

# Zacks Small-Cap Research

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CytoSorbents Corporation (CTSO) is an early revenue-stage, critical-care focused medical device company attempting to revolutionize the treatment of life-threatening illnesses in the intensive care unit (ICU) using blood purification. Their goal is to prevent or treat multi-organ organ failure, the leading cause of death in the ICU, with an immunomodulatory approach that removes excessive cytokines, toxins and other inflammatory mediators that can damage vital organs. The approach uses a unique biocompatible porous polymer bead technology to remove a broad range of toxins from the circulatory system and other bodily fluids that cannot be removed by standard hemodialysis or hemofiltration.

### **Organ Failure: focus needs to be on prevention as opposed to just treatment**

Patients with critical care illnesses such as sepsis, trauma, burn injury, acute respiratory distress syndrome and pancreatitis are some of the most seriously-ill and difficult to treat patients in the hospital. Treatments that exist today are primarily supportive care therapies that help keep the patient alive, but do not actively help patients get better. As an example, in severe lung injury, patients are placed on mechanical ventilation when they can no longer breathe on their own. Mechanical ventilation prevents the patient from dying of lung failure, with the hope that the lungs will eventually heal on their own. Unfortunately, the spontaneous healing process can take weeks, assuming the patient does not die first, and is often plagued by complications such as lung injury caused by the ventilator, hospital-acquired pneumonias and other infections. Another example is severe acute pancreatitis, in which digestive enzymes and caustic fluids from the pancreas leak into the abdominal cavity and blood, causing severe tissue damage, pain, inflammation, swelling and organ failure. This is a life-threatening condition where the only available treatment is pain control, aggressive hydration and organ-support when vital organs fail.

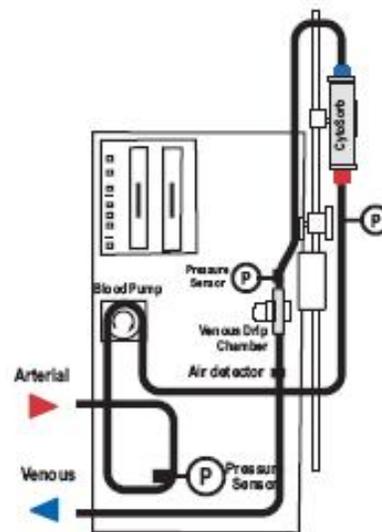
Despite the need for better treatments and the heavy cost to the healthcare system, little has been approved that can improve outcome in these complex diseases. One of the problems is that the attempted treatments have been too targeted. Normally, specific targeting is desirable as it can prevent unwanted adverse events but in these critical care illnesses, where the body's entire physiology is massively deranged with multiple organ systems affected, targeted therapies are often too little, too late. These treatments, which attempt to restore balance, can themselves also be dangerous. Due to the difficulties associated with effectively managing critical care illnesses, the goal should be to prevent organ failure, as opposed to treating it after the fact. Preventing organ failure has proven a significant challenge, however, with few, if any, therapies capable of doing this. CytoSorbents' technology is focused on doing just that (i.e. - preventing organ failure) through the removal of toxins from the blood that are the major causes of organ injury.

In critical care illnesses, the levels of inflammation driven by cytokines, toxins and other substances are so severe that if left unchecked, it would lead to widespread cell death, organ failure and ultimately patient instability and death. While hemodialysis and hemofiltration have been used to try and remove these toxins from blood, they have largely proven ineffective due to the inability to remove these larger toxins. Clinical trial data has shown that CytoSorb is one of the first technologies to be capable of reducing many of these toxins, with the goal of preventing the cascade of events that leads to organ failure. CytoSorbents' clinical trial has shown promising data on improving organ function and survival in high-risk, critically ill septic shock and lung failure patients.

### **CytoSorb**

The CytoSorb device consists of a cartridge containing hemocompatible, highly porous, adsorbent polymer beads that are intended to remove toxins and other substances from blood and physiologic

fluids. The cartridge incorporates industry standard connectors at either end of the device, which connect directly to an extra-corporeal circuit (bloodlines) on a stand-alone (i.e. not in series with a dialysis cartridge) basis. The extra-corporeal circuit consists of plastic tubing through which the blood flows, the CytoSorb cartridge containing adsorbent polymer beads, pressure monitoring gauges, and a blood pump (i.e. - conventional dialysis machine) to maintain blood flow. The patient's blood is accessed through a catheter inserted into the veins. The catheter is connected to the extracorporeal 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, recirculating system. As blood passes over the polymer beads in the cartridge, toxins (cytokines) are adsorbed from the blood. Each treatment, which lasts about six hours and processes approximately 20 - 30 blood volumes, uses a new cartridge - representing a recurrent revenue source for CytoSorbents. As CytoSorb runs on existing dialysis machines, there is no upfront capital costs to hospitals and affords CytoSorbents a large target market to sell to.



CytoSorb was CE Marked for sale in Europe in March 2011. The target markets for CytoSorb are in the clinical care settings where cytokines are elevated ("cytokine storm") such as with sepsis, trauma, acute respiratory distress syndrome, severe burns and acute pancreatitis. It also can be used on-label in other acute conditions where cytokines are elevated such as in cardiac surgery or autoimmune disease flares. As such, CytoSorb targets a multi-billion dollar total addressable market where very few treatment alternatives exist. The route for U.S. regulatory approval (the initial U.S. target indication would likely be sepsis) would likely be the PMA pathway – which will require the company to conduct U.S.-based clinical trials - the scope, size, duration, cost, etc. of which are unknown but which may become more clear in the coming months. In 2007 the FDA approved an IDE for CytoSorbents to conduct a small U.S. sepsis safety study. Given the positive results of the European sepsis trial and the fact that the European trial incorporated much of the FDA's guidance from the IDE, CytoSorbents now hopes to use their positive European trial data to request an IDE modification to allow for U.S. efficacy-powered studies which would eventually support a PMA filing. CytoSorbents hopes to have the IDE amended for approval of either a large (~ 300 - 500 patients) pivotal study or a more targeted study (~150 patients) stratified for mortality risk factors (such as age and cytokine levels). Assuming positive results, CytoSorbents would then use data from one or more of these studies to support an eventual PMA submission. While a smaller study would incorporate a more narrow indication (e.g. aged 65 and over), it would likely require significantly less time and money to complete than would a larger study with a more diverse patient population. In addition, a more narrow indication would not necessarily meaningfully limit the commercial opportunity in the U.S. as physicians could use the device outside the approved indication (i.e. - off-label) and the vast majority of sepsis patients are 65+ years old and/or have elevated cytokine levels anyway.

CytoSorbents hopes to meet with the FDA to discuss a possible modification to their IDE in the near-term (specific timelines have not been announced).

We note, however, that enrollment, completion and data analysis of even a smaller pivotal U.S. trial is not a near term event and may require many millions of dollars to self-fund (a larger study would be longer and even more costly). Another possible option that is on the table is to fund this through a co-development agreement with potential strategic partners, which could significantly reduce the amount of outside capital that CytoSorb would need to raise. In the meantime, CytoSorbents expects to focus on the European market, generate additional clinical data from smaller studies (including a confirmatory dosing study), publish existing data from their European sepsis trial, and further investigate (including discussions with the FDA) the requirements to gain U.S. approval of CytoSorb.

### **CytoSorb Reduces Cytokine Storm**

Cytokines are small proteins that, in moderation, normally help stimulate and regulate the immune system. They are secreted by cells and are used extensively in cell-to-cell communications. When the immune system fights pathogens, cytokines not only signal white blood cells to attack the infection, they also stimulate those cells to produce more cytokines. There are two types of cytokines that are produced, pro-inflammatory cytokines (such as tumor necrosis factor-alpha, interleukin-1, and interleukin-6) and anti-inflammatory cytokines (such as interleukin-10 and interleukin-1 receptor antagonist). Under normal circumstances the body regulates this "feedback loop", keeping the production of cytokines and immune cells at a safe level. In some instances, however, the body fails to properly regulate the level of cytokines, resulting in an excess of cytokines and rapid multiplication of immune cells. Elevated levels of cytokines can be harmful - in chronic yet less serious cases (when cytokines are only moderately elevated), this can cause autoimmune disorders such as rheumatoid arthritis. In acute cases where cytokine levels spike as a result of disease or infections, this is called a "cytokine storm". In a more mild form, such as might be experienced with the flu, cytokine storm can result in fever, chills, fatigue, nausea, and body aches. In more severe cases (which is common with intensive care unit patients), cytokine storm can result in very serious and sometimes fatal reactions by the body including blood clotting, shock, lung injury and cell death, leading to multiple organ failure and infection, frequently resulting in patient death.

CytoSorbents' European Sepsis Trial showed that CytoSorb significantly reduced cytokines in patients with severe sepsis or septic shock in the setting of lung injury. The purpose of the trial, which was performed at 14 sites in Germany, was to demonstrate safety and statistically significant reduction of key cytokines such as interleukin-6 (IL-6) in patients with sepsis and respiratory failure. A secondary endpoint was reduction in mortality. Targeted enrollment was 100 patients, randomized to either treatment with CytoSorb for seven days plus standard of care (SOC) or only SOC (control). SOC included antibiotics, fluids, mechanical ventilation and other usual therapy consistent with the typical treatment of sepsis.

Taking into account all 100 patients, the treatment was well-tolerated with no serious device related adverse events reported in more than 300 human treatments in the trial. This is consistent with all studies to-date, which have shown no serious device-related adverse events in over 650 human treatments. Of the 100 patients enrolled, 4 ultimately withdrew, 22 were part of a sepsis pilot study, and 31 were used only for safety data due to a failure of the protocol for randomized enrollment at two trial sites that introduced bias into the trial and made the control and treatment arms not comparable. Safety and efficacy data were collected and analyzed on the remaining 43 patients (18 in treatment cohort, 25 control), most of which suffered from multiple organ failure. Of these patients, septic shock was present in 94% of treatment and 100% of control, acute respiratory distress syndrome in 67% of treatment and 56% of control, and renal failure in 39% of treatment and 24% of control. The 43-patient analysis showed CytoSorb statistically significantly ( $p < 0.05$ ) reduced circulating levels of key cytokines from whole blood on the average of 30%-50% over the 7 day treatment period. Specifically CytoSorb statistically significantly reduced the following cytokines; IL-6 by 49% ( $p = 0.01$ ), IL-1ra by 37% ( $p = 0.001$ ), MCP-1 by 50% ( $p = 0.002$ ), and IL-8 by 30% ( $p = 0.002$ ).

Additionally, an analysis of two subgroups of patients that were classified as being at high risk of death, specifically in patients with very high cytokine levels (IL-6 1,000 pg/mL and/or IL-1ra 16,000 pg/mL) and patients aged 65 and over, was done which showed a statistically significant reduction in mortality in

CytoSorb treated patients. In the high cytokine level group, 28-day mortality (28 days is widely accepted as the standard time mortality endpoint in sepsis studies) was 0% in the CytoSorb cohort versus 63% in the control cohort (statistically significant  $p=0.03$ ,  $n=14$ : 6 treatment / 8 control). It also showed a trend (i.e. - potentially meaningful but not statistically significant) to benefit in fewer patients on mechanical ventilation at 28 days (33% treatment vs. 88% control) and fewer days in the ICU (24 days treatment vs. 28 days control). In the 65 and over group, 14-day mortality was 0% in the CytoSorb cohort versus 36% in the control cohort (statistically significant  $p=0.04$ ,  $n=21$ : 10 treatment / 11 control) suggesting a potential protective effect with treatment. With only 7 days of treatment, the mortality benefit in this 65+ year-old subgroup was not significantly different at 28 days (40% treatment vs. 45% control), though trends to benefit were observed with fewer mechanically ventilated patients at 28 days (60% treatment vs. 73% control), and improvements in the MODS organ failure scores during treatment. CytoSorbents noted that although the trial protocol did not allow CytoSorb therapy beyond the 7-day treatment period, the company and its scientific advisors believe that a longer duration of treatment may have yielded even greater benefit.

Relative to the subgroup analysis, as we noted earlier, in lieu of a larger, more expensive U.S. clinical study which might encompass a relatively diverse patient population, CytoSorbents may look to focus their efforts for U.S. regulatory approval on a more high-risk patient segment, such as 65+ years-old (this will likely be part of the near term discussions with FDA related to modification of the IDE). Per the Centers for Disease Control and Prevention (CDC), patients 65 and older account for approximately two-thirds of all sepsis-related hospitalizations – which means a more narrow focus on high-risk patients (such as 65+ years old) may not substantially reduce the overall commercial opportunity for CytoSorb.

### **Sepsis: Highly Lethal and Difficult/Costly To Treat**

Sepsis, more commonly known as blood poisoning and one of the top 10 causes of death, is initially caused by a serious infection such as pneumonia or a urinary tract infection. However, it often triggers a massive cytokine-driven immune response, leading to severe inflammation throughout the entire body. The initial onset of fever, chills, fatigue, pain and nausea drive patients to seek medical care. Worsening cytokine storm can lead to more serious complications that need to be managed in the ICU such as cell death, circulatory collapse, organ failure, immune suppression and additional infections, loss of limbs, and frequently death.

Sepsis is aggressive and difficult to treat. Today, standard of care therapy focuses on trying to kill the causative organism (bacteria, virus, fungi) with antibiotics or anti-viral therapy. Additional therapy in the ICU includes supportive measures such as providing fluid support, nutrition, tight metabolic control, drugs to increase the blood pressure, and mechanical support such as mechanical ventilation and dialysis. Treatment often fails, however, as evidenced by the 30%+ sepsis-related mortality rate.

The problem is that while there are broad-spectrum antibiotics to treat the infection, there are currently no effective therapies to treat the out-of-control immune response and the production of cytokines and other toxins that are ultimately responsible for killing the patient via multiple organ failure and additional infections. CytoSorb is trying to address this problem with a broad spectrum cytokine filter that is designed to modulate the immune response-preventing or reducing the development of organ failure, and helping the immune system function properly so that it can fight infection and not damage the body.

In the U.S. and Europe, there are more than 1 million and 1.5 million new cases, respectively, of severe sepsis and septic shock annually - worldwide there are about 18 million cases per year. In Germany, CytoSorbents' initial geographic market with CytoSorb, there are approximately 150k cases of sepsis each year. CytoSorbents' value-added proposition for its device in the sepsis application is its effectiveness coupled with lower cost of treatment relative to existing therapy, which can be substantial. Relative to the burden and cost to treat sepsis, CytoSorbents notes that on average; sepsis patients are treated in the intensive care unit (ICU) for 16 days and for a total of 25 days in the hospital, treatment cost per day in ICU is ~\$2k - \$3k/patient (in both U.S. and Europe), total hospital cost is ~\$50k/patient, overall cost of sepsis in the U.S. is ~\$18 billion/year and in Germany is ~\$6 billion/year (where it also accounts for ~1/3 of the total ICU budget).

Based on current reimbursement, CytoSorbents expects to sell their device for at least \$500 per cartridge. With each treatment requiring a new cartridge and approximately seven treatments expected per patient for sepsis, CytoSorbents estimates the combined European and U.S sepsis opportunity at around \$9 billion (~\$3,500 per patient treatment x ~2.5 million patients). In Germany, with about 150k sepsis cases annually, the total addressable market opportunity is estimated to be roughly \$500+ million (~\$3,500 x 150k patients).

While CytoSorbents' trial focused on sepsis and lung injury, the company's cytokine reduction approach is designed to more broadly address the Systemic Inflammatory Response Syndrome (SIRS), a serious condition related to systemic inflammation, organ dysfunction, and organ failure. The company conducted its first major CytoSorb trial in sepsis and lung injury, both critical areas known to have high cytokine levels in need of modulation. CytoSorbents intends to continue research in other critical care applications that may benefit from this immunomodulatory approach such as acute respiratory distress syndrome, trauma, burn injury, severe acute pancreatitis and autoimmune disease flares - which, the company notes, could increase the total addressable market in the U.S. and Europe to approximately \$15 billion. CytoSorbents believes that CytoSorb could also be used in cardiac procedures where cardiopulmonary bypass (a machine used to bypass the heart and lungs that oxygenates and pumps blood to the rest of the body) is used, such as in coronary artery bypass graft (CABG) surgery for coronary artery disease, heart and lung transplant, left-ventricular assist device (LVAD) implantation, valve surgery, and others. Cardiopulmonary bypass is a well-known activator of excessive cytokine production that can lead to organ dysfunction or failure after the procedure. There are approximately 1 million cardiopulmonary bypass procedures done in the U.S. and Europe each year. CytoSorbents views this as a potential near-term opportunity and believes CytoSorb could offer a superior, simpler and more direct alternative to the conventional use of leukoreduction filters during cardiopulmonary bypass procedures which have shown to be ineffective in reducing cytokines.

### **Sepsis-Related Contracts / Grants**

Over the past decade CytoSorbents has been a recipient or participated in multiple grants related to the development of technology for the treatment of critical illnesses and sepsis. We discuss two of these which we view as of particular interest:

- **U.S. Army SBIR Trauma Grants:** In December 2011, the U.S. Army Medical Research and Materiel Command awarded CytoSorbents a Phase I Small Business Innovation Research (SBIR) grant entitled Investigation of CytoSorb cytokine and myoglobin removal in the treatment of trauma valued at \$100,000 over six months. CTSO has since completed the Phase I portion (i.e. - planning phase) and in September 2012 was awarded the Phase II portion. The Phase II portion is worth up to \$1M and will include animal studies. A Phase III grant could follow which would entail human studies. This program is intended to yield animal and human data that can be used to treat trauma patients in the future. This directly addresses the major reasons why warfighters die - sepsis and infection, polytrauma, and burn injury - which could potentially open the door to other military funding programs if successful. Similar to the DARPA awards, we view the Phase II SBIR grant significant not only from a near-term revenue and cash flow perspective, but potentially more importantly it provides CytoSorbents and their technology with greater awareness, expanded applications beyond sepsis and trauma (into burn and smoke injury), and further credible validation (U.S. Army has clearly taken notice and CTSO notes that the U.S. Air Force also has expressed interest in their technology).
- **DARPA Dialysis Like Therapeutics Program:** The Defense Advanced Research Project Agency (DARPA) is part of the U.S. Defense Department which is responsible for funding radical innovations such as the internet, global positioning system (GPS) technology, and robotic surgery. In early 2011 DARPA issued a Broad Agency Announcement soliciting innovative research proposals under a program titled "*Dialysis-Like Therapeutics (DLT)*" to manage sepsis. CytoSorbents applied and in August 2012 the company announced that it was awarded a milestone-based contract worth up to \$3.8 million (also assumes all milestones are met) over five years, including \$1.5 million in the first year (CTSO began realizing revenue from this contract in Q3 2012 and recognized ~\$1.3 million to-date). As DLT is a collaboration with several different

companies and universities being awarded contracts related to the project, CytoSorbents' technology is one piece of this puzzle.

CytoSorbents contribution to the DLT program is developing their next-generation porous polymers and the company expects to broaden the scope of targeted substances to include a wide range of toxins in addition to cytokines. In addition, as the DARPA DLT Broad Agency Announcement strongly encourages technologies that do not require anticoagulation, CytoSorbents expects to incorporate that capability into its polymer technology.

### Other Critical-Care Applications

While sepsis has been the major targeted focus in CytoSorb's clinical trials to-date, the device may have utility in a variety of critical care applications where elevated cytokine levels can compromise patient health and lead to serious complications such as Multiple Organ Dysfunction Syndrome (MODS) and/or Multiple Organ Failure (MOF). Specifically, CytoSorbents points to patients with acute respiratory distress syndrome, severe burn injury, trauma, and pancreatitis as all potentially benefiting from treatment with their device (in fact most patients in the European Sepsis trial suffered from acute respiratory distress syndrome). CytoSorbents estimates that the combined U.S./Europe market opportunity for their device in all other critical care applications outside of sepsis is approximately \$15 billion, including ~\$900 million in Germany. Relative to these applications, CytoSorb is pursuing investigator-initiated studies - in both animals and human pilot studies - funding of which may be pursued solely by CytoSorbents, through grants, partnerships, or a combination of one or more of these. Meanwhile, CE Mark allows CytoSorb to be used in Europe in any application where cytokines are elevated.

The company is also investigating the use of CytoSorb in the prevention and treatment of post-operative complications of cardiopulmonary bypass surgery with the objective to reduce ventilator and oxygen therapy requirements and reduce post-surgical complications and costs. Prevention and treatment of organ dysfunction in brain-dead organ donors is another area where CytoSorb may hold promise - although this is not a near-term focus for the company.

### Pipeline

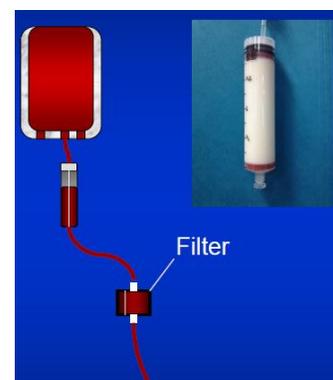
CTSO is also working on other products aside from CytoSorb (although CytoSorb is clearly the front-runner where the company is dedicating the bulk of their resources). The pipeline includes HemoDefend, BetaSorb and ContrastSorb.

**HemoDefend**, with expected applications in purification of blood used for transfusions, uses a new optimized version of CytoSorbents' polymer technology designed to capture contaminants in blood that can cause adverse events and transfusion reactions. Blood can become contaminated either from the donor or during storage as the blood ages. HemoDefend is designed to safeguard the quality and safety of the blood supply by removing contaminants such as antibodies, free hemoglobin, cytokines, and bioactive lipids in whole blood, packed red blood cells, and platelets that can cause transfusion reactions such as life-threatening Transfusion Related Acute Lung Injury (TRALI) and lethal allergic reactions. The technology uses a mixture of different beads and can be tailored to remove specific substances of interest.

"Beads in a Bag"



In-Line Filter Configuration



According to the World Health Organization (WHO), there are more than 80 million blood donations each year worldwide with each donation generating multiple blood transfusion products such as packed red blood cells (pRBCs), platelets, fresh frozen plasma, and cryoprecipitate. Every year there is an estimated 150 - 200 million transfusions administered worldwide with, according to the American Red Cross, more than 30 million in the U.S. alone. CytoSorbents target market for the technology are pRBCs, platelets, and whole blood, which represent more than half of all blood transfusions annually. HemoDefend can be configured either as an in-line filter design or what the company has termed "Beads in a Bag".

With "**Beads in a Bag**" (currently CytoSorbents' main focus with HemoDefend) the beads are placed directly into a blood storage bag during bag manufacturing and blood or separated blood components are then later added to the bag. Purification begins instantly and continues throughout the duration of storage, maximizing removal efficiency. The beads are neutrally buoyant, eliminating the need for mixing and simplifying the purification process. An integrated filter in the bag prevents beads from leaving the bag during the transfusion process. The polymer beads meet 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, recombinant proteins, ligands, or drugs. Because of this, they have a very long shelf life that is consistent with blood storage bag manufacturing standards. No special equipment or handling is required, making it ideal for mainstream and military applications, as well as for use in less developed countries.

CTSO has stated in the past that they will look to out-license their HemoDefend technology (a company such as a blood storage bag manufacturer may have particular interest) and had received very positive feedback when they attended an American Association of Blood Banks conference in 2011. Development of HemoDefend still at an early point and we have little visibility relative to the development and regulatory approval strategy or chances of (eventual) commercialization (as well as the commercial opportunity for the product) at this point. The company did recently provide a brief update on HemoDefend, however, noting that they refined the filter which now allows a unit of blood to flow through in under a half-hour, within the requirements for blood transfusions. CTSO is now working to reduce unit production costs including optimizing packaging. Beads in a Bag was also the subject of CTSO's poster presentation at the 2012 American Association of Blood Banks conference.

**BetaSorb** is also in the pipeline. BetaSorb was the company's initial hemoperfusion device and was designed to improve the removal of mid-sized toxins from blood during dialysis in patients with end-stage renal disease (ESRD), or more commonly known as chronic kidney disease (CKD). According to the U.S. National Kidney Foundation there are over 340k Americans with chronic kidney disease on dialysis. BetaSorb's specific target is removal of  $\beta_2$  microglobulin (B2M) from the blood of chronic kidney failure patients who are on long-term dialysis. In people undergoing long-term dialysis, B2M can aggregate into fibrous proteins called amyloid fibers which can deposit in the joints (a disease known as "dialysis-related amyloidosis" or DRA), resulting in pain/stiffness and even bone fractures, eventually leading to disabling musculoskeletal complications. Actual prevalence of DRA is not known, although past studies (done prior to high-flux dialyzers becoming commonplace) have indicated that incidence is roughly 20% of patients that have been on dialysis.

BetaSorb is physically and largely functionally similar to CytoSorb but the two devices use different polymers and differ in their targeted uses - BetaSorb was developed for chronic use while CytoSorb targets acute care usage in the intensive care unit. BetaSorb is intended to be used in series with a dialysis cartridge, while CytoSorb can be used as a stand-alone device, or in series with a dialysis cartridge if the patient has kidney injury. Both are used with standard hemodialysis machines found in hospitals today.

Relative to the future of BetaSorb, we feel that there are a number of unknowns regarding further development, regulatory approval strategy, and the commercial opportunity for the device – the most glaring unknown right now is the approvability of the device (as chronic use can result in the removal of essential substances from the blood – most notably albumin). CytoSorbents has since improved on the technology and developed newer generations of BetaSorb that are specifically designed for chronic treatment (although further optimization will be necessary). Another potentially limiting factor is the relatively small size of the DRA market - which we estimate (roughly) at about 80k people in the U.S. and roughly a similar number in Europe. Although anticipated use of BetaSorb would be 3 times per week for life in this patient population, compared to the 2 million - 3 million patients in the sepsis and other critical care markets (i.e. - CytoSorb's market) in the U.S. and Europe combined, DRA seems like a significantly less attractive patient segment.

In May 2013 CTSO announced **ContrastSorb** as their latest pipeline candidate. ContrastSorb is being designed to prevent contrast-induced nephropathy (CIN), a condition that patients with compromised kidney function are susceptible to when undergoing procedures that require use of a contrast agent such as image-guided cardiology and certain radiology procedures. CIN has been estimated to be a ~\$500 million/yr market. Current standard of care to address CIN, which is essentially indiscriminately flushes the contrast agent from the body, is often times ineffective. CTSO believes their ContrastSorb technology may be a more effective option to remove contrast agents from these high risk patients.

### **Recent Results and Progress Are Encouraging**

CytoSorbents reported results for the first quarter ending March 31, 2013 on May 16th. Importantly, revenue from product sales is showing significant growth, on both a sequential and yoy basis. On the operational side, the company's awareness-building efforts continue to ramp up and are bearing early fruit, the number of key opinion leaders using or interested in CytoSorb continues to grow, clinical trials in Europe remain on-track, a manuscript has been accepted for journal publication, the distribution and sales footprint is expanding, CTSO scored an add-on grant funding, and additional experienced personnel were brought on. In summary, we think CTSO is making exceptionally strong headway on the early commercialization of CytoSorb, on awareness building including getting in front of an increasing number of KOL's and attendance at key events and conferences, and in further validation of the technology via clinical studies as well as scoring additional government grants.

In May CTSO entered a distribution agreement with L.I.N.C Medical Systems to distribute CytoSorb in the U.K. and Ireland. This significantly beefs up CTSO's distribution in Europe, where the company started rolling out their device around the middle of last year. Their European footprint now encompasses several countries including Germany, Austria, Switzerland, U.K., and Ireland which is serviced by a combination of CTSO's small sales force and third party distribution. We continue to expect somewhat of a measured roll-out throughout the remainder of 2013 and believe CTSO will continue to look to further broaden their footprint in Europe.

The company also added to their leadership, bringing on an experienced V.P. of Business Development with a background which includes a senior venture development role at Johnson & Johnson (JNJ) and adding a full-time CFO with a background with biopharma and medical device companies. In April CTSO announced the establishment of a Trauma Advisory Board, consisting of members with vast experience in the fields that CytoSorbents is directly focused on - namely, critical care and trauma. All of the board members are medical doctors with impressive credentials in their respective fields of expertise (trauma, critical care, burn injury).

Q1 revenue came in at \$371k which included product sales and grant income of \$176k and \$195k, respectively. Product sales increased 942% yoy and were up 100% sequentially. As product sales are what will be the long-term driver of CTSO, this early success is a clear positive. Net income and EPS were (\$2.22) million and (\$0.01) compared to (\$2.09) million and (\$0.01) in Q1 2012. The yoy decline in net income is mostly a result of higher SG&A due in large part to CTSO recently scaling up their sales and marketing efforts following the launch in Germany. We expect SG&A to be leverageable going forward.

## **Burgeoning Interest In CytoSorb**

Of particular significance is growing interest in CytoSorb from clinicians and key opinion leaders. This, along with the ongoing dosing study in Germany, is what we think will be pivotal in accelerating uptake and interest of CytoSorb for clinical use as well as providing support for initiation of U.S. clinical studies. In a fairly short period of time CTSO has introduced the device to and garnered meaningful interest from some highly influential thought leaders in the field of sepsis and other critical care illnesses. Future recommendations and potentially published manuscripts from some of these thought leaders, including investigators from the German dosing study, could wield meaningful influence - the fruits of which we think may be seen in the short-to-mid term.

Indications are that early feedback relative to safety and efficacy is very encouraging. As an example, the company notes in a recent investor presentation specific instances where CytoSorb was credited with helping save the lives of critically ill patients. Also of significance is that while CytoSorb has largely been used in instances where the patient is so critically ill that there's little to lose by trying the device, with the recent additional confidence of its efficacy this is now starting to progress where the device is being introduced at an earlier stage of intervention (another sign of substantial support, in our opinion). Another particular highlight is progress with CytoSorb in complications from cardiac surgery, a potentially significant market. We had viewed this as more of a back-burner application but with this program moving forward and an unmet need for a clearly effective standard of care, we think this application could potentially begin to bear fruit in the mid-term. This will be something we will keep an eye on.

Summary of recent operational and financial highlights;

### **Commercialization**

- Direct sales of CytoSorb commenced in Germany, Austria and Switzerland
- Agreement penned in May with L.IN.C Medical Systems to distribute CytoSorb in the U.K. and Ireland
- Q4 2012, the first quarter that CTSO's sales team was fully active, generated commercial revenue of \$88k. Product revenue grew 100% sequentially to \$176k in Q1. Commercial sales are expected to climb, facilitated by a growing sales force, distribution agreements, additional validation studies to further support use of CytoSorb, already established reimbursement in Germany and Austria, and fruits from awareness building efforts, among other catalysts

### **Validation / Regulatory**

- CTSO recently noted that more than 80 (up from 60 in just the last few months) key opinion leaders (KOL) are either using CytoSorb, want to use it or are planning to use it in clinical trials. CTSO is also in the planning stage for several more investigator initiated studies. CytoSorb studies include those for both sepsis-related (which encompasses severely ill patients with acute lung injury, trauma, and complications from flu) as well as cardiac surgery patients. Human sepsis studies have been ongoing. Relative to cardiac surgery, preliminary testing has been completed and human pilot studies are expected to be initiated in the near-term
- Dosing study (Europe) ongoing with more patients being enrolled. CytoSorb has been used for up to 24 hours over 7 days with no serious device related events reported. CTSO will expand the study to ten leading hospitals in Germany. Data from the study is expected to be used to further supplement the data from the European Sepsis trial as well as support to shape protocol for a U.S. study. We think data from this dosing study could be available in 2013
- CTSO recently noted that a number of case study reports have been borne from ongoing studies with one now accepted for publication
- Initial feedback from physicians using CytoSorb in clinical practice with critically ill patients, including those with septic shock and multiple organ failure (which includes the initial indications addressed by CytoSorb), have been encouraging with outcomes including a

- dramatic reduction in IL-6 levels (which was also an endpoint in the European Sepsis Trial), stabilized organ failure, and patient recovery
- Continuing to pursue U.S. regulatory approval pathway
- Award of the Phase II Small Business Innovation Research grant from the U.S. Army, worth up to \$1 million
- Awarded additional phase I option on U.S. Army grant in April worth \$50k

#### **Awareness-building**

- Presentations, exhibitions and research talks at several scientific meetings. Anticipate this will continue and will also be supplemented by presentations by key opinion leaders which are using CytoSorb
- Most recently, in March CTSO exhibited at the International Symposium on Intensive Care and Emergency Medicine in Brussels, Belgium which attracted 6k participants. CTSO noted feedback and interest in CytoSorb from clinicians and potential new customers and distributors was overwhelmingly positive. In addition, there were two presentations related to CytoSorb;
  - Dr. Kellum (University of Pittsburgh Medical Center) presented on his findings from his recently published article in the journal, Molecular Medicine. His presentation, entitled "Reversing sepsis-induced immune suppression" was attended by more than 300 people
  - Dr. Schadler (Kiel University) presented his poster titled, "A multicenter randomized controlled study of an extracorporeal cytokine hemoadsorption device in septic patients"

#### **Inflection Point Could Come In 2014**

We model very modest yet sequentially growing sales of CytoSorb in Germany and other parts of Europe during 2013, reflecting measured progress with implementation of the sales/marketing strategy. We model revenue in 2013 to come from a combination of government contracts (i.e. DARPA / US Army SBIR phase II) and product sales. We assume increased awareness and visibility of CytoSorb results in a greater rate of burgeoning interest materializing during the year. We think CTSO could generate almost \$2.9 million of revenue in 2013.

Our modeled revenue in 2014 and beyond includes mostly sales of CytoSorb (with a relatively small % contribution from contracts/grants). Assuming positive results from company-sponsored and investigator-led studies as well as supportive feedback from hospitals and critical care professionals, we think 2014 could be more of an inflection point for CytoSorb and mark the beginning of a significantly greater ramp in commercial sales. We think CTSO could generate approximately \$6.7 million of revenue in 2014.

Based on the current ambiguity relative to what the FDA will be looking for to support a potential future PMA submission and the real risk of delays (from a best-case-scenario launch in 2016), we do not incorporate any contribution from sales of CytoSorb in the U.S. until an assumed soft-launch sometime in 2017. We will update our assumptions if appropriate when there is more clarity on the U.S. regulatory strategy and related timelines.

#### **CTSO Attractive Investment**

Despite certain risks and uncertainties, we think CTSO offers an attractive investment opportunity given the large markets that CytoSorb addresses, the unmet need for a consistently effective critical-care intervention, positive initial trial data, early and burgeoning interest from seemingly influential physicians throughout the world, growing commercial sales (albeit still relative minimal in aggregate), regular grant awards (which provides both revenue and additional validation of the technology), and experienced leadership (spearheaded by CTSO's CEO, Dr. Phil Chan, a Cornell and Yale educated, Harvard residency, medical doctor).

Based on our 10-year DCF model, which uses a 15% discount rate to account for certain risks and uncertainties that CytoSorb faces (several of which we detailed in our initiation report), the shares are

valued at approximately \$0.50. Our model and assumptions will be updated commensurate with news flow which could also influence the valuation. As it is now, we value the company at \$0.50/share, implying upside to the current share price and reflecting our Outperform rating.