CytoSorbents Corporation (NASDAQ: CTSO)
2017 First Quarter Earnings and Operating Results Conference Call
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This official company transcript has been edited for clarity and does not differ materially in content from the actual conference call except where noted. Slide numbers have been inserted to allow readers to follow along with the associated presentation

Operator:

Good day everyone and welcome to the CytoSorbents First Quarter 2017 Operating and Financial Results Conference Call. Today's conference is being recorded. At this time, I'd like to turn the conference over to our moderator, Amy Phillips, please go ahead.

Amy Phillips – Moderator:

Thank you and good afternoon. Welcome to CytoSorbents First Quarter 2017 Operating and Financial Results conference call. Joining me today from the Company are:

- Dr. Phillip Chan, Chief Executive Officer and President
- Vincent Capponi, Chief Operating Officer
- Kathleen Bloch, Chief Financial Officer
- Dr. Christian Steiner, VP of Sales and Marketing from Germany
- Chris Cramer, VP of Business Development

Before I turn the call over to Dr. Chan, I'd like to remind listeners that during the call, management's prepared remarks may contain forward-looking statements which are subject to risks and uncertainties. Management may make additional forward-looking statements in response to your questions today. Therefore, the Company claims protection under Safe Harbor for forward-looking statements contained in the Private Securities Litigation Reform Act of 1995. Actual results may differ from results discussed today and therefore, we refer you to a more detailed discussion of these risks and uncertainties in the Company's filings with the SEC.

Any projections as to the Company's future performance represented by management include estimates as of today May 8, 2017, and we assume no obligation to update these projections in the future as market conditions change. During today's call, we will have an overview presentation covering the financial and operating highlights for third quarter first quarter by Dr. Chan and Ms. Bloch. Following that presentation, we will open the line to your questions during the live Q&A session with the rest of the management team.

At this time, it's now my pleasure to turn the call over to Dr. Phillip Chan. Dr. Chan, go ahead please.

Phillip Chan

Thank you very much Amy and thank you everyone for joining the call today. After going over a quick overview on the Company, Kathy will discuss financial highlights for the quarter after which I will cover excerpted slides from the REFRESH I clinical trial presentation from the American Association for Thoracic Surgery Conference last Monday, and then will conclude with major initiatives for the remainder of 2017.

Slides 4-7

CytoSorbents is a leader in critical care immunotherapy leading the prevention or treatment of life threatening inflammation in the ICU in cardiac surgery using CytoSorb® blood purification. Unfortunately, millions of people die every year from uncontrolled deadly inflammation during diseases like sepsis, trauma, burn injury, cytokine release syndrome from cancer immunotherapy, liver failure, surgical complications, pancreatitis, liver failure, influenza, and many other illnesses where inflammation plays a deadly role, for which there are no effective therapies that can control both this deadly inflammation, and still keep the immune system intact.

And that is where CytoSorb comes in. CytoSorb removes the fuel to the fire of inflammation, targeting a $20 billion opportunity in critical care in cardiac surgery. CytoSorb is approved in the European Union as the only specifically approved extracorporeal cytokine filter, with a broad indication for use in any situation where cytokines are elevated. CytoSorb also removes many other different inflammatory mediators such as free hemoglobin, bacterial toxins, myoglobin, activated complement, and many other inflammatory mediators in an approximately 10 to 60 kilodalton molecular weight range.

CytoSorb also works with standard dialysis and heart and lung machines, and as we will talk about later, it also works with standard extracorporeal membrane oxygenation, or ECMO, machines. It has now been well-tolerated in more than 23,000 human treatments, up from 20,000 in the last quarter. Our goal with CytoSorb is to try to control this deadly inflammation in order to try to prevent or treat organ failure, which is a direct result of this deadly inflammation that is the cause of nearly half of all deaths in the ICU today. In doing so, we hope to be able to improve patient outcomes and survival while decreasing the cost of ICU and patient care.

With that, I'd like to turn it over to Kathy to talk about our financial highlights. Kathy?

Kathleen Bloch

Slides 8-13

Thank you, Phil, and good afternoon everyone. For today's call, I will be providing an update regarding CytoSorbents' first quarter 2017 financial results including product sales progress and an update around our recent equity raise and cash runway.

Turning to our quarterly financial results, CytoSorbents product sales for first quarter of 2017 were approximately $2.6 million, which is an increase of 63% over first quarter of 2016 product sales of approximately $1.6 million. Grant and other income grew 143% from $212,000 in Q1 2016

to $517,000 in Q1 2017, and total revenues which includes product sales and grant income increased by 72% to $3.1 million in Q1 2017 as compared to $1.8 million in Q1 of 2016.

Now, let's take a look at our quarter-over-quarter product sales. Our first quarter product sales for 2017 were approximately $2.6 million which were just slightly and near $17,000 below our Q4 2016 product sales. This is coming off a very robust quarter of growth in Q4 2016. One factor that impacted our Q1 2017 sales was that in Germany, we saw some delays in ordering pending official approval of reimbursement rates related to our new dedicated reimbursement code for CytoSorb. Many hospitals have now finalized these rates, which in most cases is significantly higher than what was achieved previously, covering the full cost of the device, and in most cases, up to the full cost of the procedure. This is expected to benefit future sales growth. Most importantly, the underlying drivers of revenue growth remained unchanged and management continues to be optimistic about continuing sales growth particularly with regard to the second half of 2017.

At December 31, 2016, our trailing 12-month product sales were $8.2 million. Now it has climbed to $9.2 million for the 12-month ended March 31, 2017 as depicted in this chart. Overall, we believe our annual product sales exhibits a very strong growth trajectory and we expect continuation of this trend in the future.

In terms of growth catalysts, we are first seeing a healthy market with continued strong interest in CytoSorb with good organic growth across the board in critical care and cardiac surgery. Secondly, as we've already discussed, the finalization of reimbursement rates in Germany is expected to be a very significant driver for direct sales in the future. Third, we expect continued growth from our strategic partners and distributors. Fourth, we are looking forward to the ramp up as a result of the co-marketing agreement that we have in place with Fresenius Medical Care. Fifth, we continue to discover new indications where our therapy is being used successfully, including ECMO for example, that we will talk more about, later. And finally, the generation of more and more clinical data will be another major catalyst to sales.

Finally, let's turn to our working capital position. As of March 31, 2017, we had approximately $3.2 million in cash, and in April 2017, as a result of our $11.5 million equity financing we added another $10.3 million in net proceeds, bringing our cash on hand to $13.5 million. We additionally have another $5 million available to us from our debt facility with Bridge Bank, which is available to further extend our operating runway into the second half of 2018 at which time we expect to be at or very close to operating breakeven.

As of March 31, 2017, we have approximately 30.3 million common shares on a fully diluted basis. As a result of the April equity financing, total outstanding shares on a fully diluted basis are currently 32.9 million.

And now, I'd like to turn the call back to Phil. Phil?

Phillip Chan

Slides 14-27

Thank you, Kathy. There have been many requests from both analysts and shareholders for us to review the REFRESH I data and so we thought that we would try to do that on today's call.

The study, entitled "Use of a Novel Hemoadsorption Technology to Reduce Plasma Free Hemoglobin during Complex Cardiac Surgery: Results of the Safety and Feasibility REFRESH I Study," was presented by Dr. Thomas Gleason, the Chair of Cardiac Surgery at the University of Pittsburgh Medical Center, on behalf of the REFRESH I investigators.

It has been known for a long time that cardiopulmonary bypass causes inflammation. When you are trying to operate on the heart, you must crack open the chest and expose the beating heart. In order to operate on the heart, you usually need to stop the heart from beating. But when you do so, you need to use a heart-lung or cardiopulmonary bypass machine, which oxygenates and pumps blood the rest of the body during the operation.

Unfortunately, cardiopulmonary bypass, which is also called CPB, despite many advances, still continues to generate high quantities of inflammatory mediators including free hemoglobin from the hemolysis of red blood cells caused by cardiotomy suction, blood shear, and blood transfusions; the activation of complement particularly C3a and C5a, which are caused by blood contact with air and artificial surfaces; and last but not least, cytokines that are caused by the trauma of the surgery, ischemia reperfusion injury, as well as endotoxin generation.

Plasma free hemoglobin has long been known as a direct contributor to cell and tissue injury, organ dysfunction, and death in many cases. For example, in the past, companies had tried to develop blood substitutes using plasma free hemoglobin, but it actually increased mortality.

The reasons why plasma free hemoglobin is so toxic is due to many different factors. First, it is a very potent scavenger of nitric oxide, one of the most potent vasodilators in your body. When you do not have these vasodilators present, constriction of blood vessels can occur, leading to pulmonary hypertension, systemic hypertension, and decreased blood flow to vital organs leading to organ damage such as acute kidney injury, intestinal ischemia, cognitive dysfunction, and other problems.

Plasma free hemoglobin is also a very potent generator of oxygen free radicals, due to the highly reactive iron species found in hemoglobin that can cause blood vessel injury. Last but not least, hemoglobin is a pigment that gives blood its characteristic red color. When hemoglobin is in the red blood cell, it is nontoxic, but when it is released into the blood stream because of hemolysis of these red blood cells, hemoglobin can wind up in the kidneys causing renal tubular injury which can contribute to kidney failure in many cases.

Peak plasma free hemoglobin levels are most closely correlated with acute kidney injury in cardiac surgeon patients. This is a table taken from a study done by a cardiothoracic surgeon named Windsant who has done a lot of research on free hemoglobin and the risk of developing acute kidney injury. What you can see from this graph is that those patients with very low free hemoglobin levels, here less than 60 milligrams per deciliter, did not typically get acute kidney

injury, while those with peak plasma free hemoglobin levels greater than 120 milligrams per deciliter are at risk of developing acute kidney injury.

With this knowledge and other related literature from the field, we began modeling this *in vitro*. On the bottom of the slide you can see the *in vitro* set up we used, where a bag of bovine whole blood is put into a circuit using a circulation pump as well as the CytoSorb filters. Post-filters, you see an infusion pump that is injecting plasma free hemoglobin directly into the blood system at a constant level for a total of 180 minutes. This was designed to simulate the ongoing hemolysis that happens during open heart surgery where blood is continuously hemolyzing due to blood shear forces as well as cardiotomy suction.

When you look at the graph above, the line in red is the control that does not benefit from CytoSorb, where the levels of free hemoglobin rise very linearly with this infusion of free hemoglobin. But when CytoSorb is used by opening up this valve and letting blood flow through the cartridges at one hour into these experiments, CytoSorb is capable of reducing free hemoglobin very efficiently in this *in vitro* system. This modeling led to the REFRESH I study which was a prospective, open labeled, randomized controlled trial where control patients received standard of care and the treatment group received standard of care plus dual 300ml CytoSorb cartridges in the cardiopulmonary bypass circuit.

The inclusion criteria were patients 18-80 years of age, undergoing elective non-emergent, complex cardiac surgery with cardiopulmonary bypass expected to last longer than three hours; meaning that these patients were getting roughly at least two hours of CytoSorb treatment. The exclusion criteria excluded patients undergoing very simple procedures that were typically not associated with long CPB pump times and were not associated with high levels of free hemoglobin. The study also excluded severely ill patients that required procedures such as heart lung transplant, left ventricular assist device (LVAD) implantation, and other conditions such as endocarditis. The study also excluded patients that had pre-existing end-stage organ failure or were expected to have near-term death.

The schematic diagram of the extracorporeal circuit is fairly straightforward. Blood is pumped with the CPB machine pump to the oxygenator, which oxygenates blood, and roughly a tenth of the overall blood flow was diverted back to the venous reservoir through dual CytoSorb cartridges in parallel; while the remainder of the blood flow goes to the rest of the body.

A total of 52 patients were enrolled with 49 randomized and three withdrawing consent prior to the surgery. Of the 46 patients that remained, all were part of the safety population divided equally with 23 patients in the control and 23 patients in the CytoSorb treatment group. 38 patients had valid plasma free hemoglobin levels and were in the plasma free hemoglobin reduction group.

In the safety population demographics, there was a slight tendency for CytoSorb patients to be older, to have more females, and to have more current smokers, which is a risk factor for adverse outcomes. What was interesting about the study is that it highlights current practice during the cardiac surgery. Patients typically undergo multiple procedures because the cardiac surgeon is trying to avoid having to take the patient back to surgery a second time, which can be very difficult due to the scarring and abnormal tissue architecture.

This was consistent with what we saw in our study. Roughly 75% of patients had multiple cardiac surgery procedures in the control and 89% in the CytoSorb group underwent multiple procedures. But it turns out that not all procedures are equal in terms of generating plasma free hemoglobin and those involving valve replacement – which includes either multiple valve replacement or valve replacement plus another procedure like coronary artery bypass graft (CABG) or aortic reconstruction - these are the ones that have a highest levels of plasma free hemoglobin compared to non-valve replacement surgeries. That is despite the length of the bypass being typically shorter in the valve cases compared to the non-valve cases.

On the next slide, you see what the data looks like from these valve replacement patients undergoing plasma free hemoglobin reduction. What you can see here is that amongst cases where the cardiopulmonary bypass time is less than five hours, there were significant reductions in the plasma free hemoglobin achieved by CytoSorb and that was statically significant after the pre-specified three hour CPB time, particularly at 3.5 and 4 hours of CPB time. It is very interesting that when you look at this graph and the slopes of these two graphs that it is very similar to what we saw in our *in vitro* system. Here you see the levels of the 120 and 60 milligrams per deciliter. These were very similar to those associated or not associated with acute kidney injury in some of the previous studies that have been reported in the literature. These are very encouraging data.

We also showed the statistically significant reduction of activated complement C3a and C5a during surgery, and in C5a post-surgery as well. Activated complement is also associated with mortality in a wide range of extracorporeal blood purification technologies including dialysis and others.

In terms of adverse events, there were roughly equal numbers of adverse events in both the control and CytoSorb treatment group. There was also a comparable number of serious adverse events as well. The mortality was not significantly different with one death out of 23 in the control group and two out of 23 in the treatment group. There were no unanticipated device related effects. There were only two device related adverse events and those were both related to lower platelets.

And when we looked at platelets, there are a few things to note. First, it's very important to note that patients undergoing cardiopulmonary bypass and cardiac surgery are heavily anti-coagulated during surgery. In fact, they are not expected to clot at all during surgery because these procedures are dealing with the arterial blood supply and any clots in the arterial blood supply can lead to devastating embolic phenomenon. For example, clots going to the brain can cause a stroke, clots going to intestine can cause intestinal ischemia or infarction, clots going to the kidneys, heart, and others can also be life-threatening.

So, patients undergoing cardiothoracic surgery are very anti-coagulated. In addition, cardiopulmonary bypass itself reduces platelets, as seen in the first hour of CPB, in both control and treatment arms, before CytoSorb is even started. At this time point, you can already see a separation between these two curves, which we cannot quite explain. Then with CytoSorb treatment, there is another transient drop in platelets during surgery but this drop is stable with the return of platelet levels back to baseline by the time that they reach the intensive care unit.

In the postoperative period, there were no significant differences in coagulation parameters or bleeding complications and there were no significant differences in median transfusions from the time of surgery throughout the entire ICU stay; with packed red blood cells requiring one unit

versus one in the control, p-value = 0.15, platelets were two versus one control and plasma one versus zero control. So, as we move forward in future studies, this is obviously something that will continue to look at, but in this trial, it was not associated with any serious device related events.

In summary, plasma free hemoglobin was related to cardiopulmonary bypass length, but importantly, also to procedure type. Plasma free hemoglobin was highest in high cardiotomy suction and complex cases like valve replacement where CytoSorb significantly reduced plasma free hemoglobin and activated complement. There were no significant differences in the rates of AEs or SAEs between the groups. Treatment caused a transient thrombocytopenia during cardiopulmonary bypass of unknown significance. Again, these patients are highly anti-coagulated during the surgery.

In terms of REFRESH II, the goal is to compare CytoSorb versus control in a much larger study enriched for high hemolysis patients that have high plasma free hemoglobin levels, just like valve replacement patients. So, this provides a pre-defined way of potentially enriching the next trial with those at highest risk of plasma free hemoglobin levels and by correlation the highest risk of developing acute kidney injury and other organ injury. We plan to correlate this reduction in plasma free hemoglobin and activated complement with reduced organ dysfunction like acute kidney injury, reduced stroke risk, reduced incidence of respiratory dysfunction, as well as others. Last but not least, we look to confirm the safety and risk benefit of the treatment in this larger study.

Slides 28-32

So, with that, let me transition now to catalysts we have in place for the remainder of the year. In terms of financing and investor relations, as Kathy mentioned, we completed an $11.5 million equity financing managed by Cowen and Company, one of the leading mid-tier healthcare investment banks in the United States, as well as our existing investment banking syndicate, which you can see below in the figure. This accomplished many things including 1) strengthening our balance sheet and enabling us to fund our commercial expansion and clinical trials strategy 2) We gained the support from Cowen and interest from other leading mid-tier healthcare investment banks 3) We met with a large number of fundamental investors that formed a base from which we plan to grow institutional sponsorship and drive liquidity of the stock - which is one of the things that we need to improve 4) It also represents another example of our growth in standing in the investment community by being able to attract these high-quality investors, as well as these leading mid-tier banks. We are now finalizing the evaluation of well-known investor relations firms with the goal of starting a new program very soon targeting both institutional and retail investors and will have more detail on that in a future press release.

The second thing that we're doing is gearing up our clinical infrastructure. As we've mentioned before, we plan to initiate the U.S. REFRESH II trial later this year, pending FDA approval. We are also planning other smaller company sponsors RCTs in different areas including sepsis at a relatively modest cost. And we are currently in process of bringing in key hires that are expected by the summer to help build out our clinical infrastructure. One of the things that you see at the bottom here is a picture from this year's 4th International CytoSorb Users' Meeting. It was another great success with more than 120 participants from 22 countries, with an exciting number of presentations given. The quality of the data has grown from what was initially case report studies, to now a lot of case series and even small randomized controlled trials. We are pleased that the

level and the quality of this data is growing and the numbers of people using it continue to grow worldwide. Just as an aside, there would have been many more people but this event is held in a hotel auditorium that was maxed out at capacity.

Another major catalyst are the numerous clinical studies being published. This slide represents a sampling of a lot of the clinical activity that is ongoing. But in terms of accepted publications, a breakthrough publication on 22 patients in refractory septic shock has been accepted that showed an unexpectedly high shock reversal rate with CytoSorb treatment and much improved survival compared to historical controls.

We also are announcing that one of the biggest endocarditis case series to-date in cardiac has been completed involving 39 patients. Endocarditis is an infection of the heart valve often caused by either poor dentition and the seeding of bacteria in the mouth to the bloodstream, infecting the heart valve, but it also plays very heavily on the growing intravenous drug use epidemic, particularly heroin, where IV drug use has led to contamination of the blood with skin bacteria that can seed heart valves and destroy them within days. These patients act very similarly to septic patients but with the added complication of a heart valve that has been destroyed. These patients are typically very unstable going into surgery, and require a lot of medication and attention to keep their blood pressure stable both during and after surgery. Similar to the findings of this study, we have now seen in many institutions, in many different countries, where patients are very stable going through surgery and require very little in the way of hemodynamic support following the surgery with typically very good outcomes.

And last but not least, one of the first review articles on CytoSorb in septic shock has been accepted, summarizing the positive clinical results so far while confirming safety in a third-party written article. We also have a lot of published cases as well including a case series on septic shock patients describing that early intervention is very important for survival. This is how CytoSorb is being used predominantly in the treatment of patients today, but it also includes many different cases, including one of the largest animal sepsis studies to-date that demonstrated increased survival and improved cardiac function in septic rats. But we also have many pending publications including a submitted manuscript for the REFRESH I trial.

An interim analysis of our international CytoSorb registry involving about 200 patients that has also been submitted. There is a 30-patient case series in septic shock and many case reports on a wide variety of topics like anti-depressant overdose, toxic shock syndrome, and many others. As I've mentioned in the past, I would urge you to visit our www.CytoSorb.com product website. Here, you can find our breaking news “Case of the Week” – that describes how CytoSorb is being used to help patients across the world in places like Sweden, Russia, Italy, Chile, Germany and many other countries.

Another major initiative that we have is the launch of a new therapeutic extracorporeal membrane oxygenation, or ECMO, kit. To explain this in a little more detail, respiratory failure or failure of the lungs is often caused by excessive inflammation that causes the blood vessels of the lung to become leaky, allowing fluid and cells to go from the blood into the air sacs of the lung, essentially drowning a patient from the inside out. Today, respiratory failure is often supported by mechanical ventilation, but it can be dangerous. For example, the oxygen that you pump into the lungs can cause oxygen toxicity to tissues, while the pressure and volume trauma on the lungs causes continued ongoing damage to the lungs. When patients are on mechanical ventilation for long periods of time, they can develop other serious complications like ventilator-acquired

pneumonia, a pneumothorax, aspiration, and potential ventilator dependence caused, in part, by a weakness of their diaphragm because they are not working to breathe, they are having machine doing for them. ECMO is a supportive care therapy that was pioneered by our Chief Medical Officer, Dr. Robert Bartlett, and it has been increasing in popularity as an alternative to mechanical ventilation to enable gas exchange with the blood and sometimes to provide hemodynamic support in critically-ill patients.

ECMO typically has been reserved as a rescue therapy for those failing mechanical ventilation, but there has been a trend to maybe use ECMO earlier as a lung preservation strategy. The problem with standard mechanical ventilation and ECMO, however, is that they are used just to keep a patient alive, but they do not do anything to directly address the underlying cause of why the lungs are so diseased in the first place, which is often caused by uncontrolled inflammation. This is really where this new concept of therapeutic ECMO comes in, which is the combination of ECMO and CytoSorb. We call this "new" but in fact it's been now used in more than an estimated 1,000 treatments as a lung preservation strategy for gas exchange in the intensive care unit, and we are now ready to launch a specific ECMO kit that will enable the safe and rapid connection of CytoSorb to the ECMO pump system that is found in many intensive care units around the world. Going forward, we think that this is going to be a significant driver of our volume given that a typical ECMO patient will use multiple cartridges during their intensive care unit stay.

Slides 33

Last but not least, one of our major initiatives is manufacturing. As we mentioned previously, our original goal was to re-site our entire manufacturing facility to a new business facility, but instead of doing that, we've now secured new space at our current complex allowing us to extend our scaled-up manufacturing at a fraction of the cost, estimated at less than 20% of what we had initially budgeted for, and plan to bring this new facility online by 2018. This new facility is expected to quadruple our production capability in two phases to approximately $80 million in revenue, and we have already begun build out of the space and have placed orders for much of the capital equipment, and we expect this site to be validated and operational by early 2018.

With that, I thank you for your attention and that ends our formal remarks. Moderator, we can open it up for the Q&A period.

Question-and-Answer Session

Operator

Thank you. And our first question will come from Gabrielle Zhou with Maxim Group.

Gabrielle Zhou

Hi, good afternoon everyone, thanks for taking the question. Phil, can you walk us through your clinical plan on the REFRESH II trial? What is the size and timeline as well as the endpoints for the study? Thank you.

Phillip Chan

Thank you, Gabrielle. Currently we are anticipating a 300 to 500-patient trial in a patient population that is enriched for those are undergoing valve replacement surgery, where the levels

of plasma free hemoglobin are expected to be high and the risk of developing organ injury and acute kidney injury are high as well. This is pending discussions with the FDA, but we believe that the ultimate endpoint will be a clinical endpoint such as acute kidney injury or a composite endpoint. We will have more clarification on that soon, and we will back to you with more detail.

Operator

Next, we move to Difei Yang with Aegis Capital.

Difei Yang

Phil, would you walk us through the IP strategy and how the competitive landscape will evolve as some of the patents expire?

Phillip Chan

We recently announced the issuance of our 32nd issued U.S. patent that is a composition of matter patent that is expected to cover CytoSorb in the United States. It was also issued in Russia, Japan, China, as well as Australia and New Zealand and is pending in other countries around the world. This is a key patent that extends the worldwide protection of CytoSorb through 2031 and maintains protection in the United States to 2026. We have a very broad range of patents covering both composition of matter, methods of manufacturing, device configurations, as well as clinical applications. And we believe that this is a very formidable patent portfolio that is intended to protect our technology in many countries going forward.

Also, last year we announced the development of CytoSorb-XL, a next generation product to CytoSorb. This again is a new composition of matter patent that is pending worldwide. This polymer not only removes a broad range of cytokines, inflammatory mediators and bacterial toxins, but also removes bacterial endotoxin as well, which is an important inflammatory mediator in gram-negative sepsis, and is anticipated to potentially add up to 20 additional years of patent protection. Currently, the competitive landscape for sepsis therapies continues to be relatively limited in terms of those targeting blood purification. We are one of the leaders in the European Union and our goal is to continue to file key patents, but also to run faster and innovate faster, to be able to stay ahead.

Difei Yang

Thank you for the additional color. Changing the subject to immuno-oncology…it is well-known that one of the side effects in CAR T-cell immunotherapy is cytokine release syndrome or cytokine storm. Could you walk us through how you think about potentially partnering with these cancer immunotherapy companies and inserting CytoSorb® as a standard of care therapy in this field?

Phillip Chan

Thank you, this plays directly to one of our major announcements in the last quarter with the joining of the Dr. Carl June, who is the pioneer of CAR T-cell immunotherapy at the University of Pennsylvania Abramson Cancer Center. They were one of the first to demonstrate that taking someone's T-cells out of the body, putting a chimeric antigen receptor into them that makes them into hunter killer cells, and putting them back into the body can actually lead to potential cures in refractory leukemia and lymphoma patients. It is one of the most important innovations in cancer

immunotherapy. And it's not just CAR-T-cell immunotherapy that causes cytokine release syndrome, which is a subset of the cytokine storm that CytoSorb is intended to treat, but there are many other cancer immunotherapies that can lead to this unwanted excessive inflammatory response.

I think Dr. Carl June joining our Scientific Advisory Board is a tremendous validation of the potential of our technology in the cancer field. His involvement is intended to help us branch out into many different areas of cancer immunotherapy where CytoSorb has the potential ability to modify the immune system to fight cancer in a number of different ways. And not just to control cytokine release syndrome – a dreaded complication of cancer immunotherapy, but potentially to help tune the immune system to fight cancer. There are many potential strategic partners in this space. I think one of our major goals is to get CytoSorb approved in the United States so that they can be used on-label for the treatment of things like cytokine-released syndrome. One of the other press releases that we put out last quarter detailed the successful CytoSorb treatment cases in hemophagocytic lymphohistiocytosis, or HLH, and how similar it is to cytokine release syndrome. This has provided strong support on how CytoSorb could potentially help patients with cytokine release syndrome. This is a developing story and Dr. Carl June's involvement has just been very recent. We will look to update everyone in the near future.

Difei Yang

Thanks Phil. If I could slip in one last question on the U.S. commercial strategy. How do you think about partnerships? Or do you plan to go alone? What would be an ideal profile for the partner for CytoSorbents? Thanks.

Phillip Chan

In the United States, we are not yet approved, but we are on the path to potential U.S. approval by 2020 with this REFRESH II trial in complex cardiac surgery, should everything go well. If we do achieve U.S. approval in cardiac surgery, one potential strategy is to go after this market ourselves with our own direct sales force. We certainly have a lot of experience in building new markets such as what we have done in Europe and the rest of world. And the nice thing about the cardiac surgery market is that it can be easily targeted by a relatively small sales force since most of the major cardiac surgery centers are in the major universities or public hospitals within the major cities.

That said, it is also a market that could potentially be partnered with a major strategic player in the area of cardiac surgery. We're already working with one of the largest cardiac surgery companies in the world, Terumo Cardiovascular, but we also have a lot of interest from other major players as well. So, there are a lot of options open. I think we are focused on trying to drive a successful REFRESH II trial first, but we will certainly have more detail in the future should we be able to achieve U.S. approval in cardiac surgery.

Operator

And we will move next to Andrew D'Silva with B. Riley.

Andrew D'Silva

Just had a few quick questions, with a couple of bookkeeping ones. First, were there any unusual stocking orders or lack of stocking orders during the last quarter, due to the dedicated reimbursement code or otherwise? And then if you could provide a small update on how things are going in Belgium and Luxembourg?

Phillip Chan

Kathy, did you want to take that?

Kathleen Bloch

Thanks Andy, I would say the answer is no. We did have a very minor decline in direct sales in Germany, which we believe is directly correlated to that reimbursement code just sort of revealing itself during the quarter. We expect that should resolve going forward.

Phillip Chan

And maybe Christian, if you could comment on sales in Belgium and Luxembourg?

Christian Steiner

As you know, direct sales cover not only Germany, but also Austria and Switzerland, with the recent addition of Belgium and Luxembourg, and we will very soon start in Singapore. The most advanced markets outside Germany are Austria and Switzerland, where I think we will see similar development as we have seen in Germany. We have started selling here later than in Germany, but the markets are so close together, and many doctors are also visiting the congresses inside Germany where there is growing word of mouth about the therapy. In Belgium and in Luxembourg, we have started much later, so we need some more time to prepare the market, but then I think it will go in the same way.

Andrew D'Silva

Great. Thank you very much. And then Kathy, just a quick follow-up question. R&D was substantially lower sequentially and year-over-year for the first quarter. Should we expect that to be the run rate until our REFRESH 2 Trial starts?

Kathleen Bloch

Yes, until we start REFRESH 2, our R&D expenses should stay at that level and in fact may be offset further by increased activity from the government grant program that should continue through the remainder of this year.

Andrew D'Silva

Do you have an anticipation of when that should ramp back up for REFRESH 2?

Kathleen Bloch

It will be gradual in Q3 and then into Q4 it will begin to build.

Andrew D'Silva

Okay, perfect. And then just touching on the co-marketing relationship that you established with Fresenius, you have obviously highlighted this as a second half of the year catalyst or event that we should we looking for. How is your existing distributor base reacting to this co-marketing deal with Fresenius?

Phillip Chan

Yes, I'll turn it over to Chris for some more commentary, but I should clarify a very important part of this co-marketing agreement. We, meaning either CytoSorbents in our direct territories or our strategic partners and distributors in other countries, will remain the sole seller of CytoSorb in these countries. Fresenius' sales force will ring in the sales for ancillary products like blood sets and fluids and other dialysis hemofilters that are often used with our therapy, but there is definitely a very sharp division between who sells CytoSorb - which is us, and who sells the other ancillary products - which is them. The general feedback that we've gotten from some of our distributors has been that this can help drive sales of CytoSorb in their territories, and I think that is actually positive. So, Chris can you add a little more color?

Chris Cramer

Sure, thanks Phil. Hi, Andy. I think Phil hit the nail on the head. FMC is providing the introduction to their customer base and generating leads that will help open the door to more CytoSorb sales by our direct sales team or distributors. So, in terms of the control of the product and the strategic decisions about how to market and sell it, that hasn't changed. So far we haven't heard anything negative about that, and I am hoping we can continue that.

But just while you've asked the question, I just wanted to give a quick update. Right now, we expect a second half 2017 launch. Program development is underway and we are making good progress. I would estimate that we are around 75% of the way through the design set up, and we have been very actively involved with FMC in the design of this. We are typically on a weekly call working through a lot of the detail like clarifying the sales and marketing process to make sure there is no confusion about who owns what, coming up with joint marketing material, and planning out the training and rollout strategy. So, I think it's moving in the right direction.

Andrew D'Silva

Chris, thanks that was very helpful. Phil, you have a lot of great detail about the pilot trial in you prepared remarks. If you could refresh my memory, activated complement was not actually an endpoint that you are looking at in the REFRESH I trial. Was this an additional data point that was positive above and beyond the endpoint that you are looking for, is that correct?

Phillip Chan

Yes, activated complement was one of the exploratory endpoints. Complement is a normal component of the immune system, but when activated unintentionally, as occurs during cardiac surgery, it has been associated with increased risk of death. In fact, in the dialysis field, there were cellulosic cuprophan dialysis membranes that activated complement and were eventually taken off the market due to safety concerns and increased mortality. Activated complement can cause a host of problems such as causing severe tissue damage, compromising immune cell function, and a wide variety of other complications.

Operator

We will move to Brian Marckx with Zacks Investment Research.

Brian Marckx

On the reimbursement in Germany, can you talk about when the new reimbursement rate became effective?

Phillip Chan

The new reimbursement code and the negotiated rates around that code, are all retroactive to January 1, 2017. So even though that these hospitals have been negotiating their operating budgets, which includes procedures like the CytoSorb therapy during the first quarter, any decisions made on reimbursement rates go back to January 1. I think it's just one of those things where there is that little bit of uncertainty that causes people to just wait a little bit in terms of ordering. But as Kathy mentioned, many of these hospitals have now established these new reimbursement rates, which we expect to help accelerate orders going forward.

Just to remind you in the past what we had seen is that some hospital administrators had been urging their clinicians to be more selective with CytoSorb because the reimbursement that they were getting at that time was typically only 60% to 100% of the cost of the cartridge, but did not cover the cost of the procedure. They were not looking at any of the cost benefit issues related to CytoSorb treatment, such as potential decreases in ICU or hospital stay, and were just looking at it as a simple “cost-in” versus “cost-out” issue. The value of this new reimbursement code is that it now offers a much more robust reimbursement for the hospital.

And we've heard from many hospital administrators that this is what they needed to be able to open up the gates to more CytoSorb usage, which is what a lot of clinicians in hospitals around Germany have been waiting for. So, I think that on one hand, we saw a little impact on sales waiting for these rates to be finalized. But, on the whole, we expect it will be a very good thing because it removes one of the major economic bottlenecks that are limiting sales. This is one of the major reasons why we think that, particularly in the second half of the year, we are going to see significant increases in direct sales and a continuation of our direct sales growth.

Brian Marckx

Okay, that's helpful Phil. Can you talk about REFRESH I and then how it relates to REFRESH 2? What are your thoughts in terms of valve replacement surgery? And how that affects plasma free hemoglobin? Is it specifically related to how long the actual procedure is? Or is there something else that increases free hemoglobin?

Phillip Chan

Yes, valve replacement surgery is one of the most common complex cardiac surgeries that are performed in United States, roughly counting for more than half of all complex cardiac surgery cases. Valve replacement surgery is more or less a surrogate for those surgical procedures that require a long cardiopulmonary bypass times, but more importantly a lot of cardiotomy suction under negative pressure suction that causes red blood cells to hemolyze and explode, releasing hemoglobin into the blood stream. When they go into these surgical procedures, there is a lot of

blood in the field. And in order to cut out a heart valve and repair the ring that holds the valve in place and make sure there are no leaks, etc, the surgeon is continuously aspirating blood away from the field so that they can visualize the heart valves and see if any leaks are happening. Because of that high amount of cardiotomy suction, we actually see that even though the cardiopulmonary bypass times are relatively shorter than non-valve procedures, they produced much higher levels of free hemoglobin.

And so, on one hand, what it means is that our market is potentially much larger than valve replacement surgery alone. It includes those complex cardiac surgery procedures that have a lot of cardiotomy suction and where the patient is expected to be on bypass more than three hours. But it is also very convenient to have identified the sub-population of multiple valve replacement and valve replacement in conjunction with another procedure for our next trial that we can use to enrich for those with the highest levels of free hemoglobin and therefore are at the highest risk of developing organ injury, particularly kidney injury.

Brian Marckx

So, will the REFRESH II inclusion criteria specifically include valve replacement surgery?

Phillip Chan

It will include specifically valve replacement surgery.

Brian Marckx

So, in terms of REFRESH I and acute kidney injury, do you have that or expect to have the data or where there be data on specifically on acute kidney injury?

Phillip Chan

So, these data are included in the paper that was submitted for publication so I can't really discuss these data here today publicly. The REFRESH I study was powered to look at safety and feasibility of CytoSorb therapy, but the goal of REFRESH II is to look at the efficacy of CytoSorb on the reduction in acute kidney injury and other things like stroke, respiratory failure, need for vasopressor support, days in the intensive care unit and other types of clinical and economic outcomes in a much larger study that is powered specifically to look at these points. So, I think that moving forward, we feel comfortable that looking at organ injury is something that is very doable.

Brian Marckx

Okay and as a primary end point acute kidney injury?

Phillip Chan

Right now the discussion amongst our advisors has been around focusing on a single clean endpoint like acute kidney injury versus a composite endpoint. Some favor the former, but a number of our other investigators and advisors favor a composite end point that enables you to power a study with fewer patients, but still yet achieve statistical significance in a composite endpoint that includes many different adverse events including acute kidney injury, stroke and

other endpoints. Some would argue that the composite endpoint is ultimately what patients and doctors care about, as it would point to a lower risk of the procedure overall. This is a matter of active discussion right now and something that we look to finalize very shortly.

Operator

And gentlemen, we have time one more question that will be from Swayampakula Ramakanth with H.C. Wainwright.

Swayampakula Ramakanth

This is RK from HCW. Most of my questions have been answered, however I was just wondering regarding some of these collaborations. Given the overlap in territories, how do you manage the sales? When do you record the sale?

Phillip Chan

We record the sale of our product when it leaves our dock, and when they take possession of the devices, which is typically during transit from our facilities to theirs. We are now selling two different SKUs, with CytoSorb as the core of both SKUs. In cardiac surgery, we are selling the cardiopulmonary bypass kit which includes both the CytoSorb cartridge as well as a number of other accessory products within the kit that allows easy hook up to a cardiopulmonary bypass machine in the operating room. In the ICU, we are selling the CytoSorb cartridge itself as a second SKU and that plugs right into the blood line set that Fresenius sells in the intensive care unit. The third SKU that we will have shortly is our ECMO kit that we already discussed.

Swayampakula Ramakanth

If we start thinking about Germany, how can they help grow revenue as you cross $10 million in sales this year? What could the contribution from Germany be?

Phillip Chan

Last year we disclosed that Germany accounted for roughly 60% of our overall product sales for 2016. But even at these levels, it really just scratches the surface of the massive opportunity in Germany alone. We have stated previously that each of the major 400 hospitals in Germany could be a $1 million to $3 million account, and we disclosed last year that one of these hospitals has already exceeded $1 million in sales in 2016. We estimate that the total addressable market in Germany is approximately $1 billion to $1.5 billion. For example, there are about 154,000 cases of severe sepsis and septic shock in Germany alone, more than 80,000 open heart surgeries, and many, many cases of other critical illnesses like trauma, liver failure, lung injury, and others. So, these are very large markets that we are just beginning to penetrate. If shareholders think that our sales have plateaued here in what we believe is merely the pause that refreshes, no pun intended, but if they think this is a plateauing of our sales, I would be very pressed to argue that point because we believe that we are just getting started. This reimbursement is really the key to much broader usage, adoption, and sales throughout Germany going forward.

Swayampakula Ramakanth

Thank you, Phillip. I may have one last question. On the PR, you had introduction of VetResQ products for the animal health industry. Could you kindly elaborate a little bit more about this product?

Phillip Chan

VetResQ rescue is a product that has similar underlying technology to our CytoSorb technology. It is designed to actively remove a wide range of inflammatory mediators that are present in critically-ill animals, particularly domesticated animals like cats and dogs, but also for high value animals like horses and foals. The goal is to reduce these inflammatory mediators and toxins that are present in a wide variety of illnesses such as sepsis, pancreatitis, trauma and other things… just like humans, in fact. We brought this product to the U.S. market because of requests from existing veterinarians and pet owners. But to be clear, it is not the core market we are focusing on. It is the human clinical market for CytoSorb that we put the vast majority of our resources. But I think that the VetResQ product fills a major medical gap in animal health, and is an important new tool to veterinarians and to many people who have pets. The VetResQ therapy is now commercially available in the United States.

Operator

That concludes our question-and-answer session at this time everyone. For those of you having questions that we weren't able to address today, we apologize and we ask that you please contact Amy Vogel, Investor Relations, with these questions. And at this time, I would like to turn the call back to management for any additional or closing remarks.

Phillip Chan

Thank you very much. And thank you everyone for taking the time today to participate on the call. We certainly appreciate your continued interest and support, and if you do have any other questions as the moderator mentioned, please contact Amy Vogel at avogel@cytosorbents.com and we'll try to get you answers to your questions, where possible. In the meantime, we hopefully will have an opportunity to meet with many of you at our Annual Meeting June 6, 2017 in New York City and look forward to the next update on the quarterly call. Thank you very much.

Operator

Everyone that concludes our conference for today, I'd like to thank everyone for their participation. You may now disconnect your line.