

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 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, this trial still appears to be 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 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, so