH I (REduction of FREe Hemoglobin) amongst 20 patients and three U.S. clinical sites. The FDA subsequently approved an amendment to the protocol, expanding the trial to be a 40 patient randomized controlled study (20 treatment, 20 control) in eight clinical centers. REFRESH I represents the first part of a larger clinical trial strategy intended to support the approval of CytoSorb in the U.S. for intra-operative use during cardiac surgery.

The study is designed to evaluate the safety of CytoSorb when used intra-operatively in a heart-lung machine to reduce plasma free hemoglobin and cytokines in patients undergoing complex cardiac surgery. The length, complexity and invasiveness of these procedures cause hemolysis and inflammation, leading to high levels of plasma free hemoglobin, cytokines, activated complement, and other substances. These inflammatory mediators directly correlate with the incidence of serious post-operative complications such as kidney injury and failure. The goal of CytoSorb is to actively remove these inflammatory and toxic substances as they are being generated during the surgery and reduce complications. As of December 31, 2016, enrollment was complete with 46 patients. A total of 38 patients were evaluable and completed all aspects of the study.

The primary safety and efficacy endpoints of the study were the assessment of serious device related adverse events and the change in plasma free hemoglobin levels, respectively. On October 5, 2016, we announced positive top-line safety data. In addition, following a detailed review of all reported adverse events in a total of 46 enrolled patients, the independent DSMB found no safety concerns related to the CytoSorb device, achieving the primary safety endpoint of the trial and fulfilling a key requisite to move forward with a larger, definitive pivotal study. In addition, the therapy was well-tolerated and technically feasible, implementing easily into the cardiopulmonary bypass circuit without the need for an additional external blood pump. This study represents the first randomized controlled trial demonstrating the safety of intra-operative CytoSorb use in patients undergoing high risk cardiac operations.

Investigators of the REFRESH I trial have submitted an abstract with data, including free hemoglobin data, from the REFRESH I trial to the American Association of Thoracic Surgery (AATS) conference to be held in late April 2017, and a manuscript is being prepared for journal submission. In parallel, the Company plans to meet with the FDA to discuss the results of REFRESH I in anticipation of filing an IDE application to initiate a pivotal REFRESH 2 trial in 2017.

APPLICATION: Prevention and treatment of organ dysfunction in brain-dead organ donors to increase the number and quality of viable organs harvested from donors

Potential Benefits: If CytoSorb is able to prevent or reduce high-levels of cytokines from accumulating in the bloodstream of brain-dead organ donors, we believe CytoSorb may be able to mitigate organ dysfunction and failure, which results from severe inflammation following brain-death. The primary goals for this application are:

- improving the viability of organs which can be harvested from brain-dead organ donors, and
- increasing the likelihood of organ survival following transplant.

Background and Rationale: When brain death occurs, the body responds by generating large quantities of inflammatory cytokines. This process is similar to the systemic inflammatory response syndrome and sepsis. A high

percentage of donated organs are never transplanted due to this response, which damages healthy organs and prevents transplant. In addition, inflammation in the donor may damage organs that are harvested and reduce the probability of graft survival following transplant. CytoSorb treatment in a porcine animal model of brain death demonstrated a reduction in cytokines as well as a preservation of cardiac function compared to untreated controls.

There is a shortage of donated organs worldwide, with approximately 100,000 people currently on the waiting list for organ transplants in the U.S. alone. Because there are an insufficient number of organs donated to satisfy demand, it is vital to maximize the number of viable organs donated, and optimize the probability of organ survival following transplant.

Projected Timeline: Studies have been conducted under a \$1 million grant from the Health Resources and Services Administration (“HRSA”), an agency of the U.S. Department of Health and Human Services. Researchers at the University of Pittsburgh Medical Center and the University of Texas, Houston Medical Center have completed the observational and dosing phases of the project. The results were published in *Critical Care Medicine*, January 2008. The next phase of this study, the treatment phase, would involve viable donors treated with the CytoSorb device. In this phase of the project, viable donors will be treated and the survival and function of organs in transplant recipients will be tracked and measured. The treatment phase would be contingent upon further discussion with the FDA and HRSA regarding study design, as well as obtaining additional funding.

The VetResQ Device (Animal Health Critical Care)

APPLICATION: Adjunctive Therapy in the Treatment of Sepsis, Pancreatitis and Other Critical Illnesses in Animals

Potential Benefits and Rationale: In January 2017, the VetResQ device became commercially available for the United States veterinary market. VetResQ is a broad spectrum blood purification adsorber based upon similar underlying technology to CytoSorb and has been configured in 3 sizes (30, 100 and 300mL sized cartridges) to accommodate treatment of small, medium, and large animals such as cats, dogs, and high-value animals such as foals and horses. VetResQ is compatible with standard hemodialysis, continuous renal replacement therapy (“CRRT”), and hemoperfusion blood pumps. Like CytoSorb, VetResQ is designed to help treat (via hemoadsorption of cytokines, bacterial toxins and other inflammatory mediators) deadly inflammation and toxic injury in animals with critical illnesses such as septic shock, toxic shock syndrome, toxin-mediated diseases, pancreatitis, trauma, liver failure, drug intoxication, and lung injury. Critical illness in animals is similar to that in humans. Based upon cumulative studies, VetResQ is capable of reducing a broad range of excessive inflammatory mediators and toxins that could otherwise cause direct tissue injury or serious systemic inflammation that can rapidly lead to instability, organ failure, and death. VetResQ is available in the U.S. only for veterinary animal usage and is not for human use.

Projected Timeline: VetResQ is now available for commercial purchase for animal health applications in the United States. The FDA has been notified of the launch and we have provided the FDA with the related instructions for use and a marketing brochure.

The CytoSorb-XL Device (Critical Care)

APPLICATION: Adjunctive Therapy in the Treatment of Sepsis and other critical illnesses

Potential Benefits and Rationale: The CytoSorb-XL device is a next-generation porous polymer under advanced development and targets the same markets as CytoSorb. Through novel patent-pending chemistry, CytoSorb-XL adds the ability to reduce Gram negative bacterial endotoxin (lipopolysaccharide) to broad spectrum cytokine, exotoxin, and other inflammatory mediator removal. CytoSorb-XL removed comparable amounts of endotoxin when compared *in vitro* against the leading standalone endotoxin filter, Toraymyxin (Toray, Japan). This could potentially increase the effectiveness of CytoSorb in sepsis and septic shock caused by Gram negative bacteria.

Projected Timeline: CytoSorb-XL is in advanced pre-clinical development as a potential next generation polymer to CytoSorb. It is expected to follow a similar path to E.U. approval as CytoSorb, expected within 4-5 years.

The HemoDefend Blood Purification Technology Platform (Acute and Critical Care)

APPLICATION: Reduction of contaminants in the blood supply that can cause transfusion reactions or disease when administering blood and blood products to patients.

Potential Benefits: The HemoDefend blood purification technology platform is designed to reduce contaminants in the blood supply that can cause transfusion reactions or disease. It is a development stage technology that is not yet approved in any markets, but is comprised of our highly advanced, biocompatible, polymer bead technology. If this technology is successfully developed and then incorporated into a regulatory approved product, it could have a number of important benefits, including:

- reduce the risk of transfusion reactions and improve patient outcome;
- improve the quality, or extend the shelf life of stored blood products;
- improve the availability of blood and reduce blood shortages by reducing the limitations of donors to donate blood; and
- allow easier processing of blood.

Background and Rationale: The HemoDefend technology platform was built upon our successes in designing and manufacturing porous polymer beads that can remove cytokines. We have expanded the technology to be able to remove substances as small as drugs and bioactive lipids, to proteins as large as antibodies from blood that can cause transfusion reactions and disease. Although the frequency of these reactions are relatively low (approximately 3% to 5%), the sheer number of blood transfusions is so large, that the number of transfusion reactions, ranging from mild to life-threatening, is substantial, ranging from several hundreds of thousands to millions of reactions each year. In critically-ill patients, the risk of transfusion reactions is significantly higher than in the general population and can increase the risk of death because their underlying illnesses have depleted protective mechanisms and have primed their bodies to respond more vigorously to transfusion-associated insults.

A number of retrospective studies have also suggested that administration of older blood leads to increased adverse events and even increased mortality, compared with blood recently harvested. Biological studies have demonstrated the accumulation of erythrocyte storage lesions that compromise the function and structural integrity of packed red blood cells and have also demonstrated the accumulation of substances during blood storage that can lead to transfusion reactions. Three adult, prospective, randomized, controlled studies, RECESS (completed), ABLE (completed), and TRANSFUSE (ongoing) were designed to evaluate the morbidity and mortality in cardiovascular surgery patients, critically ill patients, and critically-ill patients, respectively, treated with either “new or fresh” or “older” blood. The RECESS Trial was a randomized, controlled trial in a total of 1,098 evaluable patients undergoing complex cardiac surgery given fresh blood (≤ 10 days old) as compared to older blood (≥ 21 days old). The overall conclusion was that the age of blood had no statistically significant impact on the progression to organ dysfunction (as measured by the multiple organ dysfunction syndrome score) or death. However, a statistically significant increase in

hepatobiliary-related serious adverse events (5% fresh vs 9% older, $p=0.02$) was related to hyperbilirubinemia, possibly caused by hemolysis and release of free hemoglobin in old blood. The serious adverse event rate in both new and old blood groups was approximately 50%, which is considered high for this group of patients. There are many details and subgroup analyses that were not discussed, particularly an analysis of those patients receiving more units of blood than average, as the risk of adverse events is cumulative. The ABLE Trial was a randomized, controlled trial in 2,430 critically-ill patients receiving either fresh (≤ 7 days) or standard issue blood. There was no difference in 90-day mortality between the two groups. The outcomes of the RECESS and ABLE trials do not alter the current pressing need for better solutions to purify transfused blood products in order to reduce transfusion-related adverse events and improve clinical outcome, but suggest that age of blood is not the critical factor.

Projected Timeline: The HemoDefend platform is a development stage product based on our advanced polymer technology. The base polymer is ISO 10993 biocompatible, meeting standards for biocompatibility, hemocompatibility, cytotoxicity, genotoxicity, acute sensitivity and complement activation. HemoDefend has demonstrated the *in vitro* removal of many different substances from blood such as antibodies, free hemoglobin, cytokines and bioactive lipids. We have also prototyped a number of different implementations of the HemoDefend technology, including the “Beads in a Bag” blood treatment blood storage bag, and standard in-line blood filters. The technology has been supported by the NHLBI, a division of the National Institute of Health, under a Phase I and more recently, an awarded \$1.5M Phase II SBIR contract. Under the Phase II program, we expect to advance the in-line filter to human testing. We seek to out-license this technology to a strategic partner in the transfusion medicine space, but may elect to continue our development in parallel with out-licensing efforts.

ContrastSorb (Radiology and Interventional Radiology)

APPLICATION: Removal of IV contrast in blood administered during CT imaging, an angiogram, or during a vascular interventional radiology procedure, in order to reduce the risk of contrast-induced nephropathy.

Potential Benefits: IV contrast can lead to CIN, in susceptible patients. Risk factors include chronic kidney disease and renal insufficiency caused by age, diabetes, congestive heart failure, long-standing hypertension, and others co-morbid illnesses. CIN can lead to increased risk of patient morbidity and mortality. Removal of IV contrast by ContrastSorb may:

- reduce the risk of acute kidney injury
- improve the safety of these procedures and reduce the risk of morbidity and mortality

Background and Rationale: Contrast-induced nephropathy is the acute loss of renal function within the first 48 hours following IV contrast administration. IV contrast is widely administered to patients undergoing CT scans, to enhance the images and make it easier to identify anatomic structures. IV contrast is also administered during vascular interventional radiology procedures and angiography of blood vessels in the brain, heart, limbs, and other parts of the body to diagnose and treat atherosclerosis (narrowing of blood vessels due to cholesterol deposits), vascular injury, aneurysms, etc. The reported risk of CIN undergoing contrast enhanced CT scans has been reported to be 2% to 13%. For coronary intervention, the risk has been estimated to be as high as 20% to 30% in high risk patients with pre-existing renal insufficiency, and other risk factors. The use of low osmolar IV contrast, hydration of patients pre-procedure, orally administration of N-acetylcysteine, and other agents to prevent CIN have demonstrated modest benefit in some clinical studies, but in many cases, the results across studies have been equivocal and inconsistent. In high risk patients, the direct removal of IV contrast from the blood with ContrastSorb to prevent CIN represents a potentially more effective alternative.

Projected Timeline: ContrastSorb has demonstrated the high efficiency single pass removal of IV contrast and is in the process of optimization. The underlying polymer is made of the same ISO 10993 biocompatible polymer as CytoSorb, but with different structural characteristics. The ContrastSorb device is a hemoperfusion device similar in construction to CytoSorb and BetaSorb. Assuming successful optimization of the ContrastSorb polymer, safety and efficacy of IV contrast removal will need to be established in human clinical studies. We seek to out-license this technology to a potential strategic partner.

The BetaSorb Device (Chronic Care)

APPLICATION: Prevention and treatment of health complications caused by the accumulation of metabolic toxins in patients with chronic renal failure

Potential Benefits: If BetaSorb is able to prevent or reduce high levels of metabolic waste products from accumulating in the blood and tissues of long-term dialysis patients, we anticipate that certain health complications characteristic to these patients can be prevented or mitigated. The primary goals for this application are to:

- improve and maintain the general health of dialysis patients;
- reduce disability and improve the quality of life of these patients
- reduce the total cost of patient care; and
- increase life expectancy.

Background and Rationale: Our BetaSorb device is intended for use on patients suffering from chronic kidney failure who rely on long-term dialysis therapy to sustain life. Due to the widely recognized inability of dialysis to remove larger proteins from blood, metabolic waste products, such as beta₂-microglobulin, accumulate to toxic levels and are deposited in the joints and tissues of patients. Specific toxins known to accumulate in these patients have been linked to their severe health complications, increased healthcare costs, and reduced quality of life.

Researchers also believe that the accumulation of toxins may play an important role in the significantly reduced life expectancy experienced by dialysis patients. In the U.S., the average life expectancy of a dialysis patient is five years. Industry research has identified links between many of these toxins and poor patient outcomes. If our BetaSorb device is able to routinely remove these toxins during dialysis and prevent or reduce their accumulation, we expect our BetaSorb device to maintain or improve patient health in the long-term. We believe that by reducing the incidence of health complications, the annual cost of patient care will be reduced and life expectancy increased.

The poor health experienced by beta₂-microglobulin patients is illustrated by the fact that in the U.S. alone, more than \$33 billion is spent annually caring for this patient population. according to the United States Renal Data System, at a cost of approximately \$88,000 per patient annually.

Projected Timeline: We have collected a significant amount of empirical data for the development of this application. As the developer of this technology, we had to undertake extensive research, as no comparable technology was available for reference purposes. We have completed four human pilot studies, including a clinical pilot of six patients in California for up to 24 weeks in which our BetaSorb device removed the targeted toxin, beta₂-microglobulin, as expected. In total, we have sponsored clinical studies utilizing our BetaSorb device on 20 patients involving approximately 345 total treatments. Each study was conducted by a clinic or hospital personnel with us providing technical assistance as requested.

As discussed above, due to practical and economic considerations, we are focusing our efforts and resources on commercializing our CytoSorb device for critical care and cardiac surgery applications. Following commercial introduction of the CytoSorb device, and with sufficient additional resources, we may continue development of the BetaSorb resin and may conduct additional clinical studies using the BetaSorb device in the treatment of end stage renal disease patients.

Commercial and Research Partners

Biocon Ltd

In September 2013, we entered into a strategic partnership with Biocon Ltd. (“Biocon”), India’s largest biotech company, with an three-year initial Distribution Agreement, for India and select emerging markets under which Biocon has the exclusive commercialization rights for CytoSorb initially focused on sepsis. Biocon committed to annual minimum purchases to maintain marketing exclusivity. Either party may terminate the Distribution Agreement upon the occurrence of a material breach or default of any contractual obligation by the other party and the failure of the breaching party to cure the default within thirty (30) days written notice of the breach. After the first 12 months of the Distribution Agreement, either party may terminate such agreement for convenience upon 60 days’ written notice. The Agreement contains standard representations and warranties of the parties.

On October 30, 2014, we entered into the First Amendment to the Distribution Agreement with Biocon, which, among other things, provided for the extension of the term of the original agreement to September 20, 2017. Pursuant to the First Amendment, the Biocon partnership was expanded to include all critical care applications and cardiac surgery. In addition, Biocon committed to higher annual minimum purchases of CytoSorb to maintain distribution exclusivity and committed to conduct and publish results from multiple investigator-initiated studies and patient case studies. Otherwise, the original terms of the Distribution Agreement remain in full force and effect.

Fresenius Medical Care AG

In December 2014, we entered into a multi-country strategic partnership with Fresenius to commercialize the CytoSorb therapy. Under the terms of this agreement, Fresenius has exclusive rights to distribute CytoSorb for critical care applications in France, Poland, Sweden, Denmark, Norway, and Finland. The partnership will allow Fresenius to offer an innovative and easy way to use blood purification therapy for removing cytokines in patients that are treated in the ICU. In January 2017, the Fresenius partnership was expanded. The terms of the revised three-year agreement extend Fresenius' exclusive distributorship of CytoSorb for all critical care applications in their existing territories through 2019 and include guaranteed minimum quarterly orders and payments, evaluable every one and a half years. In addition, we have entered into a new comprehensive co-marketing agreement with Fresenius. Under the terms of the agreement, CytoSorbents and Fresenius will jointly market CytoSorb and Fresenius' CytoSorb compatible blood tubing sets to Fresenius' critical care customer base in all countries where CytoSorb is being actively commercialized. CytoSorb will continue to be sold by our direct sales force or through our international network of distributors and partners, while Fresenius will sell all ancillary products to their customers. Fresenius will also provide a written endorsement of CytoSorb for use with their multiFiltrate and multiFiltratePRO acute care dialysis machines that can be used by us and our distribution partners to promote CytoSorb worldwide. Training and preparation for this co-marketing program is ongoing and it is expected co-marketing activity will commence during the second half of 2017.

Fresenius Medical Care is the one of the world's largest, integrated provider of products and services for individuals with chronic kidney failure. Through its network of more than 2,100 dialysis clinics in North America, Europe, Latin America, Asia-Pacific, and Africa, Fresenius Medical Care provides dialysis treatment to hundreds of thousands of patients around the globe. Fresenius Medical Care is also the world's largest provider of dialysis products, such as hemodialysis machines, dialyzers and related disposable products.

Separately, in 1999, we entered into an exclusive, long-term agreement with Fresenius Medical Care for the global marketing and distribution of our BetaSorb device for the treatment of renal disease, which we cancelled in 2015. We may or may not pursue our BetaSorb product after the commercialization of the CytoSorb product. At such time as we determine to proceed with our proposed BetaSorb product, if ever, we will need to conduct additional clinical studies using the BetaSorb device to obtain European or FDA approval.

Terumo Cardiovascular Group

In September 2016, we entered into a multi-country strategic partnership with Terumo Cardiovascular Group to commercialize CytoSorb for cardiac surgery applications. Under the terms of the agreement, Terumo has exclusive rights to distribute the CytoSorb CPB procedure pack for intra-operative use during cardiac surgery in France, Sweden, Denmark, Norway, Finland and Iceland. Terumo launched CytoSorb in its six exclusive countries in

December 2016.

University of Pittsburgh Medical Center

Two government research grants by the National Institutes of Health (“NIH”) and the U.S. Department of Health and Human Services have been awarded to investigators at the University of Pittsburgh to explore the use of adsorbent polymers in the treatment of sepsis and organ transplant preservation. Under “Sub Award Agreements” with the University of Pittsburgh, we have been developing polymers for use in these studies.

A grant of \$1 million was awarded to the University of Pittsburgh Medical Center in 2003. The project seeks to improve the quantity and viability of organs donated for transplant by using CytoSorb to detoxify the donor’s blood. The observational and dosing phases of the study, involving 30 viable donors and eight non-viable donors, respectively, have been completed. The next phase of this study, the treatment phase, will involve viable donors. We are not currently focusing our efforts on the commercialization of CytoSorb for application in organ donors. The treatment phase would be contingent upon further discussion with the FDA and HRSA regarding study design, as well as obtaining additional funding.

In September 2005, the University of Pittsburgh Medical Center was awarded a grant of approximately \$7 million from NIH entitled “Systems Engineering of a Pheresis Intervention for Sepsis (SEPsIS)” to study the use of adsorbent polymer technology in the treatment of severe sepsis. The study, which lasted for a total of five years, commenced in September 2005. Under a SubAward Agreement, we worked with researchers at the University of Pittsburgh - Critical Care Medicine Department. We believe that the only polymers used in this study were polymers we have developed specifically for use in the study, which are similar to the polymers used in our devices. Under the SubAward Agreement, for our efforts in support of the grant during 2006 through 2010, we received approximately \$402,000.

These grants represent a substantial research cost savings to us and demonstrate the strong interest of the medical and scientific communities in our technology.

Researchers at UPMC have participated in nearly every major clinical study of potential sepsis intervention during the past twenty years. Drs. Derek Angus and John Kellum were investigators for Eli Lilly's sepsis drug, Xigris®. Dr. Kellum, a member of the UPMC faculty since 1994, is the Chairman of our Severe Sepsis and Inflammatory Disease Advisory Board. Dr. Kellum's research interests span various aspects of Critical Care Medicine, but center on critical care nephrology (including acid-base, and renal replacement therapy), sepsis and multiple organ failure, and clinical epidemiology. He is Professor and Vice Chair for Research in the Critical Care department, and Director of the Center for Critical Care Nephrology ("CRISMA") at the University of Pittsburgh Medical Center, has authored more than 400 publications and has received numerous research grants from foundations and industry.

Advisory Boards

From time to time our management meets with scientific advisors who sit on our Scientific Advisory Board, our Medical Advisory Board – Critical Care Medicine, our Medical Advisory Board – Chronic Kidney Failure / Dialysis and our Scientific Advisory Board – Cardiac Surgery.

Our Scientific Advisory Board consists of three scientists with expertise in the fields of fundamental chemical research, and polymer research and development.

Our Sepsis Advisory Board consists of four medical doctors, one of whom is affiliated with UPMC, with expertise in critical care medicine, sepsis, multiple organ failure and related clinical study design.

Our Trauma Advisory Board consists of four medical doctors with expertise in trauma, burn injury and critical care medicine.

Our Cardiac Surgery Advisory Board consists of seven medical doctors with experience in cardiac surgery and complications caused by inflammation generated by the surgery.

We compensate members of our Advisory Boards at the rate of \$2,000 for each full-day meeting they attend in person; \$1,200 if attendance is by telephone. When we consult with members of our Advisory Board (whether in person or by telephone) for a period of less than one day, we compensate them at the rate of \$200 per hour. We also reimburse members of our Advisory Boards for their travel expenses for attending our meetings.

Royalty Agreements

With Principal Stockholder

In August 2003, in order to induce Guillermina Vega Montiel, a principal member of RenalTech International, LLC at the time, to make a \$4 million investment in RenalTech International, LLC, we granted Ms. Montiel a perpetual royalty equal to three percent of all gross revenues received by us from sales of CytoSorb in the applications of sepsis, cardiopulmonary bypass surgery, organ donor, chemotherapy and inflammation control. In addition, for her investment, Ms. Montiel received 1,230,770 membership units of RenalTech International, LLC. Such membership units ultimately were converted into and became 7,420 shares of our common stock following our June 30, 2006 merger. For the year ended December 31, 2016 we have recorded royalty costs of approximately \$243,000.

With Purolite

In 2003, Purolite filed a lawsuit against us asserting, among other things, co-ownership and co-inventorship of certain of our patents. On September 1, 2006, the United States District Court for the Eastern District of Pennsylvania approved a Stipulated Order and Settlement Agreement under which we and Purolite agreed to the settlement of the action. The Settlement Agreement provides us with the exclusive right to use our patented technology and proprietary know how relating to adsorbent polymers for a period of 18 years. In particular, the Settlement Agreement relates to several of our issued patents and several of our pending patent applications covering our biocompatible polymeric resins, our methods of producing these polymers, and the methods of using the polymers to remove impurities from physiological fluids, such as blood.

Under the terms of the Settlement Agreement, we have agreed to pay Purolite royalties of 2.5% to 5% on the sale of those of our products, if and when those products are sold commercially, that are used in direct contact with blood. However, if the first product we offer for commercial sale is a biocompatible polymer to be used in direct contact with a physiological fluid other than blood, royalties will be payable with respect to that product as well. The royalty payments provided for under the Settlement Agreement would apply to our currently envisioned CytoSorb, VetResQ, and BetaSorb products. For the year ended December 31, 2016 per the terms of the license agreement we have recorded royalty costs of approximately \$324,000.

Following the expiration of the 18 year term of the Settlement Agreement, the patents and patent applications that are the subject of the Settlement Agreement should have expired under current patent laws, and the technology claimed in them will be available to the public. However, following such time, we would continue to exclusively own any confidential and proprietary know how.

Product Payment & Reimbursement

CytoSorb

Germany

Effective January 1, 2017, we achieved a permanent dedicated reimbursement code in Germany that will provide for specific and enhance reimbursement for our CytoSorb device. We believe that this dedicated reimbursement code will provide our customers with a path to negotiate higher reimbursement that not only covers the cost of the device, but

the procedural costs as well. Reimbursement can also be covered by the standard “diagnosis related group” (“DRG”) acute care reimbursement. Under this system, hospitals would purchase CytoSorb and subtract the cost from a pre-determined lump-sum payment made by the payor to the hospital based on the patient’s diagnosis.

Europe (excluding Germany)

Payment for our CytoSorb device for the removal of cytokines in patients with life-threatening illnesses is country dependent in Europe. We intend to pursue reimbursement of CytoSorb in other major territories, with our partners, such as France, England, Italy and Spain, representing the other four economic leaders in Europe. There can be no assurances that reimbursement will be granted or that additional clinical data may not be required to establish reimbursement.

United States

Critical care applications such as those targeted by our CytoSorb device involve a high mortality rate and extended hospitalization, coupled with extremely expensive ICU time. In view of these high costs and high mortality rates, we believe acceptance of our proprietary technology by critical care practitioners and hospital administrators will primarily depend on safety and efficacy factors rather than solely based on cost.

CytoSorb is not yet approved in the U.S., and we have not fully accessed the potential for reimbursement for the device. Payment for our CytoSorb device in the U.S. for the treatment and prevention of sepsis and other related acute care applications is anticipated to fall under the diagnosis-related group (“DRG”) prospective repayment system, which is currently the predominant inpatient hospital reimbursement methodology in the U.S. Under this system, hospital reimbursement is generally based upon pre-determined amounts payable for specific diagnoses (e.g. septic shock with respiratory failure), regardless of the number of services provided during the patient’s stay. If CytoSorb can improve outcomes and reduce the costs of ICU treatment and hospital length of stay, it could potentially save hospitals a significant amount of money.

Competition

General

We believe that our products represent a unique approach to disease states and health complications associated with the presence of larger toxins (often referred to as middle molecular weight toxins) in the bloodstream, including sepsis, acute respiratory distress syndrome, trauma, severe burn injury, pancreatitis, post-operative complications of cardiac surgery, damage to organs donated for transplant prior to organ harvest, and renal disease. Researchers have explored the potential of using existing membrane-based dialysis technology to treat patients suffering from sepsis. These techniques are unable to effectively remove the middle molecular weight toxins. We have demonstrated the ability of CytoSorb to reduce key cytokines in the blood of human patients with predominantly septic shock and acute respiratory distress syndrome. In a post-hoc subgroup analysis of our European Sepsis Trial, we have also demonstrated statistically significant improvements in mortality in patients at high risk of death, including patients with either very high cytokine levels or patients older than age 65, both of which have a high predicted mortality. Larger studies are needed to confirm these preliminary data.

The CytoSorb, VetResQ, CytoSorb XL, DrugSorb, ContrastSorb, and BetaSorb devices consist of a cartridge containing adsorbent polymer beads. The cartridge incorporates industry standard connectors at either end of the device which connect directly to an extra-corporeal circuit (bloodlines) on a standalone basis. The extra-corporeal circuit consists of plastic tubing through which the blood flows, our cartridge containing our adsorbent polymer beads, pressure monitoring gauges, and a blood pump to maintain blood flow. The patient's blood is accessed through a catheter inserted into his or her veins. The catheter is connected to the extra-corporeal circuit and the blood pump draws blood from the patient, pumps it through the cartridge and returns it back to the patient in a closed loop system. As blood passes over the polymer beads in the cartridge, toxins are adsorbed from the blood, without removing any fluids from the blood or the need for replacement fluid or dialysate.

There are three common forms of blood purification, including hemodialysis, hemofiltration, and hemoperfusion. All modes are generally supported by standard hemodialysis machines. All take blood out of the body to remove toxins and unwanted substances from blood, and utilize extracorporeal circuits and blood pumps. Dialysis and hemofiltration remove substances from blood by diffusion and ultrafiltration, respectively, through a semi-permeable membrane, allowing the passage of certain sized molecules across the membrane, but preventing the passage of other, larger molecules. Hemoperfusion utilizes solid or porous sorbents to remove substances based on pore capture and surface adsorption, not filtration.

CytoSorb is a hemoperfusion cartridge, using an adsorbent of specified pore size, which controls the size of the molecules which can pass into the adsorbent and vastly increases the area available for surface adsorption. As blood flows over our polymer adsorbent, middle molecules such as cytokines flow into the polymer adsorbent and are

adsorbed. Our devices do not use semipermeable membranes or dialysate. In addition, our devices do not remove fluids from the blood like hemodialysis or hemofiltration. Accordingly, we believe that our technology has significant advantages as compared to traditional dialysis techniques, including ease of use.

Our HemoDefend platform is a development-stage technology utilizing a mixture of proprietary porous polymer beads that target the removal of contaminants that can cause transfusion reactions or cause disease in patients receiving transfused blood products. The HemoDefend beads can be used in multiple configurations, including the common in-line filter between the blood bag and the patient as well as a unique, patent-pending “Beads in a Bag” treatment configuration, where the beads are placed directly into a blood storage bag.

Sepsis

Researchers have explored the potential of using existing membrane-based dialysis technologies to treat patients suffering from sepsis. These techniques are unable to effectively remove middle molecular weight toxins, which leading researchers have shown to cause and complicate sepsis. The same experts believe that a blood purification technique that efficiently removes, or significantly reduces, the circulating concentrations of such toxins might represent a successful therapeutic option. CytoSorb has demonstrated the ability to remove middle molecular weight toxins, such as cytokines, from circulating blood in a statistically significant manner.

Medical research during the past two decades has focused on drug interventions aimed at chemically blocking or suppressing the function of one or two inflammatory agents. In hindsight, some researchers now believe this approach has little chance of significantly improving patient outcomes because of the complex pathways and multiple chemical factors at play. Clinical studies of these drug therapies have been largely unsuccessful. An Eli Lilly drug, Xigris®, cleared by the FDA in November 2001, is the first and only drug to be approved for the treatment of severe sepsis. Clinical studies demonstrated that use of Xigris® resulted in an average absolute 6% reduction in 28-day mortality, and an absolute 13% reduction in 28-day mortality in the most severe sepsis patients. The drug remains controversial and is considered expensive when compared to the percentage of patients who benefit. In 2011, after completing a follow up study required by the FDA, it was subsequently determined that Xigris® does not have a statistically significant mortality benefit, and in October 2011, Eli Lilly withdrew Xigris® from all markets worldwide.

Development of most other experimental therapies has been discontinued, including Eritoran from Eisai, CytoFab from BTG/Astra Zeneca, Talactoferrin from Agennix, and others. There are few therapies in current development. In April 2015, Leading Biosciences began a 260 patient randomized, controlled Phase 2 clinical SSAIL trial in septic shock patients using its investigational orally administered drug, LB1148, also known as tranexemic acid. Tranexemic acid is a serine protease inhibitor, designed to inhibit digestive enzymes and preserve and promote healing of the intestine's mucosal barrier, with the goal of preventing the escape of potent digestive enzymes into the blood, which could exacerbate sepsis. Leading Biosciences expected completion of the trial in December 2016. If this product is successful, it would represent a competitive, although potentially complementary, therapeutic approach to CytoSorb.

Currently, there are two late stage trials ongoing. In November 2012, an 800 patient Phase III randomized controlled study began for Recomodulin (ART 123, Artisan/Asahi Kasei), a recombinant human thrombomodulin, for the treatment of septic patients with coagulopathy. In mid-2013, following an interim analysis of safety data, the DSMB recommended that the trial continue. The primary completion date of the trial was expected to be March 2015, however, based on a February 2017 business update, the trial is still enrolling patients. Recomodulin has been approved in Japan since 2009 for the treatment of disseminated intravascular coagulation, a late complication of sepsis, at a cost of \$5,800 per treatment. Although it has other activity, it works primarily by a similar anticoagulant mechanism to Xigris. Because of this, it has only demonstrated a limited mortality benefit, in earlier studies (~9%: 34.6% control vs 26% treatment), similar to that seen in Xigris' initial PROWESS Trial (~6%: 31% control vs 25% treatment) and is unlikely to have greater benefit in larger scale studies. However, if this product is successful, it would represent a competitive, although potentially complementary, therapeutic approach to CytoSorb.

Atox Bio is a development stage company in clinical studies with peptide therapeutics that are designed to prevent superactivation of the immune response by certain toxins such as toxic shock syndrome toxin. It is currently focused on necrotizing soft tissue infections. The investigational peptide, AB103, is being evaluated in the ACCUTE Trial, a Phase 3 randomized controlled trial in 40 investigative sites in the U.S in 290 patients with necrotizing soft tissue infections. Primary outcomes include 28-day survival, amputation, and reduction in the modified sequential organ failure assessment score. The estimated study completion date is January 2018. If this product is successful, it would represent a competitive, although potentially complementary, therapeutic approach to CytoSorb.

Using a medical device to treat sepsis remains a relatively novel treatment approach. Toray Industries currently markets an endotoxin removal cartridge called Toraymyxin™ for the treatment of sepsis in Europe, Japan, and 16 other countries, but is not yet approved in the United States. To date, it has been used in more than 100,000 treatments since 1994. Toraymyxin does not directly reduce cytokines. Spectral Medical Inc. has obtained exclusive development and commercial rights in the U.S. for Toraymyxin, with plans to combine the use of its endotoxin activity assay to create a theranostic product. Spectral is collaborating with Toray on the EUPHRATES trial, combining an endotoxin assay with extracorporeal endotoxin removal by Toraymyxin, a polymyxin-B immobilized polystyrene fiber cartridge. The study began in June 2010 and is still enrolling patients. Endotoxemia is a result of Gram negative sepsis, which only accounts for 45% of cases of sepsis. It is a potent stimulator of cytokine storm. However, all anti-endotoxin strategies have failed pivotal studies to date, believed to be the result of intervening too late in the sepsis cascade. The original trial was designed as a randomized control trial in 360 patients with septic shock and high endotoxin levels (≥ 0.60 EAA units) as confirmed by Spectral's EAA. In a second interim analysis finalized in April 2014, following the enrollment of 184 patients with 28-day follow-up, the DSMB recommended that the trial continue. However, the expected trial size was increased to 650 patients and the exclusion criteria was modified to only accept sicker patients with a multiple organ dysfunction syndrome score greater than 9. In September 2015, Spectral reported that the composite mortality in the new subgroup had risen to ~50%, from ~30% previously. New statistical analysis on patients in the new subgroup, and comparable patients in a European treatment registry, led to a sample size recalculation of 446 evaluable patients. Spectral announced in June 2016 that they had completed enrollment for the EUPHRATES trial. In October 2016, Spectral announced top-line results that the trial did not meet the main goal of absolute reduction in 28 day all-cause mortality, but reiterated safety of treatment and potential benefit in the sickest group of patients (multiple organ dysfunction score > 9). There have been now several large scale studies failing to demonstrate a benefit of Toraymyxin on 28-day mortality in sepsis. Toraymyxin represents a competitive, although potentially complementary, therapeutic approach to CytoSorb.

Each of the following technologies claims to remove inflammatory mediators such as cytokines, or to treat sepsis, and represents a potential competitive alternative to CytoSorb. Toray markets its Hemofeel CH1.0 polymethylmethacrylate membrane (“PMMA”) in Japan and it has been used in several non-controlled, or historically controlled, clinical or case studies treating patients with sepsis, acute respiratory distress syndrome and pancreatitis. We are not aware of any prospective, randomized controlled studies using this PMMA hemofilter in patients with sepsis. Without such studies, it is difficult to assess the true impact of this technology in these conditions. Gambro AB launched its Prismaflex eXeed system in August 2009 and introduced the SepteX high molecular weight cutoff hemodialyzer in Europe, intended to treat patients with acute renal failure and the removal of inflammatory mediators from blood. Gambro also launched the oXiris dialyzer, based upon the AN60 CRRT membrane, to bind endotoxin. To our knowledge, neither are specifically approved for the treatment of sepsis. In September 2013, Baxter International, Inc. acquired Gambro AB. Fresenius has launched a similar high molecular weight cut off filter called the Ultraflux EMiC2. To our knowledge, there has been a lack of published data on the treatment of sepsis with these devices. Bellco S.R.L, acquired by Medtronic in February 2016, also sells the CPFA (coupled plasma filtration and adsorption) system in Europe. This uses a sorbent cartridge to remove cytokines from plasma. However, because the sorbent cannot treat blood directly, it requires the cost and complexity of an additional plasma separator to treat blood. This system is similar to the I.M.P.A.C.T. System being currently commercialized outside of the U.S. by Hemolife Medical Inc. that requires a three-cartridge system and a proprietary blood pump. According to Hemolife, the product is in product registration in 32 countries with initial shipments to the EU and Asia Pacific in process. We believe that CytoSorb, which can treat whole blood directly, and which works with standard hemodialysis pumps already found in hospitals worldwide, has significant competitive advantages compared to these multi-cartridge sorbent systems.

Kaneka Corporation currently markets Lixelle™, a modified porous cellulosic bead, for the removal of beta₂-microglobulin during hemodialysis in Japan. Lixelle has been used in several small human pilot studies including a 5 patient pilot study in 2002 and a 4 patient pilot study in 2009. Though these studies correlate Lixelle use with cytokine reduction, they are not randomized, controlled studies and so do not control for natural cytokine clearance. To our knowledge, no large, randomized, controlled trials have been conducted with Lixelle as a treatment for sepsis. Kaneka obtained U.S. humanitarian device exemption for Lixelle in March 2015, but is restricted to treating amyloidosis in chronic dialysis patients. Kaneka has since developed a modified cellulosic resin called CTR that can also remove cytokines from experimental pre-clinical systems. In 2009, CTR was used in an 18-patient randomized, controlled trial in patients with septic shock with undisclosed improvements in APACHE II scores and IL-6 and IL-8. To our knowledge, Kaneka has not conducted or published any other study using CTR to treat human sepsis patients since then. Jafron Biomedical is an integrated dialysis company selling dialysis machines and hemodialysis and hemoperfusion cartridges containing a neutral microporous adsorption resin to purify blood of toxins in liver failure, critical illness, poisoning, and autoimmune diseases. Ube Industries, Ltd is currently developing an adsorbent resin called CF-X for the removal of cytokines. To our knowledge, Ube has not published any study using CF-X to treat human sepsis patients. CytoPherx Inc., has developed an extracorporeal system based on selective cytopheresis, or the inactivation or removal of activated leukocytes. It was enrolling a 344 patient pivotal trial that began in August 2011 and was expected to be completed by December 2014 in patients with acute kidney injury with or without severe sepsis, on continuous renal replacement therapy with the goal of reducing mortality. This system does not remove cytokines directly, but attempts to reduce the numbers of activated white blood cells that can produce cytokines or cause cell-mediated injury. The status of the trial and the company is unknown. ExThera Medical Corporation is a privately held company that has developed its Seraph™ (Selective Removal by Apheresis) platform that consists of heparin coated, solid polyurethane beads. Heparin has the ability to bind some, but not all viruses, bacteria, toxins and cytokines. In *in vitro* studies using 1 mL of human septic blood, there was no statistically different change in IL-6 or Interferon-gamma compared to control, but effected a ~50% reduction in TNF-alpha. This inability to remove a broad

range of cytokines will likely limit its efficacy as a treatment in sepsis. It has repositioned Seraph™ as a pathogen removal technology, and has started a human trial in Germany in the future. In addition, it has partnered with BioBridge Global to apply its technology to pathogen reduction in transfused blood products. Other potential competitors include the now defunct Arbios Systems, Inc. and Hemocleanse Technologies, LLC. We believe our CytoSorb cartridge has significant competitive, technological, and/or economic advantages over systems by these other companies.

Acute Respiratory Distress Syndrome

Treatment of ARDS is predominantly supportive care using supplemental oxygen, careful fluid management, multiple modes of ventilation incorporating the concepts of low tidal volume, high frequency oscillation, and prone ventilation, and extracorporeal membrane oxygenation (“ECMO”) .. Corticosteroids, nitric oxide, statins, non-steroidal anti-inflammatory drugs, and surfactant therapy have been tried, but are not indicated for the treatment of ARDS. We are not aware of any specific products approved to treat ARDS.

Severe Burn Injury

Modern management of severe burn injury patients involves a combination of therapies. From a burn standpoint, patients undergo active escharotomy and debridement of burns, the use of skin grafts and substitutes, anti-microbial dressings and negative pressure dressings. Tight fluid control, nutrition, prevention of hypothermia and infection are also priorities. Smoke and chemical inhalation injury in burn victims is also common and increasing as a cause of death in severe burn injury. Carbon monoxide and cyanide poisoning is also an issue. Supplemental oxygen and mechanical ventilation are often required and are the mainstay of supportive care treatment. Recently continuous renal replacement therapy has been used to treat patients with acute kidney injury with an improvement in survival compared to a historical control cohort. We believe CytoSorb therapy may yield improved results. We are not aware of any specific products approved to directly address inhalational lung injury or multiple organ failure in severe burn injury.

Trauma

Trauma management initially involves respiratory, hemodynamic and physical stabilization of the patient. However, in the days to weeks that ensue, the focus shifts to preventing or treating organ failure and preventing or treating infection. We are not aware of any specific therapies to prevent or treat multiple organ dysfunction or multiple organ failure in trauma. Rhabdomyolysis, or the breakdown of muscle fibers due to crush injury or other means, occurs in trauma and can lead to acute kidney injury or renal failure. Aggressive hydration, urine alkalinization, and forced diuresis are the main therapies to prevent renal injury. Continuous hemodiafiltration with super-high-flux membranes has demonstrated modest myoglobin clearance but was associated with albumin loss. In general, however, most extracorporeal therapies are not well-suited to remove myoglobin. CytoSorb reduces myoglobin, and other polymers under development, removes myoglobin, some without significant losses of albumin.

Severe Acute Pancreatitis

Treatment of severe acute pancreatitis is predominantly supportive care focused on aggressive hydration, enteral nutrition and pain control. Mechanical ventilation, hemodialysis and vasopressor use is common in cases of multiple organ failure. In cases where cholelithiasis or other obstruction is the underlying cause of the pancreatitis, endoscopic retrograde cholangiopancreatography and/or stent placement can be used to relieve the obstruction. Antibiotics are often instituted to prevent or treat infection. Surgery is sometimes indicated to remove or drain necrotic or infected portions of the pancreas. To our knowledge, there are no other specific treatments approved to treat severe acute pancreatitis or multiple organ failure that is caused by systemic inflammation in this disease.

Cardiopulmonary Bypass Surgery

There is currently a pre-existing market for the use of leukocyte reduction filters sold by Pall Corporation, Terumo Medical Corporation and others in the cardiopulmonary bypass circuit. The purpose of these devices is to reduce cytokine-producing white blood cells from blood. They do not remove cytokines, free hemoglobin, or activated complement directly and are not considered by many to be an effective solution for the reduction of these substances. We are not aware of any practical competitive approaches for removing cytokines, free hemoglobin, activated complement, and a broad range of other inflammatory mediators in patients undergoing cardiopulmonary bypass during cardiac surgery. To our knowledge, CytoSorb is the only cytokine reduction therapy capable of being placed directly into a bypass circuit in the heart-lung machine and used during cardiopulmonary bypass without the need for another pump. Modified ultrafiltration is sometimes used after termination of cardiopulmonary bypass in cardiac surgery to remove excess fluid and inflammatory substances, but has had mixed benefit. Cell saver machines that collect and wash pericardial shed blood is one potential alternative, but is typically done in batches and not a real-time filter during surgery. Alternative therapies such as “off-pump” surgeries are available but “post-bypass” syndrome and cytokine production still remain a problem in this less invasive, but more technically challenging procedure. If successful, CytoSorb is expected to be useful in both on-pump and off-pump procedures. CytoSorb is also being used with a dialysis machine to treat the development of a post-cardiac surgery systemic inflammatory response syndrome, a deadly complication of open heart surgery that if left untreated, can lead to multiple organ dysfunction syndrome, multiple organ failure, and potentially death.

Radiocontrast Removal

ContrastSorb has demonstrated the rapid, high efficiency single pass removal of IV contrast. The use of low osmolar IV contrast, oral administration of N-acetylcysteine, and other agents to prevent CIN have demonstrated modest benefit in some clinical studies, but in many cases, the results across studies have been equivocal and inconsistent. Hydration of high risk patients pre-procedure is standard of care but has limited efficacy. PLC Medical Systems, Inc., received CE Mark approval for its RenalGuard system in 2007. RenalGuard encourages excretion of IV contrast and a reduction of CIN, by administering IV hydration that matches urine output in patients receiving a loop diuretic. Hemodialysis can remove IV contrast, but is relatively slow (46% at 1 hour, 65% at 2 hours, and 75% at 3 hours) in chronic renal failure patients who lack normal renal clearance. In high risk patients, the rapid and direct removal of IV contrast from the blood with ContrastSorb to prevent CIN represents a potentially more effective alternative.

Drug Removal

Treatment of patients suffering from drug overdose often involves a number of pharmacological treatments and mechanical interventions to detoxify and stabilize the patient. Mechanical interventions include procedures such as orogastric lavage, activated charcoal, whole bowel irrigation and extracorporeal blood purification. Each method has

its own limitations, many of which are associated with the timing of administration following overdose. Blood purification with high flux dialyzers or with activated charcoal cartridges by Gambro, Fresenius, Nephros and others are typically efficient at removing hydrophilic drugs that are not protein bound. However, they are inefficient at removing drugs that have a large volume of distribution, or drugs that are hydrophobic or lipophilic. Many drugs of overdose fall into this category. Resin based hemoperfusion devices have been used to remove lipophilic drugs that are protein bound, but have historically had issues of biocompatibility. DrugSorb is a highly biocompatible resin-based hemoperfusion device that can remove a wide range of drugs of overdose *in vitro* very rapidly, with high single pass removal.

Chronic Dialysis

Although standard dialysis treatment effectively removes urea and creatinine from the blood stream (which are normally filtered by functioning kidneys), standard dialysis has not been effective in removing beta₂-microglobulin toxins from the blood of patients suffering from chronic kidney failure. High flux dialyzers by Gambro, Fresenius, Nephros and others are capable of removing some beta₂-microglobulin. However, we believe our technology would significantly improve clearance of this and other toxins. Kaneka markets Lixelle™, a cellulosic resin, outside the US to remove beta₂-microglobulin in dialysis patients. In March 2015, Lixelle received Humanitarian Device Exemption (“HDE”) approval in the U.S. for the treatment of beta-amyloidosis and removal of beta-microglobulin, a complication of chronic dialysis. HDE approval applies to the treatment of diseases with an* incidence of less than 4,000 cases a year in the U.S. annually. We know of no other device, medication or therapy considered directly competitive with our technology.

Treatment of Organ Dysfunction in Brain-Dead Organ Donors

We are not aware of any directly competitive products to address the application of our technology for the mitigation of organ dysfunction and failure resulting from severe inflammation following brain-death.

HemoDefend Purification Technology Platform for Transfused Blood Products

There are only a few directly competitive approved products to address the removal of substances from blood and blood products that can cause transfusion reactions. Leukoreduction (Pall Corporation, Terumo-BCT, Hemonetics Corporation, others) is widely used in transfusion medicine and can remove the majority of white cells that can produce new cytokines but cannot eliminate those cytokines already in blood, and cannot otherwise remove other causative agents. Automated washing of pRBC is very effective at cleansing contaminants from blood, but is impractical due to the time, cost, materials, and logistics of washing each unit of blood and is not widely used. Blood filters that utilize affinity technologies are in development to remove certain substances such as antibodies from blood, but have other issues, such as cost and concern about the stability or leachability of the affinity technology. The HemoDefend platform represents a potentially superior alternative to these methods, as it can provide comprehensive removal of a wide variety of contaminants that can trigger transfusion reactions without washing blood, requires no additional equipment, energy source, or manipulation, and can be incorporated directly into the blood storage bag or used as an in-line blood filter.

Clinical Studies

Our first clinical studies were conducted in patients with chronic renal failure. The health of these patients is challenged by high levels of toxins circulating in their blood but, unlike sepsis patients, they are not at imminent risk of death. The toxins involved in chronic renal failure are generally different from those involved in sepsis, eroding health gradually over time. The treatment of patients with chronic renal failure is a significant target market for us, although not the current focus of our efforts and resources. Our clinical studies and product development work in this application functioned to obtain safety and instrument data without the need to put the patient at additional risk (e.g. placing a new temporary dialysis catheter), with direct benefit to the development of the critical care applications on which we are now focusing our efforts.

We are focusing our research efforts on critical care and cardiac surgery applications of our technology.

Sepsis

In 2011, the CytoSorb filter received EU regulatory approval under the CE Mark as an extracorporeal cytokine filter to be used in clinical situations where cytokines are elevated. As part of the CE Mark process, we completed our randomized, controlled, European Sepsis Trial amongst 14 trial sites in Germany in 2011, with enrollment of 100 patients with sepsis and respiratory failure. The trial established that CytoSorb was sufficiently safe in this critically ill population to support the CE mark. In the European Sepsis Trial, the treatment was well-tolerated with no serious device related adverse events reported.. Although the trial was not powered to demonstrate significant reduction in other clinical endpoints such as mortality, these were also included as secondary and exploratory endpoints in the trial.

The first 22 patients in the study represented a sepsis pilot study. In the next 31 patients, a compromise of the manual randomization schedule at two trial sites led to an imbalance in the severity of illness between the control and treatment patient groups of the study. After a thorough review, the Scientific Advisory Board and the independent DSMB both recommended that due to this enrollment bias, these 31 patients should only be used for safety evaluation purposes and that new patients should be enrolled into the trial using electronic web-based randomization to randomly assign patients into either the control or treatment arms.

Excluding four patients that withdrew, the remaining 43 evaluable patients enrolled under electronic randomization (of which 25 were in the control group and 18 were in the treatment group)were relatively balanced in terms of the severity of illness in treatment and control patients, confirming the findings of the Scientific Advisory Board and the DSMB. An independent Contract Research Organization, RCRI, Inc. (Minneapolis, MN),, analyzed these 43 evaluable patients in the European Sepsis Trial and showed on a statistically significant basis ($p < 0.05$), the ability of CytoSorb to reduce circulating levels of key cytokines from whole blood in treated patients on the average of 30% to 50% over the seven day treatment period. Additionally, post-hoc subgroup analyses of the clinical outcome data from patients enrolled under electronic randomization demonstrated statistically significant reduction in mortality in patients at high risk of death in sepsis, specifically in patients with:

very high cytokine levels (IL-6 \geq 1,000 pg/mL and/or IL-1ra \geq 16,000 pg/mL) where 28-day mortality was 0% treated as compared to 63% control, $p=0.03$, $n=14$, and
an age \geq 65 (14-day mortality: 0% treated as compared to 36% control, $p=0.04$, $n=21$).

In patients aged \geq 65 years old, however, seven days of treatment with CytoSorb was not adequate to extend the observed 14-day mortality benefit out to 28-days (40% as compared to 45% control, $p=0.6$, $n=21$). These critically ill patients carried two major mortality risk factors: multiple organ failure and age \geq 65 years old, which itself confers a 2.3-fold relative risk of death. Treatment of life-threatening infections with antibiotics often requires seven to 14 days of treatment. We hypothesize that treatment of the “run-away” immune response should mirror treatment with antibiotics. We have completed enrollment of a dose ranging study (Dosing Study) in Germany amongst several clinical trial sites to evaluate the safety and efficacy of CytoSorb when used continuously for 7 days, each day with a new device and are conducting final statistical analysis of the data. Patients are being stratified for age, cytokine levels, and co-morbid illnesses in this matched pairs analysis.

At the end of 2013, we reported a clinical update on the first 28 treated patients that were enrolled in the first arm of the Dosing study (24 hours of treatment for seven days, each day with a new device). Treatment was safe and well-tolerated at flow rates up to 300 mL/min, with no serious device related adverse events. Twenty-four-hour treatment increased platelet reduction compared to six-hour treatment in the EST, but with no reported complications. Broad spectrum antibiotics, such as the carbapenem class, were compatible with CytoSorb, requiring only modest dose adjustments. IL-6 reduction continued throughout the entire 24-hour period, higher at the beginning of treatment when IL-6 levels are highest, and with an overall average instantaneous IL-6 reduction of 8% per pass. In this preliminary analysis, the overall 28-day all-cause mortality and 28-day all-cause mortality in patients 65 years and older was not statistically different from the treatment data reported in the EST (electronic randomized cohort). Severity of illness in the overall treatment groups were comparably high, with 50% or more of the treated patients (dosing $>$ EST) having an APACHE II severity of illness score $>$ 25 at the time of enrollment, predicting very high mortality of 55% or more. In comparison, the overall control patients reported in the EST (electronic randomization cohort) had a lower severity of illness with only 20% having an APACHE 2 score $>$ 25. Once final statistical analysis of the data is completed, the principal investigator and writing committee expects to submit the data for publication.

In 2007, we received FDA approval of our IDE application to run a single center sepsis study in the U.S. Assuming availability of adequate and timely funding, and continued positive results from our clinical studies, we intend to continue commercializing our product in Europe while pursuing additional sepsis studies in both the U.S. and the EU.

Cardiac Surgery

In February 2015, the FDA approved our IDE application to commence a planned U.S. cardiac surgery feasibility study called REFRESH I (REduction of FREe Hemoglobin) amongst 20 patients and three U.S. clinical sites. The

FDA subsequently approved an amendment to the protocol, expanding the trial to be a 40 patient randomized controlled study (20 treatment, 20 control) in eight clinical centers. REFRESH I represents the first part of a larger clinical trial strategy intended to support the approval of CytoSorb in the U.S. for intra-operative use during cardiac surgery.

The study is designed to evaluate the safety of CytoSorb when used intra-operatively in a heart-lung machine to reduce plasma free hemoglobin and cytokines in patients undergoing complex cardiac surgery. The length, complexity and invasiveness of these procedures cause hemolysis and inflammation, leading to high levels of plasma free hemoglobin, cytokines, activated complement, and other substances. These inflammatory mediators directly correlate with the incidence of serious post-operative complications such as kidney injury and failure. The goal of CytoSorb is to actively remove these inflammatory and toxic substances as they are being generated during the surgery and reduce complications. As of December 31, 2016, enrollment was complete with 46 patients. A total of 38 patients were evaluable and completed all aspects of the study.

The primary safety and efficacy endpoints of the study were the assessment of serious device related adverse events and the change in plasma free hemoglobin levels, respectively. On October 5, 2016, we announced positive top-line safety data. In addition, following a detailed review of all reported adverse events in a total of 46 enrolled patients, the independent DSMB found no safety concerns related to the CytoSorb device, achieving the primary safety endpoint of the trial and fulfilling a key requisite to move forward with a larger, definitive pivotal study. In addition, the therapy was well-tolerated and technically feasible, implementing easily into the cardiopulmonary bypass circuit without the need for an additional external blood pump. This study represents the first randomized controlled trial demonstrating the safety of intra-operative CytoSorb use in patients undergoing high risk cardiac operations.

Investigators of the REFRESH I trial have submitted an abstract with free hemoglobin data from the REFRESH I trial to the American Association of Thoracic Surgery (“ASST”) conference to be held in late April 2017, and a manuscript is being prepared for journal submission. In parallel, the Company plans to meet with the FDA to discuss the results of REFRESH I in anticipation of filing an IDE application to initiate a pivotal REFRESH 2 trial in 2017.

Other Critical Care Applications

There are currently more than 55 ongoing investigator initiated studies being planned, enrolling or completed our commercialized territories. These trials, which are funded and supported by renowned university hospitals and key opinion leaders, will provide invaluable information regarding the success of the device in the treatment of sepsis, cardiac surgery, trauma, burn injury, pancreatitis, liver failure, acute kidney injury, acute respiratory distress syndrome, and many other indications, and will be integral to helping us determine the ultimate course of our U.S. clinical trial pathway in critical care.

Even though we have obtained CE Mark approval, no assurance can be given that our CytoSorb product will work as intended in these studies or that we will be able to obtain FDA approval to sell CytoSorb in the U.S. Even though we have obtained CE Mark approval, there is no guarantee or assurance that we will be successful in obtaining FDA approval in the United States or approval in any other country or jurisdiction. Because of the limited studies we have conducted, we are subject to substantial risk that our technology will have little or no effect on the treatment of any indications that we have targeted.

Government Research Grants

Two government research grants by the NIH and the U.S. Department of Health and Human Services were awarded to investigators at the University of Pittsburgh to explore the use of adsorbent polymers in the treatment of sepsis and organ transplant preservation. Under “SubAward Agreements” with the University of Pittsburgh, we developed

polymers for use in these studies.

A grant of \$1 million was awarded to the University of Pittsburgh Medical Center in 2003. The project sought to improve the quantity and viability of organs donated for transplant by using CytoSorb to detoxify the donor's blood. The observational and dosing phases of the study, involving 30 viable donors and eight non-viable donors, respectively, was completed. Although the next phase of this study, the treatment phase, would have involved viable donors, we are not currently focusing our efforts on the commercialization of CytoSorb for application in organ donors. The treatment phase would be contingent upon further discussion with the FDA and HRSA regarding study design, as well as obtaining additional funding.

In addition, in September 2005, the University of Pittsburgh Medical Center was awarded a grant of approximately \$7 million from NIH entitled "Systems Engineering of a Pheresis Intervention for Sepsis (SEPsIS)" to study the use of adsorbent polymer technology in the treatment of severe sepsis. The study, which lasted for a total of five years, commenced in September 2005. Under a SubAward Agreement, we worked with researchers at the University of Pittsburgh - Critical Care Medicine Department. We believe that the only polymers used in this study were polymers we have developed specifically for use in the study, which are similar to the polymers used in our devices. Under the SubAward Agreement, for our efforts in support of the grant during 2006 through 2010, we received approximately \$402,000.

In October 2010, we were awarded a grant of approximately \$489,000 from the federal Qualifying Therapeutic Discovery Project (“QTDP”) program for two products in our pipeline including the development of CytoSorb for the treatment of sepsis and other critical care illnesses. We received half of the grant in November 2010 and the second half in February 2011.

In August 2012, we were awarded a \$3.8 million, five-year contract by DARPA for our “Dialysis-Like Therapeutics” (“DLT”), program to treat sepsis. DARPA has been instrumental in funding many of the major technological and medical advances since its inception in 1958, including development of the Internet, development of GPS, and robotic surgery. The DLT program in sepsis seeks to develop a therapeutic blood purification device that is capable of identifying the cause of sepsis (e.g., cytokines, toxins, pathogens, activated cells) and remove these substances in an intelligent, automated, and efficient manner. Our contract is for advanced technology development of our hemocompatible porous polymer technologies to remove cytokines and a number of pathogen and biowarfare toxins from blood. We are in Year 5 of the program and are currently working with the systems integrator, Battelle Laboratories, and its subcontractor NxStage Medical, who are responsible for integrating the technology developed by us and others into a final medical device design prototype, and evaluating this device in septic animals and eventually in human clinical trials in sepsis. Our work is supported by DARPA and SSC Pacific under Contract No. N66001-12-C-4199. In June 2016, this contract was amended to change the maximum funding to approximately \$3,825,000. As of December 31, 2016, we have received approximately \$3,739,000 in funding under this contract and have approximately \$86,000 remaining under this contract.

In September 2012, we were awarded a Phase II SBIR contract by the U.S. Army Medical Research and Material Command to evaluate our technology for the treatment of trauma and burn injury in large animal models. In 2013, we finalized the Phase II SBIR contract which provided for a maximum funding of approximately \$803,000 with the granting agency. This work is supported by the U.S. Army Medical Research and Material Command under an amendment to Contract W81XWH-12-C-0038. In June 2016, this contract was further amended to increase the maximum funding by \$443,000 to approximately \$1,246,000. As of December 31, 2016, we received approximately \$1,025,000 in funding under this contract and have approximately \$221,000 remaining under this contract.

In June 2013, we announced that the U.S. Air Force was funding a 30 patient, single site, randomized controlled human pilot study of CytoSorb to evaluate patients with severe trauma and rhabdomyolysis. The primary endpoint for this study was myoglobin removal. Though we did not expect to receive material direct funding from this \$3.0 million budgeted program, it was hoped that the study would generate valuable data that could be used commercially by us or in our future trauma studies. However, because of the stringency of the inclusion criteria, and because of the patient mix seen at the single clinical trial site, the study experienced difficulty in enrolling patients. In an effort to increase enrollment, in 2015 we amended the applicable study protocol to modify the key inclusion criteria and expand the number of clinical trial sites. Unfortunately, these amendments did not result in increased enrollment. In December 2016, we contacted the Contracting Officer’s representative for the study to discuss potential options and alternatives, including closing the study. Due to the continued difficulty in enrolling patients in this study and likelihood this would continue without significant modification to the protocol, we determined, together with the U.S. Air Force, to close the study. This included notification of the San Antonio Military Medical Center (primary study site) Ethics Committee that occurred and was acknowledged on January 4, 2017. In addition, we are in the process of notifying

the U.S. Food and Drug Administration that the study will officially be closed.

In September 2013, the NHLBI awarded us a Phase I SBIR contract, (contract number HHSN-268201-300044C), valued at \$203,351, to further advance our HemoDefend blood purification technology for pRBC transfusions. The University of Dartmouth collaborated with us as a subcontractor on the project, entitled “Elimination of blood contaminants from pRBCs using HemoDefend hemocompatible porous polymer beads.” The overall goal of this program is to reduce the risk of potential side effects of blood transfusions, and help to extend the useful life of pRBCs. Our performance under this contract has been completed.

In October 2015, we were awarded a Phase II SBIR contract by the NHLBI to help advance our HemoDefend blood purification technology towards commercialization for the purification of pRBC transfusions. The contract, entitled “pRBCs Contaminant Removal with Porous Polymer Beads” (contract number HHSN-268201-600006C), provides for maximum funding of approximately \$1,522,000 over a two year period. As of December 31, 2016, we have received approximately \$502,000 and have approximately \$1,020,000 remaining under this contract.

In March 2016, we were awarded a Phase I SBIR contract for its development program entitled “Mycotoxin Absorption with Hemocompatible Porous Polymer Beads.” The purpose of this contract is to develop effective blood purification countermeasures for weaponized mycotoxins that can be easily disseminated in water, food and air. This work is being funded by the U.S. Joint Program Executive Office for Chemical and Biological Defense, or JPEO-CBD, under contract number W911QY-16-P-0048 and provides for maximum funding of \$150,000. As of December 31, 2016, we received approximately \$125,000 and have approximately \$25,000 remaining under this contract.

In June 2016, we were awarded a Phase I Small Business Technology Transfer (“STTR”) contract for its development program entitled “Use of Highly Porous Polymer Beads to Remove Anti-A and Anti-B antibodies from Plasma for Transfusion”. The purpose of this contract is to develop our HemoDefend blood purification technology to potentially enable universal plasma. This work is being funded by the USAMRAA under contract W81XWH-16-C-0025 and provides for maximum funding of \$150,000. As of December 31, 2016, we received approximately \$150,000 and no funding remaining under this contract.

In July 2016, we were awarded a Phase I Small Business Innovation Research (“SBIR”) contract for its development program entitled “Investigation of a sorbent-based potassium adsorber for the treatment of hyperkalemia induced by traumatic injury and acute kidney injury in austere conditions”. The objective of this Phase I project is to develop two novel and distinct treatment options for life-threatening hyperkalemia. This work is being funded by the U.S. Army Medical Research Acquisition Activity (“USAMRAA”) under contract W81XWH-16-C-0080 and provides for maximum funding of approximately \$150,000. As of December 31, 2016, we received approximately \$75,000 and have approximately \$75,000 remaining under this contract.

In January 2017, the Company was awarded a Phase II contract to continue development of CytoSorb for fungal mycotoxin blood purification. This program will focus on demonstrating the ability of CytoSorb to absorb mycotoxins *in vivo* and improve survival in animals. This contract provides for maximum funding of \$999,996 over two years. This program is funded by the Chemical and Biological Defense (“CBD”) SBIR program. Funding is expected to begin during the first quarter of 2017.

Our business could be adversely impacted by automatic cuts in Federal spending. The American Taxpayer Relief Act (“ATRA”) of 2012, referred to generally as the fiscal cliff deal, that went into effect on March 1, 2013, enacted automatic spending cuts of nearly \$1 trillion over the next 10 years (commonly known as sequestration) that were included under the Budget Control Act of 2011. Sequestration may delay payments under the DARPA and SBIR grant agreements, although no material delays have occurred to date. The short term and long term economic impact of the sequestration will not be known until the actual spending cuts are implemented and the economic impact of the changes in the budget and taxes are known. It will take an extended number of years to understand the impact of any changes brought about from the sequester.

These grants represent a substantial research cost savings to us and we believe demonstrate the strong interest of the medical and scientific communities in our technology. We are also exploring potential eligibility in several other government-sponsored grant programs which could, if approved, represent a substantial future source of non-dilutive funds for our research programs.

Regulation

The medical devices that we manufacture are subject to regulation by numerous regulatory bodies, including the FDA and comparable international regulatory agencies. These agencies require manufacturers of medical devices to comply with applicable laws and regulations governing the development, testing, manufacturing, labeling, marketing and distribution of medical devices. Devices are generally subject to varying levels of regulatory control, the most comprehensive of which requires that a clinical evaluation program be conducted before a device receives approval for commercial distribution.

In the EU, medical devices are required to comply with the Medical Devices Directive and obtain CE Mark certification in order to market medical devices. The CE Mark certification, granted following approval from an independent Notified Body, is an international symbol of adherence to quality assurance standards and compliance with applicable European Medical Devices Directives. Distributors of medical devices may also be required to comply with other foreign regulations such as Ministry of Health Labor and Welfare approval in Japan. The time required to obtain these foreign approvals to market our products may be longer or shorter than that required in the U.S., and requirements for those approvals may differ from those required by the FDA. In Europe, our devices are classified as Class IIb, and will need to conform to the Medical Devices Directive.

In March 2011, we successfully completed our technical file review with our Notified Body, and received approval to apply the CE Mark to the CytoSorb device as an extracorporeal cytokine filter. We also achieved ISO 13485:2003 Full Quality Systems certification, an internationally recognized quality standard designed to ensure that medical device manufacturers have the necessary comprehensive management systems in place to safely design, develop, manufacture and distribute medical devices in the EU. In February 2015, we extended the coverage of our ISO 13485 Certificate with the inclusion of Canadian Quality Systems requirements. This additional level of certification will allow us to apply for product approvals in Canada in the future.

In June 2016, we successfully completed an ISO 13485:2003 annual surveillance audit maintaining our good standing with our Notified Body. In September 2016, we were granted a two-year renewal for the CytoSorb CE Mark.

In the U.S., specific permission from FDA to distribute a new device is usually required (that is, other than in the case of very low risk devices), and we expect that some form of marketing authorization will be necessary for our devices. Marketing authorization is generally sought and obtained in one of two ways. The first process requires that a pre-market notification (510(k) Submission) be made to the FDA to demonstrate that the device is as safe and effective as, or “substantially equivalent” to, a legally marketed device that is not subject to pre-market approval (“PMA”). A legally marketed device is a device that (i) was legally marketed prior to May 28, 1976, (ii) has been reclassified from Class III to Class II or I, or (iii) has been found to be substantially equivalent to another legally marketed device following a 510(k) Submission. The legally marketed device to which equivalence is drawn is known as the “predicate”

device. Applicants must submit descriptive data and, when necessary, performance data to establish that the device is substantially equivalent to a predicate device. In some instances, data from human clinical studies must also be submitted in support of a 510(k) Submission. If so, these data must be collected in a manner that conforms with specific requirements in accordance with federal regulations including the Investigational Device Exemption (IDE) and human subjects protections or “Good Clinical Practice” regulations. After the 510(k) application is submitted, the applicant cannot market the device unless FDA issues “510(k) clearance” deeming the device substantially equivalent. After an applicant has obtained clearance, the changes to existing devices covered by a 510(k) Submission which do not significantly affect safety or effectiveness can generally be made without additional 510(k) Submissions, but evaluation of whether a new 510(k) is needed is a complex regulatory issue, and changes must be evaluated on an ongoing basis to determine whether a proposed change triggers the need for a new 510(k), or even PMA. The 510(k) clearance pathway is not available for all devices: whether it is a suitable path to market depends on several factors, including regulatory classifications, the intended use of the device, and technical and risk-related issues for the device.

The second, more rigorous, process requires that an application for PMA be made to the FDA to demonstrate that the device is safe and effective for its intended use as manufactured. This approval process applies to most Class III devices. A PMA submission includes data regarding design, materials, bench and animal testing, and human clinical data for the medical device. Again, clinical trials are subject to extensive FDA regulation. Following completion of clinical trials and submission of a PMA, the FDA will authorize commercial distribution if it determines there is reasonable assurance that the medical device is safe and effective for its intended purpose. This determination is based on the benefit outweighing the risk for the population intended to be treated with the device. This process is much more detailed, time-consuming, and expensive than the 510(k) process. Also, FDA may impose a variety of conditions on the approval of a PMA.

In the U.S., we believe that our potential devices, if we were to pursue marketing authorization, would likely fall under the classification for “Sorbent Hemoperfusion Systems” (21 C.F.R. § 876.5870). This category of device is Class II (subject to a 510(k) and special controls) when the device is intended for the treatment of poisoning and drug overdose, and Class III (subject to premarket approval) when the device is intended for the treatment of sepsis, hepatic coma and metabolic disturbances or other life-threatening illnesses.

Both before and after a device for the U.S. market is commercially released, we would have ongoing responsibilities under FDA regulations. The FDA reviews design and manufacturing practices, labeling and record keeping, and manufacturers’ required reports of adverse experiences and other information to identify potential problems with marketed medical devices. We would also be subject to periodic inspection by the FDA for compliance with the FDA’s quality system regulations, which govern the methods used in, and the facilities and controls used for, the design, manufacture, packaging, and servicing of all finished medical devices intended for human use. In addition, the FDA and other U.S. regulatory bodies (including the Federal Trade Commission, the Office of the Inspector General of the Department of Health and Human Services, the Department of Justice (DOJ), and various state Attorneys General) monitor the manner in which we promote and advertise our products. Although physicians are permitted to use their medical judgment to employ medical devices for indications other than those cleared or approved by the FDA, we are prohibited from promoting products for such “off-label” uses, and can only market our products for cleared or approved uses. If the FDA were to conclude that we are not in compliance with applicable laws or regulations, or that any of our medical devices are ineffective or pose an unreasonable health risk, the FDA could require us to notify health professionals and others that the devices present unreasonable risks of substantial harm to the public health, order a recall, repair, replacement, or refund of such devices, detain or seize adulterated or misbranded medical devices, or ban such medical devices. The FDA may also impose operating restrictions, enjoin and/or restrain certain conduct resulting in violations of applicable law pertaining to medical devices, including a hold on approving new devices until issues are resolved to its satisfaction, and assess civil or criminal penalties against our officers, employees, or us. The FDA may also recommend prosecution to the DOJ. Conduct giving rise to civil or criminal penalties may also form the basis for private civil litigation by third-party payers or other persons allegedly harmed by our conduct.

The delivery of our devices in the U.S. market would be subject to regulation by the U.S. Department of Health and Human Services and comparable state agencies responsible for reimbursement and regulation of health care items and services. U.S. laws and regulations are imposed primarily in connection with the Medicare and Medicaid programs, as well as the government’s interest in regulating the quality and cost of health care.

Federal health care laws apply when we or customers submit claims for items or services that are reimbursed under Medicare, Medicaid, or other federally-funded health care programs. The principal federal laws include: (1) the False Claims Act which prohibits the submission of false or otherwise improper claims for payment to a federally-funded health care program; (2) the Anti-Kickback Statute which prohibits offers to pay or receive remuneration of any kind for the purpose of inducing or rewarding referrals of items or services reimbursable by a Federal health care program; (3) the Stark law which prohibits physicians from referring Medicare or Medicaid patients to a provider that bills these programs for the provision of certain designated health services if the physician (or a member of the physician’s immediate family) has a financial relationship with that provider; and (4) health care fraud statutes that prohibit false statements and improper claims to any third-party payer. There are often similar state false claims, anti-kickback, and

anti-self referral and insurance laws that apply to state-funded Medicaid and other health care programs and private third-party payers. In addition, the U.S. Foreign Corrupt Practices Act can be used to prosecute companies in the U.S. for arrangements with physicians, or other parties outside the U.S. if the physician or party is a government official of another country and the arrangement violates the law of that country.

The laws applicable to us are subject to change, and subject to evolving interpretations. If a governmental authority were to conclude that we are not in compliance with applicable laws and regulations, we and our officers and employees could be subject to severe criminal and civil penalties including substantial fines and damages, and exclusion from participation as a supplier of product to beneficiaries covered by Medicare or Medicaid.

The process of obtaining clearance to market products is costly and time-consuming in virtually all of the major markets in which we expect to sell products and may delay the marketing and sale of our products. Countries around the world have recently adopted more stringent regulatory requirements, which are expected to add to the delays and uncertainties associated with new product releases, as well as the clinical and regulatory costs of supporting those releases. No assurance can be given that any of our other medical devices will be approved on a timely basis, if at all, or that our CytoSorb® device will be approved for CE Mark labeling in other potential medical applications or that it will be approved for cytokine filtration in markets not covered by the CE Mark on a timely basis, or at all. In addition, regulations regarding the development, manufacture and sale of medical devices are subject to future change. We cannot predict what impact, if any, those changes might have on our business. Failure to comply with regulatory requirements could have a material adverse effect on our business, financial condition and results of operations.

Pertaining to our VetResQ™ device (offered for veterinary use only), in the U.S., the FDA does not require submission of a 510(k), PMA, or any pre-market approval for devices used in veterinary medicine. Device manufacturers who exclusively manufacture or distribute veterinary devices are not required to register their establishments and list veterinary devices and are exempt from post-marketing reporting. FDA does have regulatory oversight over veterinary devices and can take appropriate regulatory action if a veterinary device is misbranded or adulterated. It is the responsibility of the manufacturer and/or distributor of these articles to assure that these animal devices are safe, effective, and properly labeled.

Exported devices are subject to the regulatory requirements of each country to which the device is exported. Some countries do not have medical device regulations, but in most foreign countries medical devices are regulated. Frequently, device companies may choose to seek and obtain regulatory approval of a device in a foreign country prior to application in the U.S., as we have done, given the differing regulatory requirements. However, this does not ensure approval of a device in the U.S.

Sales and Marketing

In 2012, we established our European subsidiary, CytoSorbents Europe GmbH, a wholly-owned subsidiary of CytoSorbents Corporation. Following the completion of a controlled market release in late June 2012, CytoSorb was formally launched in Germany with reimbursement established at more than \$500 per cartridge. We recruited Dr. Christian Steiner, MD as our Vice President of Sales and Marketing and hired three additional sales representatives who completed training in the third quarter of 2012. The fourth quarter of 2012 was the first full quarter of direct CytoSorb sales with our sales force in place. We began expansion into Austria, where reimbursement for CytoSorb is now available, and Switzerland. In March 2016, we established CytoSorbents Switzerland GmbH, a wholly-owned subsidiary of CytoSorbents Europe GmbH, to conduct marketing and direct sales in Switzerland. This subsidiary began operations during the second quarter of 2016. From the beginning of the controlled market release in the fourth quarter of 2011 through the end of December 31, 2016, we achieved cumulative sales of CytoSorb of approximately \$16,395,000. During this time period, the CytoSorb device represented substantially all of our product sales. At the end of 2016, we had hundreds of KOLs worldwide who are either using CytoSorb or supporting its use in clinical

practice and/or in clinical studies. These relationships with KOLs were an essential step in our initial goal of driving usage, adoption and reorders of CytoSorb as they facilitate ordering and reimbursement within the hospital, have a strong influential role within their department and amongst their peers and colleagues outside the hospital, and have the ability to conduct studies and generate data, papers and conference presentations that could drive awareness and demand.

We are approved to sell CytoSorb in all 28 countries in the EU, including Germany, United Kingdom, Italy, France and Spain, and currently have either direct sales or distributor or strategic partnership in 42 countries worldwide. We plan to expand to other countries in the EU, and with registration, other countries outside the EU that will accept CE Mark approval with a mixed direct and independent distributor strategy, that can be augmented through strategic partnerships.

In 2013, we reached agreements with distributors in the United Kingdom, Ireland, Turkey, Russia, and the Netherlands. In April 2014, we announced distribution of CytoSorb in the Middle East, including Saudi Arabia, the United Arab Emirates, Kuwait, Qatar, Bahrain, and Oman (the GCC) and Yemen, Iraq, and Jordan through an exclusive agreement with Techno Orbits. In August 2014, we announced exclusive distribution of CytoSorb in Taiwan with Hemoscien Corporation, which was subsequently terminated by us in March 2015 due to the complexity of Taiwanese FDA product registration. In December 2014, we entered into an exclusive agreement with Smart Medical Solutions S.R.L., to distribute CytoSorb for critical care applications in Romania and the neighboring Republic of Moldova. In 2015, we announced exclusive distribution agreements with Aferetica SRL to distribute CytoSorb in Italy, AlphaMedix Ltd. to distribute CytoSorb in Israel, TekMed Pty Ltd. to distribute CytoSorb in Australia and New Zealand, and Hoang Long Pharma to distribute CytoSorb in Vietnam. In June 2016, we announced an exclusive distribution agreement with Palex Medical SA to distribute CytoSorb in Spain and Portugal. In September 2016, we announced an exclusive agreement with Armaghan Salamat Kish Group (Arsak) to distribute CytoSorb in Iran. In October 2016, we announced an exclusive agreement with Foxx Medical Chile SpA to distribute CytoSorb in Chile.

We have been expanding the number and scope of our strategic partnerships. In September 2013, we entered into a strategic partnership with Biocon, Ltd., Asia's largest biotech company with an initial distribution agreement for India and select emerging markets, under which Biocon will have the exclusive commercialization rights for CytoSorb initially focused on sepsis. In October 2014, the Biocon partnership was expanded to include all critical care applications and cardiac surgery. In addition, Biocon committed to higher annual minimum purchases of CytoSorb to maintain distribution exclusivity and conduct and publish results from multiple Investigator Initiated studies and patient case studies.

In December 2014, we entered into a multi-country strategic partnership with Fresenius Medical Care AG & CO KGaA to commercialize the CytoSorb therapy. Under the terms of the agreement, Fresenius Medical Care has exclusive rights to distribute CytoSorb for critical care applications in France, Poland, Sweden, Denmark, Norway, and Finland. The partnership will allow Fresenius Medical Care to offer an innovative and easy to use blood purification therapy for removing cytokines in patients that are treated in the ICU. To promote the success of CytoSorb, Fresenius will also engage in the ongoing clinical development of the product. This includes the support and publication of a number of small case series and patient case reports as well as the potential for future larger, clinical collaborations. In January 2017, the Fresenius partnership was expanded. The terms of the revised three-year agreement extend Fresenius' exclusive distributorship of CytoSorb for all critical care applications in their existing territories through 2019 and include guaranteed minimum quarterly orders and payments, evaluable every one and a half years. In addition, we have entered into a new comprehensive co-marketing agreement with Fresenius. Under the terms of the agreement, Cytosorbents and Fresenius will jointly market CytoSorb and Fresenius' CytoSorb compatible blood tubing sets to Fresenius' critical care customer base in all countries where CytoSorb is being actively commercialized. Fresenius will also provide a written endorsement of CytoSorb for use with their multiFiltrate and multiFiltratePRO acute care dialysis machines that can be used by us and our distribution partners to promote CytoSorb worldwide. Training and preparation for this co-marketing program is ongoing and it is expected that co-marketing activity will commence during the second half of 2017.

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A significant portion of our revenues are from product sales in Germany. Substantially all of our grant and other income are from grant agencies in the United States. The following table provides a geographic summary of revenues:

	2016	2015	2014
Product Sales:			
United States	\$—	\$—	\$—
Germany	4,985,049	2,353,998	1,405,125
All other countries	3,220,987	1,689,821	1,730,262
Grant and other income:			
United States	1,321,807	735,863	987,438
Germany	—	11,934	—
All other countries	—	—	—
Total Revenue	\$9,527,843	\$4,791,616	\$4,122,825

In 2016, one direct customer, HDZ Herz and Diabeteszentrum NRW, accounted for approximately 11 percent of total revenue. In 2015, one grant agency, DARPA, accounted for approximately 14 percent of revenue. In 2014, one distributor, Biocon, Ltd, accounted for approximately 12 percent of total revenue.

We maintain a small amount of property and equipment in Germany. These assets were less than one percent of total assets for the years ending December 31, 2016, 2015 and 2014, respectively.

Intellectual Property and Patent Litigation

The medical device market in which we primarily participate is in large part technology driven. As a result, intellectual property rights, particularly patents and trade secrets, play a significant role in product development and differentiation. However, intellectual property litigation to defend or create market advantage is inherently complex, unpredictable and is expensive to pursue. Litigation often is not ultimately resolved until an appeal process is completed and appellate courts frequently overturn lower court patent decisions.

Moreover, competing parties frequently file multiple suits to leverage patent portfolios across product lines, technologies and geographies and to balance risk and exposure between the parties. In some cases, several competitors are parties in the same proceeding, or in a series of related proceedings, or litigate multiple features of a single class of devices. These forces frequently drive settlement not only of individual cases, but also of a series of pending and potentially related and unrelated cases. In addition, although monetary and injunctive relief is typically sought, remedies are generally not determined until the conclusion of the proceedings, and are frequently modified on appeal. Accordingly, the outcomes of individual cases are difficult to time, predict or quantify and are often dependent upon the outcomes of other cases in other forums, both domestic and international.

We rely on a combination of patents, trademarks, trade secrets and non-disclosure agreements to protect our intellectual property. We hold 32 issued U.S. patents, some of which have foreign counterparts, and additional patent applications pending worldwide that cover various aspects of our technology. The issued patents expire at various dates ranging from one to ten years. The following table provides a brief description of our patents that have been issued in the U.S.:

Product Group	Description/Indications	Patent Term	Patent Expiration	Patent Type
CytoSorb	Method of Removing Beta-2 Microglobulin Using Hypercrosslinked Polystyrene-Type Resins	20 Years	7/30/2017	Standard
CytoSorb	Method of Removing Beta-2 Microglobulin Using Polymers with Surface-Exposed Vinyl Groups Modified for Biocompatibility	20 Years	7/30/2017	Standard
CytoSorb	Devices, Systems & Methods for Reducing Cytokines, Etc in Plasma and Other Separated Blood Components	20 Years	7/30/2017	Standard
CytoSorb	Biocompatible Devices, Systems & Methods for Reducing levels of Pro-Inflammatory and Anti-Inflammatory Stimulators or mediators in Blood	20 Years	7/30/2017	Standard

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CytoSorb	Methods for reducing levels of pro-inflammatory or anti-inflammatory stimulators or mediators in the blood	20 Years	7/30/2017	Standard
CytoSorb	Biocompatible Devices, Systems & Methods for Reducing levels of Pro-Inflammatory and Anti-Inflammatory Stimulators or mediators in Blood	20 Years	7/30/2017	Standard
CytoSorb	Biocompatible Devices, Systems, and Methods for Reducing Levels of Pro-Inflammatory or Anti-Inflammatory Stimulators or Mediators in the Blood	20 Years	7/30/2017	Standard
CytoSorb	Devices, Systems, and Methods for Reducing Levels of Pro-Inflammatory or Anti-Inflammatory Stimulators or Mediators in Blood Products	20 Years	7/30/2017	Standard
CytoSorb	Material for Purification: DVB Copolymer with Surface Vinyl Groups Modified to One of Four Functional Groups	20 Years	2/6/2018	Standard
CytoSorb	Method of Producing Material: Chloromethylated Styrene or DVB Polymers with Chlorine Replaced for Improved Biocompatibility	20 Years	2/6/2018	Standard

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CytoSorb	Method of Purification Using DVB Copolymer with Surface-Exposed Vinyl Groups Modified for Biocompatibility	20 Years	2/6/2018	Standard
CytoSorb	Material and Method of Producing: Chloromethylated Styrene or DVB Polymers with Chlorine Replaced for Improved Biocompatibility	20 Years	2/6/2018	Standard
CytoSorb	Method of Producing Material: DVB Copolymer with No Endotoxin Contamination	20 Years	2/6/2018	Standard
CytoSorb	Material for Purification: DVB Copolymer with Surface Vinyl Groups Modified in Three Ways for Biocompatibility	20 Years	2/6/2018	Standard
CytoSorb	Method of Purification Using Chloromethylated Styrene or DVB Polymers with Chlorine Replaced for Improved Biocompatibility	20 Years	2/6/2018	Standard
CytoSorb	Method of Producing Material: Polymer with Modification of Surface-Exposed Vinyl Groups	20 Years	2/6/2018	Standard
CytoSorb	Material and Method of Producing: Chloromethylated Polymers with Chlorine Replaced for Improved Biocompatibility	20 Years	2/6/2018	Standard
CytoSorb	Method of Producing Material: Polymer with Modification of Surface-Exposed Vinyl Groups	20 Years	12/14/2018	Standard
CytoSorb	Method of and Device for Introducing Fluids into a Patient's Body	20 Years	2/14/2020	Standard
CytoSorb	Perfusion Device Combining Adsorbing Material and Hollow Fibers to Filter and Recombine Plasma	20 Years	4/17/2020	Standard
CytoSorb	Method of Peritoneal Dialysis	20 Years	4/27/2020	Standard
CytoSorb	Material and Method of Producing: Biocompatible Polymeric Adsorbents Using a One-Pot Process	20 Years	10/10/2020	Standard
CytoSorb	Protective clothing	20 Years	2/14/2021	Standard
CytoSorb	Devices, systems, and methods for reducing levels of pro-inflammatory or anti-inflammatory stimulators or mediators in the blood	20 Years	4/10/2021	Standard
CytoSorb	Method of Producing Devices	20 Years	4/25/2021	Standard
CytoSorb	Hemocompatible Coated Polymer and Related One-Step Methods	20 Years	10/18/2022	Standard
CytoSorb	Hemocompatible Coated Polymer and Related Methods	20 Years	10/18/2022	Standard
CytoSorb	Hemocompatible Coated Polymer and Related One-Step Methods	20 Years	10/18/2022	Standard
CytoSorb	Hemocompatible Polymer Systems And Related Devices	20 Years	10/18/2022	Standard
CytoSorb	Size-Selective Hemoperfusion Polymeric Adsorbents	20 Years	11/20/2026	Standard
CytoSorb	Size-Selective Hemoperfusion Polymeric Adsorbents	20 Years	11/20/2026	Standard
CytoSorb	Size Selective Polymer System	20 Years	11/2/2026	Standard

There can be no assurance that pending patent applications will result in issued patents, that patents issued to us will not be challenged or circumvented by competitors, or that such patents will be found to be valid or sufficiently broad to protect our technology or to provide us with a competitive advantage. Certain of these patents also have foreign counterparts.

We also rely on non-disclosure and non-competition agreements with employees, consultants and other parties to protect, in part, trade secrets and other proprietary technology. There can be no assurance that these agreements will not be breached, that we will have adequate remedies for any breach, that others will not independently develop equivalent proprietary information or that third parties will not otherwise gain access to our trade secrets and proprietary knowledge.

Prior to the year 2000, we engaged in discussions with the Dow Chemical Company, (“Dow”), which had indicated a strong interest in being our polymer manufacturer. After a Dow representative on our Advisory Board resigned, Dow filed and received five patents naming our former Advisory Board member as an inventor. These patents, two of which subsequently lapsed for failure to pay maintenance fees, concern the area of coating high divinylbenzene-content polymers to render them hemocompatible, and using such coated polymers to treat blood or plasma. In management’s view the Dow patents improperly incorporate our technology, are based on our proprietary technology, and should not have been granted to Dow. While we believe that our own patents would prevent Dow from producing our products as they are currently envisioned, Dow could attempt to assert its patents against us. To date, to our knowledge, Dow has not utilized their patents for the commercial manufacture of products that would be competitive with us, and we currently have no plans to challenge Dow’s patents. However, the existence of these Dow patents could result in a potential dispute with Dow in the future and additional expenses for us.

We may find it necessary to initiate litigation to enforce our patent rights, to protect our trade secrets or know-how and to determine the scope and validity of the proprietary rights of others. Patent litigation can be costly and time-consuming, and there can be no assurance that our litigation expenses will not be significant in the future or that the outcome of litigation will be favorable to us. Accordingly, we may seek to settle some or all of our pending litigation described below. Settlement may include cross-licensing of the patents which are the subject of the litigation as well as our other intellectual property and may involve monetary payments to or from third parties.

We currently hold multiple trademarks including CytoSorb®, HemoDefend™, BetaSorb™, and VetResQ™. We have spent considerable resources registering the trademark and building brand awareness and equity of the CytoSorb® tradename, which has been used in commerce since 2006. We expect to maintain and defend our various trademarks to the fullest extent possible.

Environmental Matters

We believe that there are no compliance issues associated with applicable environmental laws and regulations that would have a material adverse effect on us or our business. We incur waste removal costs in connection with both our solid and liquid wastes which are byproducts of our manufacturing process. We utilize the services of various qualified contractors to dispose of these waste products. These waste removal costs amounted to approximately \$200,000 for the year ended December 31, 2016.

Employees

As of February 1, 2017 we had 65 full-time employees. We also utilize consultants and temporary service providers who are not our employees, as necessary. None of our employees are represented by a labor union or are subject to collective-bargaining agreements.

Financial Information

Our Financial Statements and notes thereto are included elsewhere in this Annual Report on Form 10-K and incorporated herein by reference. See Item 15 of Part IV.

Item 1A. Risk Factors

Risks Related to our Business and our Industry

We have a history of losses and expect to incur substantial future losses, and the report of our auditor on our consolidated financial statements expresses substantial doubt about our ability to continue as a going concern.

We have experienced substantial operating losses since inception. As of December 31, 2016, we had an accumulated deficit of approximately \$144,465,000, which included net losses of approximately \$11,939,000, \$8,132,000 and \$9,322,000 for the years ended December 31, 2016, 2015 and 2014, respectively. Due in part to these losses, our audited consolidated financial statements have been prepared assuming we will continue as a going concern, and the auditors' report on those financial statements express substantial doubt about our ability to continue as a going concern. Our losses have resulted principally from costs incurred in the research and development of our polymer technology and general and administrative expenses. We intend to conduct significant additional research, development, and clinical study activities which, together with expenses incurred for the establishment of manufacturing arrangements and a marketing and distribution presence and other general and administrative expenses, are expected to result in continuing operating losses for the foreseeable future. The amount of future losses and when, if ever, we will achieve profitability are uncertain. Our ability to achieve profitability will depend, among other things, on continued adoption and usage of our products in the market, obtaining additional regulatory approvals in markets not covered by the CE Mark, establishing sales and marketing arrangements with third parties, satisfactory reimbursement in key territories, and raising sufficient funds to finance our activities. No assurance can be given that our product development efforts will be successful, that our current CE Mark will enable us to achieve profitability, that additional regulatory approvals in other countries will be obtained, that any of our products will be manufactured at a competitive cost and will be of acceptable quality, that reimbursement will be available or satisfactory, that we will be able to achieve profitability or that profitability, if achieved, can be sustained, or our ability to raise additional capital when needed or on terms acceptable to us. Our failure with respect to any or all of these matters would have a material adverse effect on our business, operating results, financial condition and prospects.

We will require additional capital in the future to fund our operations.

As of December 31, 2016, we had current assets of approximately \$7,828,000, including cash on hand of approximately \$5,245,000 and current liabilities of approximately \$6,090,000. For the year ended December 31, 2016, our cash burn was approximately \$8.0 million. Our current and historical cash burn is not necessarily indicative of our future use of cash and cash equivalents.

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We will require additional financing in the future in order to complete additional clinical studies and to support the commercialization of our proposed products. There can be no assurance that we will be successful in our capital raising efforts. Our long-term capital requirements are expected to depend on many factors, including:

- continued progress and cost of our research and development programs;
- progress with pre-clinical studies and clinical studies;
- the time and costs involved in obtaining regulatory clearance in other countries and/or for other indications;
- costs involved in preparing, filing, prosecuting, maintaining, defending and enforcing patent claims;
- costs of developing sales, marketing and distribution channels;
- market acceptance and reimbursement of our products; and
- cost for training physicians and other health care personnel.

We have a effective shelf registration statement with the SEC which enables us to raise up to \$100 million in equity financing. We entered into a Controlled Equity OfferingSM Sales Agreement with Cantor Fitzgerald & Co. in November 2015 for the offer and sale of up to an aggregate of \$25,000,000 of shares of our common stock. In addition, we entered into a Loan and Security Agreement dated as of June 30, 2016 with Bridge Bank, a division of Western Alliance Bank, to provide up to an aggregate of \$10,000,000 to the Company. Despite the foregoing, we expect we will require additional financing. Should the financing we require be unavailable to us, or on terms unacceptable to us when we require it, the consequences could have a material adverse effect on our business, operating results, financial condition and prospects.

In addition, in the event that additional funds are obtained through arrangements with collaborative partners or other non-dilutive sources, we may have to relinquish economic and/or proprietary rights to some of our technologies or products under development that we would otherwise seek to develop or commercialize by ourselves. Such events may have a material adverse effect on our business, operating results, financial condition and prospects.

Although historically we have been a research and development company, we are in the process of commercializing our products. There can be no assurance that we will be successful in developing and expanding commercial operations or balancing our research and development activities with our commercialization activities.

We have historically been engaged primarily in research and development activities and have generated limited revenues to date. With the launch of our CytoSorb product in the EU and abroad, there can be no assurance that we will be able to successfully manage the balance of our research and development operations with our planned commercial enterprise. Potential investors should be aware of the problems, delays, expenses and difficulties frequently encountered by an enterprise in balancing development, which include unanticipated problems relating to testing, product registration, regulatory compliance and manufacturing, with commercialization, which includes problems with market adoption, reimbursement, marketing problems and additional costs. Our products and product candidates will require significant additional research and testing, and we will need to overcome significant regulatory burdens prior to commercialization in other countries, such as the U.S., and for ongoing compliance for our CE Mark. We will also need to raise significant additional funds to complete additional clinical studies and obtain regulatory approvals in other countries before we can begin selling our products in markets not covered by our CE Mark. In addition, we may be required to spend significant funds on building out our commercial operations. There can be no assurance that after the expenditure of substantial funds and efforts, we will successfully develop and commercialize any products, generate any significant revenues or ever achieve and maintain a substantial level of sales of our products.

If users of our products are unable to obtain adequate reimbursement from third-party payers, or if reimbursement is not available in specific countries, or if new restrictive legislation is adopted, market acceptance of our products may be limited and we may not achieve anticipated revenues.

The continuing efforts of government and insurance companies, health maintenance organizations and other payers of healthcare costs to contain or reduce costs of health care may affect our future revenues and profitability, the future revenues and profitability of our potential customers, suppliers and collaborative partners, and the availability of capital. For example, in certain foreign markets, pricing or profitability of medical devices is subject to government control. In the United States, given recent federal and state government initiatives directed at lowering the total cost of health care, the U.S. Congress and state legislatures will likely continue to focus on health care reform, the cost of medical devices and on the reform of the Medicare and Medicaid systems. While we cannot predict whether any such legislative or regulatory proposals will be adopted, the announcement or adoption of these proposals could materially harm our business, financial condition and results of operations.

Our ability to commercialize our products will depend in part on the extent to which appropriate reimbursement levels for the cost of our products and related treatment are obtained by governmental authorities, private health insurers and other organizations, such as health maintenance organizations (“HMOs”). Third-party payers are increasingly challenging the prices charged for medical care. Also, the trend toward managed health care in the United States and the concurrent growth of organizations such as HMOs, which could control or significantly influence the purchase of

health care services and medical devices, as well as legislative proposals to reform health care or reduce government insurance programs, may all result in lower prices for our products. The cost containment measures that health care payers and providers are instituting and the effect of any health care reform could materially harm our ability to operate profitably.

Outside of the United States, reimbursement systems vary significantly by country. Many foreign markets often have a combination of government-managed and privately-managed healthcare systems that govern reimbursement for medical devices and related procedures. Socialized medicine is common in the EU, and reimbursement and the pricing of medical devices is often subject to governmental control. Application for reimbursement, subsequent approvals, if any, and pricing negotiations with governmental authorities can take considerable time after a device has been CE marked. Private insurance has similar challenges. CytoSorb is currently reimbursed in Germany under government-funded insurance, and in other countries may be covered under the DRG, or “lump sum payment” reimbursement, or other generalized reimbursement for acute care medical products. We are continuously working to obtain or improve upon the type and amount of reimbursement available to us in countries where CytoSorb is available, and as we attempt to move from an existing reimbursement platform to a new reimbursement platform, we may experience interruptions and/or reductions in the amount available for reimbursement. Because of this, there can be no assurance that new reimbursement will be obtained or that existing reimbursement will continue or that such reimbursement will be sufficient to adequately cover the cost of the device or treatment. As a result, our future revenues, profitability and access to capital may be negatively affected by any interruption or reduction in amounts of reimbursement. We plan to seek reimbursement for our product in other EU and non-EU countries to help further adoption. There can be no assurance when, or if, this additional reimbursement might be approved.

We depend upon key personnel who may terminate their employment with us at any time.

As of February 1, 2017, we have 65 full-time employees and several temporary employees. Our success will depend to a significant degree upon the continued services of our key management team and advisors, including, Dr. Phillip Chan, our Chief Executive Officer; Kathleen P. Bloch, our Chief Financial Officer; Vincent Capponi, our Chief Operating Officer and Dr. Robert Bartlett, our Chief Medical Officer, who works with us on a consulting basis. Although these individuals have long-term employment and consulting agreements, there can be no assurance that key management personnel or other members of our management team and advisors will continue to provide services to us. In addition, our success will depend on our ability to attract and retain other highly skilled personnel. We may be unable to recruit such personnel on a timely basis, if at all. Management and other employees may voluntarily terminate their employment with us at any time. The loss of services of key personnel, or the inability to attract and retain additional qualified personnel, could result in delays in development or approval of our products, loss of sales and diversion of management resources.

Our Chief Medical Officer works with us on a consulting basis.

Our Chief Medical Officer, Dr. Robert Bartlett, works with us on a consulting basis. Because of the part time nature of his consulting agreement, Dr. Bartlett may not always be available to provide us with his services when needed by us in a timely manner.

Acceptance of our medical devices in the marketplace is uncertain, and failure to achieve market acceptance will prevent or delay our ability to generate revenues.

Our future financial performance will depend, at least in part, upon the introduction and customer acceptance of our products. Even with CE Mark approval for our CytoSorb device as a cytokine filter, our products and product candidates may not achieve market acceptance in the countries that recognize and accept the CE Mark. Additional approvals from other regulatory authorities (such as the FDA) will be required before we can market our device in countries not covered by the CE Mark. There is no guarantee that we will be able to achieve additional regulatory approvals, and even if we do, our products may not achieve market acceptance in the countries covered by such approvals. The degree of market acceptance will depend upon a number of factors, including:

- the receipt of regulatory clearance of marketing claims for the uses that we are developing;
- the establishment and demonstration of the advantages, safety and efficacy of our polymer technology;

pricing and reimbursement policies of government and third-party payers such as insurance companies, health maintenance organizations and other health plan administrators;

our ability to attract corporate partners, including medical device companies, to assist in commercializing our products; and

our ability to effectively market our products.

Physicians, patients, payers or the medical community in general may be unwilling to accept, utilize or recommend any of our products. Approval of our CytoSorb device as a cytokine filter as well as the data we have gathered in our clinical studies to support device usage in this indication may not be sufficient for market acceptance in the medical community. We may also need to conduct additional clinical studies to gather additional data for marketing purposes. If we are unable to obtain regulatory approval or commercialize and market our products when planned, we may not achieve any market acceptance or generate revenue.

If we are unable to obtain and maintain patent protection for our products and product candidates, or if the scope of the patent protection obtained is not sufficiently broad, our competitors could develop and commercialize products and product candidates similar or identical to ours, and our ability to successfully commercialize our products and product candidates may be adversely affected.

Our commercial success will depend, in part, on our ability to obtain and maintain patent protection in the United States and other countries with respect to our products and product candidates. We seek to protect our proprietary position by filing patent applications in the United States and abroad related to our products and product candidates that are important to our business. We cannot be certain that patents will be issued or granted with respect to applications that are currently pending or that we apply for in the future with respect to one or more of our products and product candidates, or that issued or granted patents will not later be found to be invalid and/or unenforceable.

The patent prosecution process is expensive and time-consuming, and we may not be able to file and prosecute all necessary or desirable patent applications at a reasonable cost or in a timely manner. It is also possible that we will fail to identify patentable aspects of our research and development output before it is too late to obtain patent protection. Although we enter into non-disclosure and confidentiality agreements with parties who have access to patentable aspects of our research and development output, such as our employees, distribution partners, consultants, advisors and other third parties, any of these parties may breach the agreements and disclose such output before a patent application is filed, thereby jeopardizing our ability to seek patent protection.

The patent position of medical device companies generally is highly uncertain, involves complex legal and factual questions and has in recent years been the subject of much litigation. As a result, the issuance, scope, validity, enforceability and commercial value of our patent rights are highly uncertain. Our pending and future patent applications may not result in patents being issued, and even if issued, the patents may not meaningfully protect our products or product candidates, effectively prevent competitors and third parties from commercializing competitive products or otherwise provide us with any competitive advantage. Our competitors or other third parties may be able to circumvent our patents by developing similar or alternative products in a non-infringing manner.

Changes in the patent laws, implementing regulations or interpretation of the patent laws in the United States and other countries may also diminish the value of our patents or narrow the scope of our patent protection. The laws of foreign countries may not protect our rights to the same extent as the laws of the United States, and many companies have encountered significant difficulties in protecting and defending such rights in foreign jurisdictions.

We cannot be certain that our patents and patent rights will be effective in protecting our products, product candidates and technologies. In addition, certain of our existing patents expire over the next one to 10 years. Failure to protect such assets may have a material adverse effect on our business, operations, financial condition and prospects.

We may face litigation from third parties claiming that our products infringe on their intellectual property rights, or seek to challenge the validity of our patents.

Our future success is also dependent in part on the strength of our intellectual property, trade secrets and know-how, which have been developed from years of research and development. In addition to the “Purolite” litigation discussed below, we may be exposed to additional future litigation by third parties seeking to challenge the validity of our rights based on claims that our technologies, products or activities infringe the intellectual property rights of others or are invalid, or that we have misappropriated the trade secrets of others.

Since our inception, we have sought to contract with large, established manufacturers to supply commercial quantities of our adsorbent polymers. As a result, we have disclosed, under confidentiality agreements, various aspects of our technology with potential manufacturers. We believe that these disclosures, while necessary for our business, have resulted in the attempt by potential suppliers to improperly assert ownership claims to our technology in an attempt to gain an advantage in negotiating manufacturing rights.

We have previously engaged in discussions with the Brotech Corporation and its affiliate, Purolite International, Inc. (collectively referred to as "Purolite"), which had demonstrated a strong interest in being our polymer manufacturer. For a period of time beginning in December 1998, Purolite engaged in efforts to develop and optimize the manufacturing process needed to produce our polymer products on a commercial scale. However, the parties eventually decided not to proceed. In 2003, Purolite filed a lawsuit against us asserting, among other things, co-ownership and co-inventorship of certain of our patents. On September 1, 2006, the United States District Court for the Eastern District of Pennsylvania approved a Stipulated Order and Settlement Agreement under which we and Purolite agreed to the settlement of the action. The Settlement Agreement provides us with the exclusive right to use our patented technology and proprietary know how relating to adsorbent polymers for a period of 18 years. Under the terms of the Settlement Agreement, we have agreed to pay Purolite royalties of 2.5% to 5% on the sale of certain of our products if and when those products are sold commercially.

Several years ago we engaged in discussions with the Dow Chemical Company, which had indicated a strong interest in being our polymer manufacturer. After a Dow representative on our Advisory Board resigned, Dow filed and received several patents naming our former Advisory Board member as an inventor. In management's view, the Dow patents improperly incorporate our technology and should not have been granted to Dow. The existence of these Dow patents could result in a potential dispute with Dow in the future. In the event such a dispute arises, we may be forced to spend significant time and resources to defending our position. There can be no assurances that such efforts will be successful and not have a material adverse effect on our business, operating results, financial condition and prospects.

The expiration or loss of patent protection may adversely affect our future revenues and operating earnings.

We rely on patent, trademark, trade secret and other intellectual property protection in the discovery, development, manufacturing, and sale of our products and product candidates. In particular, patent protection is important in the development and eventual commercialization of our products and product candidates. Patents covering our products and product candidates normally provide market exclusivity, which is important in order for our products and product candidates to become profitable.

Certain of our patents will expire in the next one to ten years. While we are seeking additional patent coverage which may protect the technology underlying these patents, there can be no assurances that such additional patent protection will be granted, or if granted, that these patents will not be infringed upon or otherwise held enforceable. Even if we are successful in obtaining a patent, patents have a limited lifespan. In the United States, the natural expiration of a utility patent typically is generally 20 years after it is filed. Various extensions may be available; however, the life of a patent, and the protection it affords, is limited. Without patent protection for our products and product candidates, we may be open to competition from generic versions of such methods and devices.

We have commenced the process of seeking regulatory approvals of our products and product candidates, but the approval process involves lengthy and costly clinical studies and is, in large part, not in our control. The failure to obtain government approvals, internationally or domestically, for our products and product candidates, or to comply with ongoing governmental regulations could prevent, delay or limit introduction or sale of our products and result in the failure to achieve revenues or maintain our operations.

CytoSorb has already achieved marketing authorization in the EU under the CE marking process and the Medical Devices Directive. It is manufactured at our manufacturing facility in New Jersey under ISO 13485 Full Quality Systems certification. The manufacturing and marketing of our products will be subject to extensive and rigorous government regulation in the European market, the U.S., in various states and in other foreign countries. In the U.S. and other countries, the process of obtaining and maintaining required regulatory approvals is lengthy, expensive, and uncertain. There can be no assurance that we will ever obtain the necessary additional approvals to sell our products in the United States or other non EU countries. Even if we do ultimately receive FDA approval for any of our products, we will be subject to extensive ongoing regulation. While we have received approval from our Notified Body to apply the CE Mark to our CytoSorb device, we will be subject to extensive ongoing regulation and auditing requirements to maintain the CE Mark.

Our products will be subject to international regulation as medical devices under the Medical Devices Directive. In Europe, which we expect to provide the initial market for our products, the Notified Body and Competent Authority govern, where applicable, development, clinical studies, labeling, manufacturing, registration, notification, clearance or approval, marketing, distribution, record keeping, and reporting requirements for medical devices. Different regulatory requirements may apply to our products depending on how they are categorized by the Notified Body under these laws. Current international regulations classify our CytoSorb device as a Class IIb device. Even though we have received CE Mark certification of the CytoSorb device, there can be no assurance that we will be able to continue to comply with the required annual auditing requirements or other international regulatory requirements that may be applicable. In addition, there can be no assurance that government regulations applicable to our products or the interpretation of those regulations will not change. The extent of potentially adverse government regulation that might arise from future legislation or administrative action cannot be predicted. There can be no assurances that reimbursement will be granted or that additional clinical data will be required to establish reimbursement.

We have conducted limited clinical studies of our CytoSorb device. Clinical and pre-clinical data is susceptible to varying interpretations, which could delay, limit or prevent additional regulatory clearances.

To date, we have conducted limited clinical studies on our CytoSorb product. There can be no assurance that we will successfully complete additional clinical studies necessary to receive additional regulatory approvals in markets not covered by the CE Mark. While studies conducted by us and others have produced results we believe to be encouraging and indicative of the potential efficacy of our products and technology, data already obtained, or in the future obtained, from pre-clinical studies and clinical studies do not necessarily predict the results that will be obtained from later pre-clinical studies and clinical studies. Moreover, pre-clinical and clinical data are susceptible to varying interpretations, which could delay, limit or prevent additional regulatory approvals. A number of companies in the medical device and pharmaceutical industries have suffered significant setbacks in advanced clinical studies, even after promising results in earlier studies. The failure to adequately demonstrate the safety and effectiveness of an intended product under development could delay or prevent regulatory clearance of the device, resulting in delays to commercialization, and could materially harm our business. Even though we have received approval to apply the CE Mark to our CytoSorb device as a cytokine filter, there can be no assurance that we will be able to receive approval for other potential applications of CytoSorb, or that we will receive regulatory clearance from other targeted regions or countries.

We rely extensively on research and testing facilities at various universities and institutions, which could adversely affect us should we lose access to those facilities. At the same time, relationships with these individuals and entities are the subject of heightened scrutiny and may present the potential for future healthcare enforcement risk.

Although we have our own research laboratories and clinical facilities, we collaborate with numerous institutions, universities and commercial entities to conduct research and studies of our products. We currently maintain a good working relationship with these parties. However, should the situation change, the cost and time to establish or locate alternative research and development facilities could be substantial and delay gaining CE Mark for other potential

applications of our products, our other product candidates or technologies, and/or FDA approval and commercializing our products. In addition, our interactions, communications, and financial relationships with these individuals and entities present future healthcare enforcement risks.

We are and will be exposed to product liability risks, and clinical and preclinical liability risks, which could place a substantial financial burden upon us should we be sued.

Our business exposes us to potential product liability and other liability risks that are inherent in the testing, manufacturing and marketing of medical devices. We cannot be sure that claims will not be asserted against us. A successful liability claim or series of claims brought against us could have a material adverse effect on our business, financial condition and results of operations.

We cannot give assurances that we will be able to continue to obtain or maintain adequate product liability insurance on acceptable terms, if at all, or that such insurance will provide adequate coverage against potential liabilities. Claims or losses in excess of any product liability insurance coverage that we may obtain could have a material adverse effect on our business, financial condition and results of operations.

Certain university and other relationships are important to our business and may potentially result in conflicts of interests.

Dr. John Kellum and others are critical care advisors and consultants of ours and are associated with institutions such as the University of Pittsburgh Medical Center. Their association with these institutions may currently or in the future involve conflicting interests in the event they or these institutions enter into consulting or other arrangements with competitors of ours.

We have limited manufacturing experience, and once our products are approved, we may not be able to manufacture sufficient quantities at an acceptable cost, or without shut-downs or delays.

In March 2011, we received approval from our Notified Body to apply the CE Mark to our CytoSorb device for commercial sale as a cytokine filter. We also achieved ISO 13485:2003 Full Quality Systems certification, an internationally recognized quality standard designed to ensure that medical device manufacturers have the necessary comprehensive management systems in place to safely design, develop, manufacture and distribute medical devices in the EU. We manufacture CytoSorb at our manufacturing facilities in New Jersey for sale in the EU and for additional clinical studies. Manufacturers and manufacturers' facilities are required to comply with extensive FDA requirements, including ensuring that quality control and manufacturing procedures conform to current Good Manufacturing Practices ("cGMP"). As such, we are subject to continual review and periodic inspections to assess compliance with cGMP as required by our International notified body and those FDA regulations governing companies that export medical products for sale outside the United States. Accordingly, we must continue to expend time, money and effort in all areas of regulatory compliance, including manufacturing, production and quality control. We have limited experience in establishing, supervising and conducting commercial manufacturing. If we or the third-party manufacturers of our products fail to adequately establish, supervise and conduct all aspects of the manufacturing processes, we may not be able to commercialize our products.

While we currently believe we have established sufficient production capacity to supply potential near term demand for the CytoSorb device, we will need to scale up and increase our manufacturing capabilities in the future. No assurance can be given that we will be able to successfully scale up our manufacturing capabilities or that we will have sufficient financial or technical resources to do so on a timely basis or at all.

Due to our limited marketing, sales and distribution experience, we may be unsuccessful in our efforts to sell our products.

We expect to enter into agreements with third parties for the commercial marketing, and distribution of our products. There can be no assurance that parties we may engage to market and distribute our products will:

- satisfy their financial or contractual obligations to us;
- adequately market our products; or
- not offer, design, manufacture or promote competing products.

If for any reason any party we engage is unable or chooses not to perform its obligations under our marketing and distribution agreement, we would experience delays in product sales and incur increased costs, which would harm our business and financial results.

Our results of operations can be significantly affected by foreign currency fluctuations and regulations.

A significant portion of our revenues is currently derived in the local currencies of the foreign jurisdictions in which our products are sold. Accordingly, we are subject to risks relating to fluctuations in currency exchange rates. In the future, and especially as we further expand our sales efforts in international markets, our customers will increasingly make payments in non-U.S. currencies. Fluctuations in foreign currency exchange rates could affect our revenues, operating costs and operating margins. In addition, currency devaluation can result in a loss to us if we hold deposits of that currency. We cannot predict the effect of future exchange rate fluctuations on our operating results.

If we are unable to convince physicians and other health care providers as to the benefits of our products, we may incur delays or additional expense in our attempt to establish market acceptance.

Broad use of our products may require physicians and other health care providers to be informed about our products and their intended benefits. The time and cost of such an educational process may be substantial. Inability to successfully carry out this education process may adversely affect market acceptance of our products. We may be unable to educate physicians regarding our products in sufficient numbers or in a timely manner to achieve our marketing plans or to achieve product acceptance. Any delay in physician education may materially delay or reduce demand for our products. In addition, we may expend significant funds towards physician education before any acceptance or demand for our products is created, if at all.

The market for our products is rapidly changing and competitive, and new devices and drugs, which may be developed by others, could impair our ability to maintain and grow our business and remain competitive.

The medical device and pharmaceutical industries are subject to rapid and substantial technological change. Developments by others may render our technologies and products noncompetitive or obsolete. We also may be unable to keep pace with technological developments and other market factors. Technological competition from medical device, pharmaceutical and biotechnology companies, universities, governmental entities and others diversifying into the field is intense and is expected to increase. Many of these entities have significantly greater research and development capabilities and budgets than we do, as well as substantially more marketing, manufacturing, financial and managerial resources. These entities represent significant competition for us.

Our business could be harmed by adverse economic conditions in Germany, our primary geographical market, or by economic and/or political instability in the EU caused by Brexit, or other factors.

For the year ended December 31, 2016, we derived a majority of our net product sales from sales in Germany. Despite modest European and global growth, there are many economic and political issues that could negatively impact the health of Germany's economy, the broader EU economy, and the world economy overall. Examples include the uncertainty over the United Kingdom's intent to leave the EU, also known as "Brexit", economic instability in a number of EU member countries, and changes in the political leadership in the EU and United States. Germany and other European countries face additional risks to their local economies, some of which include the impact of foreign exchange fluctuations, unemployment, tightening of monetary policy, the economic burden of immigration, diminished liquidity and reliance on debt, the rising cost of healthcare, and other factors. In addition, the German government, insurance companies, health maintenance organizations and other payers of healthcare costs continue to focus on healthcare reform and containment of healthcare costs. We cannot predict whether Germany's economy will continue to grow or decline consistent with the overall global economy, which decline would negatively impact the demand for medical devices and healthcare technologies generally and lead to reduced spending on the products we

provide. In addition, continued healthcare cost containment efforts may result in lower prices and a reduction or elimination of reimbursement for our products. Due to the concentration of our product sales in this country, any of the foregoing may have a negative impact on our revenues, business operations and financial condition.

Our business may be negatively affected if the United States and/or the countries in which we sell our products participate in wars, military actions or are otherwise the target of international terrorism.

Involvement in a war or other military action or international acts of terrorism may cause significant disruption to commerce throughout the world. To the extent that such disruptions result in (i) delays or cancellations of customer orders, (ii) a general decrease in consumer spending on healthcare technology, (iii) our inability to effectively market and distribute our products globally or (iv) our inability to access capital markets, our business and results of operations could be materially and adversely affected. We are unable to predict whether acts of international terrorism or the involvement in a war or other military actions by the United States and/or the countries in which we sell our products will result in any long-term commercial disruptions or if such involvement or responses will have any long-term material adverse effect on our business, results of operations, or financial condition.

We could be adversely affected by violations of the Foreign Corrupt Practices Act and similar worldwide anti-bribery laws.

We are subject to the Foreign Corrupt Practices Act (the “FCPA”), which generally prohibits companies and their intermediaries from making payments to non-U.S. government officials for the purpose of obtaining or retaining business or securing any other improper advantage. We are also subject to anti-bribery laws in the jurisdictions in which we operate. Although we have policies and procedures designed to ensure that we, our employees and our agents comply with the FCPA and other anti-bribery laws, there is no assurance that such policies or procedures will protect us against liability under the FCPA or other laws for actions taken by our agents, employees and intermediaries with respect to our business or any businesses that we acquire. We do business in a number of countries in which FCPA violations have recently been enforced. Failure to comply with the FCPA, other anti-bribery laws or other laws governing the conduct of business with foreign government entities, including local laws, could disrupt our business and lead to severe criminal and civil penalties, including imprisonment, criminal and civil fines, loss of our export licenses, suspension of our ability to do business with the federal government, denial of government reimbursement for our products and/or exclusion from participation in government healthcare programs. Other remedial measures could include further changes or enhancements to our procedures, policies, and controls and potential personnel changes and/or disciplinary actions, any of which could have a material adverse effect on our business, financial condition, results of operations and liquidity. We could also be adversely affected by any allegation that we violated such laws.

Cyberattacks and other security breaches could compromise our proprietary and confidential information which could harm our business and reputation.

In the ordinary course of our business, we generate, collect and store proprietary information, including intellectual property and business information. The secure storage, maintenance, and transmission of and access to this information is important to our operations and reputation. Computer hackers may attempt to penetrate our computer systems and, if successful, misappropriate our proprietary and confidential information including e-mails and other electronic communications. In addition, an employee, contractor, or other third-party with whom we do business may attempt to obtain such information, and may purposefully or inadvertently cause a breach involving such information. While we have certain safeguards in place to reduce the risk of and detect cyber-attacks, our information technology networks and infrastructure may be vulnerable to unpermitted access by hackers or other breaches, or employee error or malfeasance. Any such compromise of our data security and access to, or public disclosure or loss of, confidential business or proprietary information could disrupt our operations, damage our reputation, provide our competitors with valuable information, and subject us to additional costs which could adversely affect our business.

Risks Connected to Our Securities

The price of our Common Stock has been highly volatile due to factors that will continue to affect the price of our stock.

On December 3, 2014, we effected a twenty-five-for-one (25:1) reverse split of our Common Stock. Immediately after the reverse stock split, we changed our state of incorporation from the State of Nevada to the State of Delaware pursuant to an Agreement and Plan of Merger, dated December 3, 2014, whereby we merged with and into our recently formed, wholly-owned Delaware subsidiary. On December 17, 2014, we received approval for up-listing to The NASDAQ Capital Market and our Common Stock began trading on The NASDAQ Capital Market on December 23, 2014. Our Common Stock closed as high as \$6.90 and as low as \$3.11 per share between January 1, 2016 and December 31, 2016 on The NASDAQ Capital Market. On February 28, 2017, the closing price of our Common Stock, as reported on The NASDAQ Capital Market, was \$5.65. Historically, medical device company securities such as our Common Stock have experienced extreme price fluctuations. Some of the factors leading to this volatility include, but are not limited to:

- fluctuations in our operating results;
- announcements of product releases by us or our competitors;
- announcements of acquisitions and/or partnerships by us and our competitors; and
- general market conditions.

Although shares of our Common Stock currently trade on the NASDAQ Capital Market under the symbol “CTSO”, there is no assurance that our stock will not continue to be volatile while listed on NASDAQ in the future.

Directors, executive officers and principal stockholders own a significant percentage of the shares of Common Stock, which will limit your ability to influence corporate matters.

Our directors, executive officers and principal stockholders together beneficially own a significant percentage of the voting control of the Common Stock on a fully diluted basis. Accordingly, these stockholders could have a significant influence over the outcome of any corporate transaction or other matter submitted to stockholders for approval, including mergers, consolidations and the sale of all or substantially all of our assets and also could prevent or cause a change in control. The interests of these stockholders may differ from the interests of our other stockholders. Third parties may be discouraged from making a tender offer or bid to acquire us because of this concentration of ownership.

Our Board of Directors may, without stockholder approval, issue and fix the terms of shares of preferred stock and issue additional shares of Common Stock adversely affecting the rights of holders of our Common Stock.

On December 3, 2014, we effected a twenty-five-for-one (25:1) reverse split of our Common Stock. Immediately after the reverse stock split, we changed our state of incorporation from the State of Nevada to the State of Delaware pursuant to an Agreement and Plan of Merger, dated December 3, 2014, whereby we merged with and into our recently formed, wholly-owned Delaware subsidiary. Pursuant to the Agreement and Plan of Merger effecting the merger, we adopted the certificate of incorporation, as amended and restated, and bylaws of our Delaware subsidiary as our certificate of incorporation and bylaws at effective time of the merger. As a result, our certificate of incorporation, as amended and restated, authorizes the issuance of up to 5,000,000 shares of “blank check” preferred stock, with such designation rights and preferences as may be determined from time to time by the Board of Directors. Currently, our certificate of incorporation, as amended and restated, which was effective December 3, 2014, authorizes the issuance of up to 50,000,000 shares of Common Stock, of which approximately 24,516,000 shares remain available for issuance and may be issued by us without stockholder approval.

Anti-takeover provisions in our charter documents and under Delaware law could prevent or delay transactions that our stockholders may favor and may prevent stockholders from changing the direction of our business or our management.

After giving effect to our merger into our wholly-owned Delaware subsidiary, provisions of our certificate of incorporation, as amended and restated, and bylaws may discourage, delay or prevent a merger or acquisition that our stockholders may consider favorable, including transactions in which you might otherwise receive a premium for your shares, and may also frustrate or prevent any attempt by stockholders to change the direction or management of us. For example, these provisions:

authorize the issuance of “blank check” preferred stock without any need for action by stockholders;

eliminate the ability of stockholders to call special meetings of stockholders;

prohibit stockholder action by written consent; and

establish advance notice requirements for nominations for election to the board of directors or for proposing matters that can be acted on by stockholders at stockholder meetings.

Compliance with changing corporate governance and public disclosure regulations may result in additional expense.

Keeping abreast of, and in compliance with, changing laws, regulations and standards relating to corporate governance and public disclosure, including the Sarbanes-Oxley Act of 2002, new SEC regulations will require an increased amount of management attention and external resources. In addition, prior to the merger, our current management team was not subject to these laws and regulations, as we were a private corporation. We intend to continue to invest all reasonably necessary resources to comply with evolving standards, which may result in increased general and administrative expense and a diversion of management time and attention from revenue-generating activities to compliance activities.

Our Common Stock is thinly traded on The NASDAQ Capital Market exchange and no assurances can be made about stock performance, liquidity, or maintenance of our NASDAQ listing.

Prior to December 23, 2014, our Common Stock was quoted on the OTCQB, which provided significantly less liquidity than a securities exchange (such as the New York Stock Exchange or the Nasdaq Stock Market). On December 17, 2014, our Common Stock was approved for trading on The NASDAQ Capital Market (“NASDAQ”). Beginning on December 23, 2014, our Common Stock began trading on NASDAQ under the symbol “CTSO.” Although currently listed on NASDAQ, there can be no assurance that we will continue to meet NASDAQ’s minimum listing requirements or that of any other national exchange. In addition, there can be no assurances that a liquid market will be created for our common stock. If we are unable to maintain listing on The NASDAQ or if a liquid market for our Common Stock does not develop, our Common Stock may remain thinly traded.

Future sales of our Common Stock may cause our share price to fall.

In November 2015, we entered into a sales agreement with Cantor Fitzgerald & Co. to offer shares of our Common Stock from time to time through “at-the-market” offerings, pursuant to which we offer and sell shares of our Common Stock for an aggregate offering price of up to \$25 million. We are not obligated to make or continue to make any sale of shares of our Common Stock under the “at-the-market” offerings. Although any sale of securities pursuant to the “at-the-market” offerings will result in a concomitant increase in cash for each share sold, it may result in shareholder dilution and may cause our share price to fall.

Item 1B. Unresolved Staff Comments.

None.

Item 2. Properties.

We currently operate a facility near Princeton, New Jersey with approximately 12,900 sq. ft., housing research laboratories, clinical manufacturing operations and administrative offices, under a lease agreement which expires in May 2018. We expect to secure new, expanded facilities upon expiration of this lease. In the opinion of management, the leased properties are adequately insured, are in good condition and suitable for the conduct of our business. We also collaborate with numerous institutions, universities and commercial entities who conduct research and testing of our products at their facilities. Our monthly base rent as of August 2016 is approximately \$24,756 and additionally we

reimburse the landlord for monthly operating expenses of approximately \$15,929.

We also operate a facility in Berlin, Germany housing our sales and administrative offices and warehouse space. We entered into a lease for this office on September 1, 2016. The lease expires on August 31, 2021. We rent this space for \$6,545 per month.

Item 3. Legal Proceedings.

We are from time to time subject to claims and litigation arising in the ordinary course of business. We intend to defend vigorously against any future claims and litigation. We are not currently a party to any legal proceedings.

Item 4. Mine Safety Disclosures.

Not applicable.

PART II

Item 5. Market for Registrant’s Common Equity, Related Stockholder Matters and Issuer Purchases of Equity Securities.

Market Information

Beginning on December 23, 2014, our Common Stock began trading on NASDAQ under the symbol “CTSO.” Previously, the Company’s common stock traded in the over-the counter-market on the OTC Bulletin Board.

Price Range of Common Stock

The following table shows, for the periods indicated, the high and low bid prices per share of our common stock as reported by NASDAQ.

	High	Low
2015		
First quarter	\$14.99	\$7.89
Second quarter	\$9.02	\$5.20
Third quarter	\$7.70	\$5.80
Fourth quarter	\$8.00	\$5.57
2016		
First quarter	\$5.87	\$3.11
Second quarter	\$4.99	\$3.87
Third quarter	\$6.66	\$4.49
Fourth quarter	\$6.90	\$4.45

Approximate Number of Equity Security Holders

As of February 28, 2017, there were approximately 5,800 stockholders of record. Because shares of our Common Stock are held by depositaries, brokers and other nominees, the number of beneficial holders of our shares is larger than the number of stockholders of record.

Dividends

We have not declared or paid any cash dividends on our common stock, and we do not anticipate declaring or paying cash dividends for the foreseeable future. We are not subject to any legal restrictions respecting the payment of dividends, except that we may not pay dividends if the payment would render us insolvent. Any future determination as to the payment of cash dividends on our common stock will be at the discretion of our board of directors and will depend on our financial condition, operating results, capital requirements and other factors that our board of directors considers to be relevant.

Equity Compensation Plan

Plan category	Number of securities to be issued upon exercise of outstanding options, warrants and rights	Weighted-average exercise price of outstanding options, warrants and rights	Number of securities remaining available for future issuance under equity compensation plans (excluding securities reflected in column (a))
	(a)	(b)	(c)
Equity compensation plans approved by security holders	608,700	\$ 5.448	157,891
Equity compensation plans not approved by security holders	2,153,477	\$ 4.473	427,592
Total	2,762,177	\$ 4.688	585,483

Stock Performance Graph

The following graph shows the value of an investment of \$100 on December 31, 2011 in each of CytoSorbents Corporation common stock, the Russell 2000 Index and the NASDAQ Biotech Index. All values assume reinvestment of the pretax value of dividends and are calculated as of December 31st of each year. The historical stock price performance of the Company's common stock shown in the performance graph is not necessarily indicative of future stock price performance.

CytoSorbents Corporation vs. Russell 2000 Index and NASDAQ Biotech Index**Comparison of 5 Year Total Cumulative Return****Value of a \$100 Investment on December 31, 2011****Issuer Purchases of Securities**

There were no repurchases of the Company's securities during the year ended December 31, 2016.

Item 6. Selected Financial Data.

The following table summarizes our selected financial data for the periods and as of the dates indicated, which have been derived from our audited financial statements and related notes and should be read together with the section titled “Management’s Discussion and Analysis of Financial Condition and Results of Operations” and with our consolidated financial statements and related notes, which are included elsewhere in this Annual Report.

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	Year Ended December 31,				
	2016	2015	2014	2013	2012
Revenue:					
Sales	\$8,206,036	\$4,043,819	\$3,135,387	\$821,787	\$151,574
Grant income	1,321,807	735,863	978,271	1,600,880	1,191,362
Other revenue	-	11,934	9,167	-	-
Total revenue	9,527,843	4,791,616	4,122,825	2,422,667	1,342,936
Cost of revenue	3,953,725	2,212,546	2,133,888	1,911,565	319,298
Gross margin	5,574,118	2,579,070	1,988,937	511,102	1,023,638
Operating expenses:					
Research and development	4,783,491	3,871,069	2,431,759	1,738,938	2,532,489
Legal, financial and other consulting	1,184,788	1,089,145	896,847	908,644	627,245
Selling general and administrative	11,097,964	6,922,515	5,553,167	2,576,751	1,354,738
Total operating expenses	17,066,243	11,882,729	8,881,773	5,224,333	4,514,472
Loss from Operations	(11,492,125)	(9,303,659)	(6,892,836)	(4,713,231)	(3,490,834)
Other income (expense):					
Interest income/(expense), net	(231,805)	9,301	(310,024)	(422,843)	(564,428)
Foreign currency translation gain (loss)	(358,077)	(507,276)	(385,956)	-	-
Change in warrant liability	(175,418)	1,345,290	(2,118,498)	-	-
Total other income (expense), net	(765,300)	847,315	(2,814,478)	(422,843)	(564,428)
Loss before benefit from income taxes	(12,257,425)	(8,456,344)	(9,707,314)	(5,136,074)	(4,055,262)
Benefit from income taxes	318,550	324,606	385,642	458,279	391,756
Net loss	(11,938,875)	(8,131,738)	(9,321,672)	(4,677,795)	(3,663,506)
Preferred stock dividends	-	-	9,266,673	2,395,520	2,511,412
Net loss available to common stockholders, basic and diluted	(11,938,875)	(8,131,738)	(18,588,345)	(7,073,315)	(6,174,918)
Weighted average common shares outstanding, basic and diluted	25,433,719	24,885,809	14,382,813	9,440,763	7,929,132
Net loss per share, basic and dilute	\$(0.47)	\$(0.33)	\$(1.29)	\$(0.75)	\$(0.78)

	As of December 31,				
Consolidated Balance Sheet Data:	2016	2015	2014	2013	2012
Cash and cash equivalents	\$5,245,178	\$5,316,851	\$3,605,280	\$2,183,030	\$1,729,344
Short term investments	-	2,192,000	1,944,547	-	-
Working capital	1,738,806	6,816,548	3,101,564	422,035	862,852
Total assets	9,693,844	11,254,366	8,468,625	4,045,735	3,339,408
Preferred stock	-	-	-	15,246,350	12,887,817
Accumulated deficit	(144,464,733)	(132,525,858)	(124,394,120)	(105,805,775)	(98,732,460)
Total stockholders' equity(deficit)	(474,088)	8,210,586	3,963,183	(14,265,547)	(11,625,145)

Item 7. Management’s Discussion and Analysis of Financial Condition and Results of Operations.

The following discussion and analysis of the results of operations and financial condition for the fiscal years ended December 31, 2016, 2015 and 2014 should be read in conjunction with our financial statements, and the notes to those financial statements that are included elsewhere in this Report.

Overview

We are a leader in critical care immunotherapy commercializing our CytoSorb blood purification technology to reduce deadly uncontrolled inflammation in hospitalized patients around the world, with the goal of preventing or treating multiple organ failure in life-threatening illnesses and cardiac surgery. The technology is based upon biocompatible, highly porous polymer sorbent beads that are capable of extracting unwanted substances from blood and other bodily fluids. The technology is protected by 32 issued U.S. patents with multiple applications pending both in the U.S. and internationally. Our intellectual property consist of composition of matter, materials, methods of production, systems incorporating the technology and multiple medical uses with expiration dates ranging from one to 10 years.

In March 2011, we received EU regulatory approval under the CE Mark and Medical Devices Directive for our flagship product, CytoSorb, as an extracorporeal cytokine filter indicated for use in clinical situations where cytokines are elevated. The goal of CytoSorb is to prevent or treat organ failure by reducing cytokine storm and the potentially deadly systemic inflammatory response syndrome in diseases such as sepsis, trauma, burn injury, acute respiratory distress syndrome, pancreatitis, liver failure, and many others. Organ failure is the leading cause of death in the ICU, and remains a major unmet medical need, with little more than supportive care therapy (e.g., mechanical ventilation, dialysis, vasopressors, fluid support, etc.) as treatment options. By potentially preventing or treating organ failure, CytoSorb may improve clinical outcome, including survival, while reducing the need for costly ICU treatment, thereby potentially saving significant healthcare costs. CytoSorb is also being used during and after cardiac surgery to remove inflammatory mediators, such as cytokines and free hemoglobin, which can lead to post-operative complications including multiple organ failure.

Our CE Mark enables CytoSorb to be sold throughout all 28 countries of the EU. In addition, many countries outside the EU accept CE Mark approval for medical devices, but may also require registration with or without additional clinical studies. The broad approved indication enables CytoSorb to be used “on-label” in diseases where cytokines are elevated including, but not limited to, critical illnesses such as those mentioned above, autoimmune disease flares, cancer cachexia, and many other conditions where cytokine-induced inflammation plays a detrimental role.

As part of the CE Mark approval process, we completed our randomized, controlled, European Sepsis Trial amongst fourteen trial sites in Germany in 2011, with enrollment of 100 patients with sepsis and respiratory failure. The trial established that CytoSorb was safe in this critically-ill population, and that it was able to broadly reduce key cytokines in the blood of these patients. We plan to conduct larger, prospective studies in septic patients in the future to confirm the European Sepsis Trial findings.

In addition to CE Mark approval, we also achieved ISO 13485:2003 Full Quality Systems certification, an internationally recognized quality standard designed to ensure that medical device manufacturers have the necessary comprehensive management systems in place to safely design, develop, manufacture and distribute medical devices in the EU. We manufacture CytoSorb at our manufacturing facilities in New Jersey for sale and for additional clinical studies. We also established a dedicated reimbursement path for CytoSorb in Germany and a reimbursement path for CytoSorb in Austria.

From September 2011 through June 2012, we began a controlled market release of CytoSorb in select geographic territories in Germany with the primary goal of preparing for commercialization of CytoSorb in Germany in terms of manufacturing, reimbursement, logistics, infrastructure, marketing, contacts, and other key issues.

In late June 2012, following the establishment of our European subsidiary, CytoSorbents Europe GmbH, we began the commercial launch of CytoSorb in Germany with the hiring of Dr. Christian Steiner as Vice President of Sales and Marketing and three additional sales representatives who joined us and completed their sales training in the third quarter of 2012. The fourth quarter of 2012 represented the first full quarter of direct sales with the full sales team in place. During this period, we expanded our direct sales efforts to include both Austria and Switzerland. At the end of 2016, we had hundreds of KOLs in our commercialized territories worldwide in critical care, cardiac surgery, and blood purification who were either using CytoSorb or supporting its use in clinical practice or clinical trials.

In March 2016, we established CytoSorbents Switzerland GmbH, a wholly-owned subsidiary of CytoSorbents Europe GmbH, to conduct marketing and direct sales in Switzerland. This subsidiary began operations during the second quarter of 2016.

As of February 1, 2017, our sales force includes 13 direct sales people, one contract sales person and 11 sales support staff.

We have complemented our direct sales efforts with sales to distributors and/or corporate partners. In 2013, we reached agreements with distributors in the United Kingdom, Ireland, Turkey, Russia, and the Netherlands. In 2014, we announced distribution of CytoSorb in the Middle East, including Saudi Arabia, the United Arab Emirates, Kuwait, Qatar, Bahrain, and Oman (the GCC) and Yemen, Iraq, and Jordan through an exclusive agreement with Techno Orbits, we entered into an exclusive agreement with Smart Medical Solutions S.R.L., to distribute CytoSorb for critical care applications in Romania and the neighboring Republic of Moldova. In 2015, we announced exclusive distribution agreements with Aferetica SRL to distribute CytoSorb in Italy, AlphaMedix Ltd. to distribute CytoSorb in Israel, TekMed Pty Ltd. to distribute CytoSorb in Australia and New Zealand, and Hoang Long Pharma to distribute CytoSorb in Vietnam. In June 2016, we announced an exclusive distribution agreement with Palex Medical SA to distribute CytoSorb in Spain and Portugal. In September 2016, we announced an exclusive agreement with Armaghan Salamat Kish Group (Arsak) to distribute CytoSorb in Iran. In October 2016, we announced an exclusive agreement with Foxx Medical Chile SpA to distribute CytoSorb in Chile.

We have been working to expand the number and scope of our strategic partnerships. In September 2013, we entered into a strategic partnership with Biocon, Ltd., India's largest biotech company, with an initial distribution agreement for India and select emerging markets, under which Biocon has the exclusive commercialization rights for CytoSorb initially focused on sepsis. In October 2014, the Biocon partnership was expanded to include all critical care applications and cardiac surgery. In addition, Biocon committed to higher minimum purchases of CytoSorb to maintain distribution exclusivity and to conduct and publish results from multiple Investigator-Initiated studies and patient case studies.

In December 2014, we entered into a multi-country strategic partnership with Fresenius Medical Care AG & CO KGaA to commercialize the CytoSorb therapy. Under the terms of the agreement, Fresenius Medical Care has exclusive rights to distribute CytoSorb for critical care applications in France, Poland, Sweden, Denmark, Norway, and Finland. The partnership will allow Fresenius Medical Care to offer an innovative and easy to use blood purification therapy for removing cytokines in patients that are treated in the ICU. In January 2017, the Fresenius partnership was expanded. The terms of the revised three-year agreement extend Fresenius' exclusive distributorship of CytoSorb for all critical care applications in their existing territories through 2019 and include guaranteed minimum quarterly orders and payments, evaluable every one and a half years. In addition, we have entered into a new comprehensive co-marketing agreement with Fresenius. Under the terms of the agreement, CytoSorbents and Fresenius will jointly market CytoSorb and Fresenius' CytoSorb compatible blood tubing sets to Fresenius' critical care customer base in all countries where CytoSorb is being actively commercialized. CytoSorb will continue to be sold by our direct sales force or through our international network of distributors and partners, while Fresenius will sell all ancillary products to their customers. Fresenius will also provide a written endorsement of CytoSorb for use with their multiFiltrate and multiFiltratePRO acute care dialysis machines that can be used by us and our distribution partners to promote CytoSorb worldwide. Training and preparation for this co-marketing program is ongoing and it is expected co-marketing activity will commence during the second half of 2017.

In September 2016, we entered into a multi-country strategic partnership with Terumo Cardiovascular Group to commercialize CytoSorb for cardiac surgery applications. Under the terms of the agreement, Terumo has exclusive rights to distribute the CytoSorb CPB procedure pack for intra-operative use during cardiac surgery in France, Sweden, Denmark, Norway, Finland and Iceland. Terumo launched the product in these six countries in December 2016.

We are currently evaluating other potential distributor and strategic partner networks in other major countries where we are approved to market the device.

Concurrent with our commercialization plans, we intend to conduct or support additional clinical studies in sepsis, cardiac surgery, and other critical care diseases to generate additional clinical data to expand the scope of clinical experience for marketing purposes, to increase the number of treated patients, and to support potential future publications. We have completed a single arm, dose ranging trial in Germany amongst several clinical trial sites to evaluate the safety and efficacy of CytoSorb when used 24 hours per day for seven days, each day with a new device, and are conducting final statistical analysis of the data. Patients are being stratified for age, cytokine levels, and co-morbid illnesses in this matched pairs analysis.

In addition, we now have more than 55 investigator-initiated studies planned, enrolling or completed in Germany, Austria, Switzerland, the Netherlands, Hungary, the United Kingdom, India, and the U.S. Approximately 20 of these studies are currently enrolling patients. These trials, which are funded and supported by well-known university hospitals and KOLs, are the equivalent of Phase II clinical studies. They will provide invaluable information regarding the success of the device in the treatment of sepsis, cardiac surgery, trauma, and many other indications, and if successful, will be integral in helping to drive additional usage and adoption of CytoSorb.

In February 2015, the FDA approved our IDE application to commence a planned U.S. cardiac surgery feasibility study called REFRESH I (REduction of FREe Hemoglobin) amongst 20 patients and three U.S. clinical sites. The FDA subsequently approved an amendment to the protocol, expanding the trial to be a 40 patient randomized controlled study (20 treatment, 20 control) in eight clinical centers. REFRESH I represents the first part of a larger clinical trial strategy intended to support the approval of CytoSorb in the U.S. for intra-operative use during cardiac surgery.

The REFRESH I study is designed to evaluate the safety of CytoSorb when used intra-operatively in a heart-lung machine to reduce plasma free hemoglobin and other inflammatory mediators such as cytokines and activated complement in patients undergoing complex cardiac surgery. The length, complexity and invasiveness of these procedures cause hemolysis and inflammation, leading to high levels of toxic plasma free hemoglobin, cytokines, activated complement, and other substances. These inflammatory mediators directly correlate with the incidence of serious post-operative complications such as kidney injury and failure, hemodynamic instability, respiratory failure, and risk of stroke. The goal of CytoSorb is to actively remove these inflammatory and toxic substances as they are being generated during the surgery and reduce complications. As of December 31, 2016, enrollment was complete with 46 patients. A total of 38 patients were evaluable and completed all aspects of the study.

The primary safety and efficacy endpoints of the study were the assessment of serious device related adverse events and the change in plasma free hemoglobin levels, respectively. On October 5, 2016, the Company announced positive

top-line safety data. In addition, following a detailed review of all reported adverse events in a total of 46 enrolled patients, the independent DSMB found no safety concerns related to the CytoSorb device, achieving the primary safety endpoint of the trial and fulfilling a key requisite to move forward with a larger, definitive pivotal study. In addition, the therapy was well-tolerated and technically feasible, implementing easily into the cardiopulmonary bypass circuit without the need for an additional external blood pump. This study represents the first randomized controlled trial demonstrating the safety of intra-operative CytoSorb use in patients undergoing high risk cardiac operations.

Investigators of the REFRESH I trial have submitted an abstract with data, including free hemoglobin data, from the REFRESH I trial to the American Association of Thoracic Surgery (“AATS”) conference to held in late April 2017, and a manuscript is being prepared for journal submission. In parallel, the Company plans to meet with the FDA to discuss the results of REFRESH I in anticipation of filing an IDE application to initiate a pivotal REFRESH 2 trial in 2017.

The market focus of CytoSorb is prevention or treatment of organ failure in life-threatening conditions, including commonly seen illnesses in the ICU such as infection and sepsis, trauma, burn injury, ARDS, and others. Severe sepsis and septic shock, a potentially life-threatening systemic inflammatory response to a serious infection, accounts for approximately 10% to 20% of all ICU admissions and is one of the largest target markets for CytoSorb. Sepsis is a major unmet medical need with no approved products in the U.S. or Europe to treat it. As with other critical care illnesses, multiple organ failure is the primary cause of death in sepsis. When used with standard of care therapy, that includes antibiotics, the goal of CytoSorb in sepsis is to reduce the excessive levels of cytokines and other inflammatory toxins, to help reduce the SIRS response and either prevent or treat organ failure.

In addition to the sepsis indication, we intend to conduct or support additional clinical studies in sepsis, cardiac surgery, and other critical care diseases where CytoSorb could be used, such as ARDS, trauma, severe burn injury, acute pancreatitis, and other acute conditions that may benefit by the reductions of cytokines in the bloodstream. Some examples include the prevention of post-operative complications of cardiac surgery (cardiopulmonary bypass surgery) and damage to organs for transplant prior to organ harvest. We intend to generate additional clinical data to expand the scope of clinical experience for marketing purposes, to increase the number of treated patients, and to support potential future publications.

Our proprietary hemocompatible porous polymer bead technology forms the basis of a broad technology portfolio. Some of our products include:

CytoSorb - an extracorporeal hemoperfusion cartridge approved in the EU for cytokine removal, with the goal of reducing SIRS and preventing or treating organ failure.

VetResQ - a broad spectrum blood purification adsorber designed to help treat deadly inflammation and toxic injury in animals with critical illnesses such as septic shock, toxic shock syndrome, severe systemic inflammation, toxin-mediated diseases, pancreatitis, trauma, liver failure, and drug intoxication.

HemoDefend – a development-stage blood purification technology designed to remove contaminants in blood transfusion products. The goal of HemoDefend is to reduce transfusion reactions and improve the safety of older blood.

ContrastSorb – a development-stage extracorporeal hemoperfusion cartridge designed to remove IV contrast from the blood of high risk patients undergoing CT imaging with contrast, or interventional radiology procedures such as cardiac catheterization. The goal of ContrastSorb is to prevent contrast-induced nephropathy.

DrugSorb – a development-stage extracorporeal hemoperfusion cartridge designed to remove toxic chemicals from the blood (e.g., drug overdose, high dose regional chemotherapy).

BetaSorb – a development-stage extracorporeal hemoperfusion cartridge designed to remove mid-molecular weight toxins, such as b2-microglobulin, that standard high-flux dialysis cannot remove effectively. The goal of BetaSorb is to improve the efficacy of dialysis or hemofiltration.

We have been successful in obtaining technology development contracts from governmental agencies such as the National Institutes of Health and the U.S. Department of Defense, including the Defense Advanced Research Projects Agency, or DARPA, the U.S. Army, U.S. Special Operations Command, and the U.S. Air Force.

In August 2012, we were awarded a \$3.8 million, five-year contract by DARPA for our DLT, program to treat sepsis. DARPA has been instrumental in funding many of the major technological and medical advances since its inception in 1958, including development of the Internet, development of GPS, and robotic surgery. The DLT program in sepsis seeks to develop a therapeutic blood purification device that is capable of identifying the cause of sepsis (e.g., cytokines, toxins, pathogens, activated cells) and remove these substances in an intelligent, automated, and efficient manner. Our contract is for advanced technology development of our hemocompatible porous polymer technologies to remove cytokines and a number of pathogen and biowarfare toxins from blood. We are in Year 5 of the program and are currently working with the systems integrator, Battelle Laboratories, and its subcontractor NxStage Medical, who are responsible for integrating the technology developed by us and others into a final medical device design prototype, and evaluating this device in septic animals and eventually in human clinical trials in sepsis. Our work is supported by DARPA and SSC Pacific under Contract No. N66001-12-C-4199. In June 2016, this contract was amended to change the maximum funding to approximately \$3,825,000. As of December 31, 2016, we have received approximately \$3,739,000 in funding under this contract and have approximately \$86,000 remaining under this contract.

In September 2012, we were awarded a Phase II SBIR contract by the U.S. Army Medical Research and Material Command to evaluate our technology for the treatment of trauma and burn injury in large animal models. In 2013, we finalized the Phase II SBIR contract which provided for a maximum funding of approximately \$803,000 with the granting agency. This work is supported by the U.S. Army Medical Research and Material Command under an amendment to Contract W81XWH-12-C-0038. In June 2016, this contract was further amended to increase the maximum funding by \$443,000 to approximately \$1,246,000. As of December 31, 2016, we received approximately \$1,025,000 in funding under this contract and have approximately \$221,000 remaining under this contract.

In September 2013, the NHLBI, awarded us a Phase I SBIR contract, (contract number HHSN-268201-300044C), valued at \$203,351, to further advance our HemoDefend blood purification technology for pRBC transfusions. The University of Dartmouth collaborated with us as a subcontractor on the project, entitled “Elimination of blood contaminants from pRBCs using HemoDefend hemocompatible porous polymer beads.” The overall goal of this program is to reduce the risk of potential side effects of blood transfusions, and help to extend the useful life of pRBCs. Our performance under this contract has been completed.

In October 2015, we were awarded a Phase II SBIR contract by the NHLBI, with support fro U.S. SOCOM, to help advance our HemoDefend blood purification technology towards commercialization for the purification of pRBC transfusions. The contract, entitled “pRBCs Contaminant Removal with Porous Polymer Beads” (contract number HHSN-268201-600006C), provides for maximum funding of approximately \$1,522,000 over a two year period. As of December 31, 2016, we have received approximately \$502,000 and have approximately \$1,020,000 remaining under this contract.

In March 2016, we were awarded a Phase I SBIR contract for its development program entitled “Mycotoxin Absorption with Hemocompatible Porous Polymer Beads.” The purpose of this contract is to develop effective blood purification countermeasures for weaponized mycotoxins that can be easily disseminated in water, food and air. This work is being funded by the U.S. Joint Program Executive Office for Chemical and Biological Defense, or JPEO-CBD, under contract number W911QY-16-P-0048 and provides for maximum funding of \$150,000. As of December 31, 2016, we received approximately \$125,000 and have approximately \$25,000 remaining under this contract.

In June 2016, we were awarded a Phase I STTR contract for a development program entitled “Use of Highly Porous Polymer Beads to Remove Anti-A and Anti-B antibodies from Plasma for Transfusion”. The purpose of this contract is to develop our HemoDefend blood purification technology to potentially enable universal plasma. This work is being funded by the USAMRAA under contract W81XWH-16-C-0025 and provides for maximum funding of \$150,000. As of December 31, 2016, we received approximately \$150,000 and no funding remaining under this contract.

In July 2016, we were awarded a Phase I SBIR contract for its development program entitled “Investigation of a sorbent-based potassium adsorber for the treatment of hyperkalemia induced by traumatic injury and acute kidney injury in austere conditions”. The objective of this Phase I project is to develop two novel and distinct treatment options for life-threatening hyperkalemia. This work is being funded by the USAMRAA under contract W81XWH-16-C-0080 and provides for maximum funding of approximately \$150,000. As of December 31, 2016, we received approximately \$75,000 and have approximately \$75,000 remaining under this contract.

In January 2017, the Company was awarded a Phase II contract to continue development of CytoSorb for fungal mycotoxin blood purification. This program will focus on demonstrating the ability of CytoSorb to absorb mycotoxins *in vivo* and improve survival in animals. This contract provides for maximum funding of \$999,996 over two years. This program is funded by the Chemical and Biological Defense (“CBD”) SBIR program. Funding is expected to begin during the first quarter of 2017.

Results of Operations

Our financial statements have been presented on the basis that it is a going concern, which contemplates the realization of revenues and the satisfaction of liabilities in the normal course of business. We have incurred losses from inception of operations. These factors raise substantial doubt about our ability to continue as a going concern.

Comparison of the year ended December 31, 2016 and 2015

Revenues:

For the year ended December 31, 2016, we generated total revenue, which includes product revenue and grant income, of approximately \$9,528,000 as compared to revenues of approximately \$4,792,000 for the year ended December 31, 2015, an increase of approximately \$4,736,000, or 99%. Revenue from product sales was approximately \$8,206,000 for the year ended December 31, 2016, as compared to approximately \$4,044,000 in the year ended December 31, 2015, an increase of approximately \$4,162,000 or 103%. This increase was largely driven by an increase in direct sales from both new customers and repeat orders from existing customers, along with an increase in distributor sales.

Grant income increased by approximately \$586,000 to approximately 1,322,000 in 2016 from \$736,000 in 2015 as a result of revenue received from existing grants as well as revenue received from several new grants awarded during 2016.

Cost of Revenue:

For the years ended December 31, 2016 and 2015, cost of revenue was approximately \$3,954,000 and \$2,213,000, respectively, an increase of approximately \$1,741,000, or 79%. This increase is related to an increase in product cost of revenue of approximately \$1,198,000 attributable to increased sales in 2016. Product gross margins were approximately 67% for the year ended December 31, 2016, as compared to approximately 62% for the year ended December 31, 2015 due to a favorable mix of sales prices and, to a lesser extent, a reduction in our product costs. Grant income related expenses increased by approximately \$544,000 during the year ended December 31, 2016 as compared to the year ended December 31, 2015 due to progress made in meeting grant milestones on both existing and new grants.

Research and Development Expenses:

Our research and development costs were approximately \$4,783,000 and \$3,871,000 for the years ended December 31, 2016 and 2015, respectively, an increase of approximately \$912,000, or 24%. This increase in research and development expenditures is related to an increase in costs related to our various clinical studies and trials of approximately \$833,000, an increase in stock-based compensation of approximately \$584,000 due to milestone options awarded to the Company's research and development employees during the year ended December 31, 2016, an increase in salaries related to non-clinical research and development activities of approximately \$14,000 and an increase in supplies and other research and development expenses of approximately \$25,000. These increases were offset by an increase in direct labor and other costs being deployed toward grant-funded activities of approximately \$544,000, which had the effect of decreasing the amount of our non-reimbursable research and development costs.

Legal, Financial and Other Consulting Expenses:

Our legal, financial and other consulting costs were approximately \$1,185,000 and \$1,089,000 for the years ended December 31, 2016 and 2015, respectively, an increase of approximately \$96,000, or 9%. The increase of approximately \$51,000 was due to an increase in accounting and auditing fees of approximately \$65,000 due to fees incurred which were related to the audit of our internal controls as required by The Sarbanes-Oxley Act of 2002 and increases in consulting fees of approximately \$151,000. These increases were offset by a decrease in employment agency fees of approximately \$81,000 related to fees incurred in 2015 related to the hiring of senior level personnel that did not recur in 2016 and a reduction in legal fees of approximately \$40,000 as a result of fees related to certain corporate initiatives in 2015 that did not recur in 2016.

Selling, General and Administrative Expenses:

Our selling, general and administrative expenses were approximately \$11,098,000 and \$6,923,000 for the years ended December 31, 2016 and 2015, respectively, an increase of approximately \$4,175,000, or 60%. The increase in selling, general, and administrative expenses was due to an increase in salaries, commissions and related costs of approximately \$1,468,000 due to headcount additions and personnel related costs, an increase in royalty expenses of approximately \$291,000 due to the increase in product sales, additional sales and marketing costs, which include advertising, and conferences of approximately \$114,000, an increase in travel and entertainment and other costs of approximately \$71,000 due to the increased headcount, an increase in stock-based compensation of approximately \$2,096,000 due to milestone options awarded to the Company's employees and restricted stock units awarded to the Company's executive staff during the year ended December 31, 2016, an increase in rent expense of approximately \$17,000 related to the new expanded office facility in Germany, an increase in bad debt expense of approximately \$65,000, an increase in sales consulting fees of approximately \$33,000 and an increase in postage and delivery costs and other general and administrative costs of approximately \$62,000. These increases were offset by a decrease in public relations fees of approximately \$42,000.

Interest Income (Expense):

For the year ended December 31, 2016, interest expense was approximately \$232,000, as compared to interest income of approximately \$9,000 for the year ended December 31, 2015. This increase in interest expense of approximately \$241,000 is directly related to interest expense incurred and amortization of loan acquisition costs related to the Company's financing facility with Bridge Bank on which \$5,000,000 was drawn on June 30, 2016.

Gain (Loss) on Foreign Currency Transactions:

For the year ended December 31, 2016, the loss on foreign currency transactions was approximately \$358,000, as compared to \$507,000 for the year ended December 31, 2015, a decrease of approximately \$129,000. This decrease is attributable to the rate of the decline in the exchange rate of the Euro for the year ended December 31, 2016 as compared to the year ended December 31, 2015. During the year ended December 31, 2016, the exchange rate of the Euro declined from \$1.09 at the beginning of the year to \$1.05 at December 31, 2016. During the year ended December 31, 2015, the exchange rate of the Euro declined from \$1.22 at the beginning of the year to \$1.09 at December 31, 2015.

Change in Warrant Liability:

We recognize warrants as liabilities at their fair value on the date of the grant because of price adjustment provisions in the warrants, then measure the fair value of the warrants on each reporting date, and record a change to the warrant liability as appropriate. The change in warrant liability resulted in other expense of approximately \$175,000 for the year ended December 31, 2016 and other income of approximately \$1,345,000 for the year ended December 31, 2015. The change in warrant liability was as a result of the change in the fair value of the warrant liability from January 1, 2016 to December 31, 2016 and from January 1, 2015 to December 31, 2015. See the consolidated financial statements for details related to the calculation of the fair value of the warrant liability.

Benefit from Income Taxes:

Our benefit from income taxes was approximately \$319,000 and \$325,000 for the years ended December 31, 2016 and 2015, respectively. These benefits were realized by utilizing the New Jersey Technology Business Tax Certificate Transfer Program whereby the State of New Jersey allows us to sell our net operating losses to a third party.

Comparison of the year ended December 31, 2015 and 2014

Revenues:

For the year ended December 31, 2015, we generated total revenue, which includes product revenue and grant income, of approximately \$4,792,000 as compared to revenues of approximately \$4,123,000 for the year ended December 31, 2014, an increase of approximately \$669,000, or 16%. Revenue from product sales was approximately \$4,044,000 for the year ended December 31, 2015, as compared to approximately \$3,135,000 in the year ended December 31, 2014, an increase of 29%. This increase was driven by the continued growth in direct sales as well as the expansion of sales to our growing distributor network, which was offset by the negative impact of the decline in the exchange rate of the Euro relative to the U.S. dollar. The impact of the decline in the exchange rate of the Euro was approximately \$637,000, or 16% of product sales, for the year ended December 31, 2015.

Grant income decreased by approximately \$242,000 from \$978,000 in 2014 to approximately \$736,000 in 2015 as a result of the conclusion of several significant grants.

Cost of Revenue:

For the years ended December 31, 2015 and 2014, cost of revenue was approximately \$2,213,000 and \$2,134,000, respectively, an increase of approximately \$79,000, or 4%. This increase is related to an increase in product cost of revenue of approximately \$354,000 attributable to increased sales in 2015. This was offset by a decrease of approximately \$292,000 of direct labor and other costs being deployed toward grant-funded activities in 2015, which has the effect of decreasing the amount of costs allocated to cost of revenue. Product gross margins were approximately 62% for the year ended December 31, 2015, as compared to approximately 63% for the year ended December 31, 2014.

Research and Development Expenses:

Our research and development costs were approximately \$3,871,000 and \$2,432,000 for the years ended December 31, 2015 and 2014, respectively, an increase of approximately \$1,439,000, or 59%. This increase in research and development expenditures is related to an increase in costs related to our various clinical studies and trials of approximately \$1,187,000 and an increase in salaries related to non-clinical research and development activities of approximately \$134,000.

Legal, Financial and Other Consulting Expenses:

Our legal, financial and other consulting costs were approximately \$1,089,000 and \$897,000 for the years ended December 31, 2015 and 2014, respectively, an increase of approximately \$192,000, or 21%. This increase is due to an increase in legal fees of approximately \$112,000 related to general corporate and governance matters, an increase in accounting fees of approximately \$87,000 due to Sarbanes Oxley compliance, and an increase in employment related fees of approximately \$10,000 related to the hiring of certain highly qualified personnel. These increases were offset by a decrease in consulting fees of approximately \$17,000.

Selling, General and Administrative Expenses:

Our selling, general and administrative expenses were approximately \$6,923,000 and \$5,553,000 for the years ended December 31, 2015 and 2014, respectively, an increase of approximately \$1,370,000, or 25%. This increase was due to increases in salaries, commissions and related costs of approximately \$959,000 due to the impact of employee hirings and approximately \$110,000 of salary increases for named executive officers; additional sales and marketing costs, which include expenses relating to advertising and conferences of approximately \$530,000; an increase in royalty and license expenses of approximately \$107,000 due to higher sales in 2015; and an increase in travel and entertainment costs of approximately \$73,000. These increases were offset by a decrease in stock compensation expense of approximately \$296,000 due to certain milestone options earned and awarded by the Board of Directors in 2014 and a reduction in public relations expense of approximately \$207,000.

Interest Expense:

For the year ended December 31, 2015, interest income was approximately \$9,000, as compared to interest expense of approximately \$310,000 for the year ended December 31, 2014. The decrease in net interest expense was solely due to the interest payable and amortization of financing costs related to our convertible notes which were converted to common stock during 2014.

Gain (Loss) on Foreign Currency Transactions:

For the year ended December 31, 2015, the loss on foreign currency transactions was approximately \$507,000, as compared to \$386,000 for the year ended December 31, 2014, an increase of approximately \$121,000. This increase is directly related to the decline in the exchange rate of the Euro at December 31, 2015 as compared to December 31, 2014. The exchange rate of the Euro to the U.S. dollar was \$1.09 per Euro at December 31, 2015, as compared to \$1.22 per Euro at December 31, 2014.

Change in Warrant Liability:

We recognize warrants as liabilities at their fair value on the date of the grant because of price adjustment provisions in the warrants, then measure the fair value of the warrants on each reporting date, and record a change to the warrant liability as appropriate. The change in warrant liability resulted in other income of approximately \$1,345,000 for the year ended December 31, 2015 and other expense of approximately \$2,118,000 for the year ended December 31, 2014. The change in warrant liability was as a result of the change in the fair value of the warrant liability from December 31, 2014 to December 31, 2015 and from March 11, 2014 (the date of our \$10,200,000 offering) to December 31, 2014. See the consolidated financial statements for details related to the calculation of the fair value of the warrant liability.

Benefit from Income Taxes:

Our benefit from income taxes was approximately \$325,000 and \$386,000 for the years ended December 31, 2015 and 2014, respectively. These benefits were realized by utilizing the New Jersey Technology Business Tax Certificate Transfer Program whereby we sold our net operating losses to the State of New Jersey.

History of Operating Losses:

We have experienced substantial operating losses since inception. As of December 31, 2016, we had an accumulated deficit of approximately \$144,465,000, which included losses of approximately \$11,939,000, \$8,132,000 and \$9,322,000 for years ended December 31, 2016, 2015 and 2014, respectively. Historically, our losses have resulted principally from costs incurred in the research and development of our polymer technology, our legal, financial and consulting expenses, and selling, general and administrative expenses, which together were approximately \$17,066,000, \$11,883,000 and \$8,882,000 for the years ended December 31, 2016, 2015 and 2014, respectively.

Liquidity and Capital Resources

Since inception, our operations have been primarily financed through the private and public placement of our debt and equity securities. At December 31, 2016, we had current assets of approximately \$7,828,000 including cash on hand of approximately \$5,245,000 and had current liabilities of approximately \$6,090,000. In December 2016, we received approximately \$319,000 in cash from the sale of our net operating losses to the State of New Jersey.

We believe that we have sufficient cash to fund our operations through the first half of 2017; however, we will need to raise additional capital to support our ongoing operations in the future. In addition, we will need to raise additional funds to support clinical trials in the U.S. and in Europe. We will be better able to assess this need once the specific protocols of these trials are finalized.

Loan and Security Agreement:

On June 30, 2016 (the "Closing Date"), the Company and its wholly-owned subsidiary CytoSorbents Medical, Inc. (together, the "Borrower"), entered into a Loan and Security Agreement (the "Loan and Security Agreement") with Bridge Bank, a division of Western Alliance Bank, (the "Bank"), pursuant to which the Bank agreed to loan up to an aggregate of \$10 million to the Company, to be disbursed in two equal tranches of \$5 million (the first tranche, the "Term A Loan", the second tranche, the "Term B Loan", and the Term A Loan and Term B Loan together, the "Term Loans"). The Company received the proceeds of the Term A Loan on June 30, 2016. The proceeds from the Term Loans will be used for working capital purposes and to fund general business requirements in accordance with the terms of the Loan and Security Agreement. The Term Loans are secured by substantially all assets of the Company, with the exception of any Intellectual Property. Outstanding balances on the Term Loans bear interest at the thirty (30) day US dollar LIBOR rate reported in the Wall Street Journal plus 7.75%, adjusted monthly. This rate was 8.38% at December 31, 2016. The carrying value of the debt approximates its fair value.

On the Closing Date, the Company was required to pay a non-refundable closing fee of \$50,000 and expenses incurred by the Bank related to the Loan and Security Agreement of \$24,000. In addition, the Company incurred legal expenses related to the Loan and Security Agreement of \$44,833. These costs, which total \$118,833, have been presented as a direct deduction from the proceeds of the loan on the consolidated balance sheet in accordance with the provisions of ASC 850. These costs are being amortized over the loan period as a charge to interest expense. For the year ended December 31, 2016, the Company recorded interest expense amounting to \$14,855 related to these costs. After accounting for the various costs outlined above, the effective interest rate on the Term A Loan was 10.0% as of June 30, 2016. Commencing on the first calendar day of the calendar month after a Term Loan is made, the Company shall make monthly payments of interest only during the term of each Term Loan. Commencing on August 1, 2017, if the Term B Loan is not made, the Company shall make equal monthly payments of principal of \$138,889, together with accrued and unpaid interest. Commencing on February 1, 2018, subject to certain conditions as outlined in the Loan and Security Agreement, if the Term B Loan is made, which is at the Company's discretion, the Company shall make equal monthly payments of principal of \$333,333, together with accrued and unpaid interest. In either event, all unpaid principal and accrued and unpaid interest shall be due and payable in full on July 1, 2020. In addition, the Loan and Security Agreement requires the Company to pay a non-refundable final fee equal to 2.5% of the principal amount of each Term Loan funded upon the earlier of the (i) July 1, 2020 maturity date or (ii) termination of the Term Loan via acceleration or prepayment. This final fee is being accrued and charged to interest expense over the term of the loan. For the year ended December 31, 2016, the Company recorded interest expense of \$15,625 related to the final fee. The Term Loans shall be evidenced by one or more secured promissory notes issued to the Bank by the Company. If the Company elects to prepay the Term Loan(s) pursuant to the terms of the Loan and Security Agreement, it will owe a prepayment fee to the Bank, as follows: (1) for a prepayment made on or after the funding date of a Term Loan through and including the first anniversary of such funding date, an amount equal to 2.0% of the principal amount of such Term Loan prepaid; (2) for a prepayment made after the first anniversary of the funding date of a Term Loan through and including the second anniversary of such funding date, an amount equal to 1.5% of the principal amount of such Term Loan prepaid; and (3) for a prepayment made after the second anniversary of the funding date of a Term Loan through June 30, 2020, an amount equal to 1.0% of the principal amount of such Term Loan prepaid.

Events of default which may cause repayment of the Term Loans to be accelerated include, among other customary events of default, (1) non-payment of any obligation when due, (2) the failure to perform any obligation required under the Loan and Security Agreement and to cure such default within a reasonable time frame, (3) the occurrence of a Material Adverse Event (as defined in the Loan and Security Agreement), (4) the attachment or seizure of a material portion of the Borrower's assets if such attachment or seizure is not released, discharged or rescinded within 10 days, and (5) if the Borrower becomes insolvent or starts an insolvency proceeding or if an insolvency proceeding is brought by a third party against the Borrower and such proceeding is not dismissed or stayed within 30 days. The Loan and Security Agreement includes customary loan conditions, Borrower representations and warranties, Borrower affirmative covenants and Borrower negative covenants for secured transactions of this type.

The Company's and CytoSorbents Medical, Inc.'s obligations under the Loan and Security Agreement are joint and severable. The obligations under the Loan and Security Agreement are secured by a first priority security interest in favor of the Bank with respect to the Company's Shares and the Borrower's Collateral, which definition excludes the Borrower's intellectual property and other customary exceptions.

Success Fee Letter:

In connection with the Loan and Security Agreement, the Borrower simultaneously entered into a Success Fee Letter (the “Letter”) with the Bank. Pursuant to the Letter, the Borrower shall pay to the Bank a success fee in the amount equal to 6.37% of the funded amount of the Term Loans (the “Success Fee”) upon the first occurrence of any of the following events (each a “Liquidity Event”): (a) a sale or other disposition by the Borrower of all or substantially all of its assets; (b) a merger or consolidation of the Borrower into or with another person or entity, where the holders of the Borrower’s outstanding voting equity securities as of immediately prior to such merger or consolidation hold less than a majority of the issued and outstanding voting equity securities of the successor or surviving person or entity as of immediately following the consummation of such merger or consolidation; (c) a transaction or a series of related transactions in which any “person” or “group” (within the meaning of Section 13(d) and 14(d)(2) of the Securities Exchange Act of 1934, as amended (the “Exchange Act”)) becomes the “beneficial owner” (as defined in Rule 13d-3 under the Exchange Act), directly or indirectly, of a sufficient number of shares of all classes of stock then outstanding of the Borrower ordinarily entitled to vote in the election of directors, empowering such “person” or “group” to elect a majority of the Board of Directors of the Borrower, who did not have such power before such transaction; or (d) the closing price per share for the Company’s Common Stock on the NASDAQ Capital Market being \$8.00 (after giving effect to any stock splits or consolidations effected after the date hereof) or more for five successive business days.

If the Success Fee is due pursuant to a Liquidity Event described in clause (d) of the definition thereof, the Company may elect, in lieu of paying the Success Fee in cash, to issue and sell to the Bank, in exchange for the Success Fee, such number of shares of the Company’s Common Stock as would be equal to the quotient (calculated by rounding up the nearest whole number) obtained by dividing (a) the Success Fee by (b) the volume weighted average price per share of the Company’s Common Stock for the same five successive business days on which the closing price per share of the Company’s Common Stock caused the Success Fee to become payable. The Bank’s right to receive the Success Fee and the Borrower’s obligation to pay such Success Fee terminate on June 30, 2021, and shall survive the termination of the Loan and Security Agreement and any prepayment of the Term Loans.

Contractual Obligations

The following table summarizes our obligations with regard to our contractual obligations as of December 31, 2016, and the expected timing of maturities of those contractual obligations. This table should be read in conjunction with the notes to financial statements included elsewhere in this Annual Report on Form 10-K.

	Less than 1 Year	1-3 Years	3-5 Years	More than 5 Years
Operating Lease Obligations	\$375,612	\$355,128	\$130,900	–

Long-term debt	833,333	3,333,334	958,333	–
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Effects of Recent Accounting Pronouncements

In August 2014, the Financial Accounting Standards Board (“FASB”) issued ASU No. 2014-15, Presentation of Financial Statements—Going Concern (Subtopic 205-40). ASU 2014-15 requires all entities to evaluate for the existence of conditions or events that raise substantial doubt about the entity’s ability to continue as a going concern within one year after the issuance date of the financial statements. The amendments in this update are effective for the annual period ending after December 15, 2016, and for annual periods and interim periods thereafter. Early application is permitted. The Company has adopted the provisions of ASU 2014-15 and have included the effects of this adoption in Note 1 to the financial statements.

In May 2014, the FASB issued ASU 2014-09, “Revenue with Contracts from Customers.” ASU 2014-09 supersedes the current revenue recognition guidance, including industry-specific guidance. The ASU introduces a five-step model to achieve its core principal of the entity recognizing revenue to depict the transfer of goods or services to customers at an amount that reflects the consideration to which the entity expects to be entitled in exchange for those goods and services. In August 2014, the FASB issued ASU 2015-14 which deferred the effective date by one year. Accordingly, the updated guidance is effective for public entities for interim and annual periods beginning after December 15, 2017 and early adoption is permitted as of the beginning of an interim or annual reporting period beginning after December 31, 2016. The Company has evaluated the impact of the updated guidance and has determined that the adoption of ASU 2014-09 is not expected to have a significant impact on its consolidated financial statements.

In April 2015, the FASB issued ASU 2015-03, “Interest-Imputation of Interest.” ASU 2015-03 requires that debt issuances costs be presented in the balance sheet as a direct deduction from the carrying amount of the debt liability. The updated guidance is effective for the fiscal years beginning after December 15, 2015, and interim periods within those fiscal years. The Company adopted the provisions of this ASU during the fiscal year ended December 31, 2016.

In July 2015, the FASB issued ASU 2015-11, “Inventory: Simplifying the Measurement of Inventory.” ASU 2015-11 clarifies current guidance regarding the valuation of inventory. ASU 2015-11 requires that inventory be measured at the lower of cost or net realizable value. This ASU does not apply to inventory that is measured using the last-in, first-out (“LIFO”) or the retail inventory method. The updated guidance is effective for public entities for fiscal years beginning after December 15, 2016, and interim periods within fiscal years beginning after December 15, 2017. The Company has evaluated the impact of the updated guidance and has determined that the adoption of ASU 2015-11 is not expected to have a significant impact on its consolidated financial statements.

In February 2016, the FASB issued ASU 2016-02, “Leases (Topic 842)”. ASU 2016-02 outlines reporting requirements for Lessees to recognize a right-of-use asset and corresponding liability on the balance sheet for all leases covering a period of greater than 12 months. The liability is to be measured as the present value of the future minimum lease payments, plus any initial direct costs. The minimum payments are discounted using the rate implicit in the lease, or, if not known, the lessee’s incremental borrowing rate. The updated guidance is effective for public entities for fiscal years beginning after December 31, 2018. The Company has evaluated the impact of the updated guidance and has determined that the adoption of ASU 2016-02 is not expected to have a significant impact on its consolidated financial statements.

In March 2016, the FASB issued ASU 2016-08 “Revenue from Contracts with Customers: Principal versus Agent Considerations (Reporting Revenue Gross versus Net).” The amendments in this Update affect the guidance in Accounting Standards Update 2014-09, Revenue from Contracts with Customers (Topic 606), which is discussed above and is not yet effective. The effective date and transition requirements for the amendments in this Update are the same as the effective date and transition requirements of Update 2015-14, also discussed above. The Company has evaluated the impact of the updated guidance and has determined that the adoption of ASU 2016-08 is not expected to have a significant impact on its consolidated financial statements.

In March 2016, the FASB issued ASU 2016-09, “Compensation – Stock Compensation (Topic 718): Improvements to Employee Share-Based Payment Accounting.” The areas for simplification in this Update involve several aspects of the accounting for share-based payment transactions, including the income tax consequences, classification of awards as either equity or liabilities, and classification on the statement of cash flows. The updated guidance is effective for public entities for fiscal years beginning after December 15, 2016. The Company has evaluated the impact of the updated guidance and has determined that the adoption of ASU 2016-09 is not expected to have a significant impact on its consolidated financial statements.

In April 2016, the FASB issued ASU 2016-10 “Revenue from Contracts with Customers: Identifying Performance Obligations and Licensing.” The amendments in this Update affect entities with transactions included within the scope of Topic 606. The scope of that Topic includes entities that enter into contracts with customers to transfer goods or services (that are an output of the entity’s ordinary activities) in exchange for consideration. The effective date and transition requirements for the amendments in this Update are the same as the effective date and transition requirements of Update 2015-14, which is discussed above. The Company has evaluated the impact of the updated guidance and has determined that the adoption of ASU 2016-10 is not expected to have a significant impact on its consolidated financial statements.

In May 2016, the FASB issued ASU 2016-12, “Revenue from Contracts with Customers (Topic 606), Narrow Scope Improvements and Practical Expedients.” The amendments in ASU 2016-12 affect only the narrow aspects of Topic 606 that are outlined in ASU 2016-12. The effective date and transition requirements for the amendments in this Update are the same as the effective date and transition requirements of Update 2015-14, which is discussed above. The Company has evaluated the impact of the updated guidance and has determined that the adoption of ASU 2016-12 is not expected to have a significant impact on its consolidated financial statements.

In August 2016, the FASB issued ASU 2016-15, "Classification of Certain Cash Receipts and Cash Payments (a consensus of the Emerging Issues Task Force)." The amendments in this update relate to eight specific types of cash receipts and cash payments which current GAAP either is unclear or does not include specific guidance on the cash flow classification issues. The amendments in this Update are effective for public business entities for fiscal years beginning after December 15, 2017, and interim periods within those fiscal years. Early adoption is permitted, including adoption in an interim period. If an entity early adopts the amendments in an interim period, any adjustments should be reflected as of the beginning of the fiscal year that includes that interim period. An entity that elects early adoption must adopt all of the amendments in the same period. The Company will adopt the provisions of this ASU for its fiscal year beginning January 1, 2017. The adoption of ASU 2016-15 is not expected to have a significant impact on its consolidated financial statements.

Critical Accounting Policies

The preparation of financial statements in conformity with accounting principles generally accepted in the United States requires management to make estimates and assumptions that affect the reported amounts of assets and liabilities and disclosure of contingent assets and liabilities at the date of the financial statements and the reported amounts of revenues and expenses during the reporting period. Actual results could differ from those estimates. We believe the following critical accounting policies have significant effect in the preparation of our consolidated financial statements.

Patents

Legal costs incurred to establish patents are capitalized. When patents are issued, capitalized costs are amortized on the straight-line method over the related patent term. In the event a patent is abandoned, the net book value of the patent is written off.

Revenue Recognition

Product Sales: Revenues from sales of products are recognized at the time when title and risk of loss passes to the customer. Recognition of revenue also requires reasonable assurance of collection of sales proceeds and completion of all performance obligations.