Zacks Small-Cap Research

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CytoSorbents Cp (CTSO- NASDAQ)

CTSO: EAP Out, IDE/PMA For Sepsis Back On The Table

Current Recommendation	**Outperform**
Prior Recommendation	N/A
Date of Last Change	06/04/2012
Current Price (12/31/15)	$5.75
Target Price	**$11.50**

OUTLOOK

CTSO continues to generate clinical outcomes data which is being used to accelerate adoption and utilization. CTSO now also focused in U.S. regulatory approval – either with a cardiac surgery and/or sepsis indication. Just received notice from FDA that EAP for critical care illness in U.S. not feasible. CTSO now looking at IDE/PMA study for U.S. approval for sepsis.

Recent restructuring of sales force caused a hiccup in sales but looks like was only a short-term issue. Product sales grew 39% from Q2 to Q3. CTSO already made replacements to sales force with 2 add'l hires expected by current year-end. Add'l distributors, including Fresenius and add'l geographic territories to come online shortly should further accelerate product sales. Interest in and use of CytoSorb from hospitals and physicians continues to increase.

SUMMARY DATA

52-Week High	**$15.24**
52-Week Low	**$5.17**
One-Year Return (%)	**-38.99**
Beta	**-0.22**
Average Daily Volume (sh)	**79,448**
Shares Outstanding (mil)	**25**
Market Capitalization ($mil)	**$154**
Short Interest Ratio (days)	**5.43**
Institutional Ownership (%)	**5**
Insider Ownership (%)	**26**
Annual Cash Dividend	**$0.00**
Dividend Yield (%)	**0.00**
5-Yr. Historical Growth Rates	
Sales (%)	**63.5**
Earnings Per Share (%)	**N/A**
Dividend (%)	**N/A**
P/E using TTM EPS	**N/A**
P/E using 2015 Estimate	**N/A**
P/E using 2016 Estimate	**N/A**
Zacks Rank	**N/A**

Risk Level	**Above Avg.,**
Type of Stock	**Small-Growth**
Industry	**Med Products**

ZACKS ESTIMATES

Revenue
(in '000 of $)

	Q1 (Mar)	Q2 (Jun)	Q3 (Sep)	Q4 (Dec)	Year (Dec)
2014	1062 A	1025 A	1162 A	874 A	4123 A
2015	723 A	964 A	1344 A	1454 E	4484 E
2016					12212 E
2017					20245 E

Earnings per Share

	Q1 (Mar)	Q2 (Jun)	Q3 (Sep)	Q4 (Dec)	Year (Dec)
2014	-0.20 A	-0.27 A	-0.22 A	-0.47 A	-1.29 A
2015	-0.19 A	0.06 A	-0.11 A	-0.10 E	-0.35 E
2016					-0.27 E
2017					-0.21 E

Zacks Projected EPS Growth Rate - Next 5 Years % **N/A**

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EAP Route Out, CTSO May Now Pursue PMA Sepsis Study

Following a request in late November for more information to support the company's EAP application, CTSO received additional feedback from FDA. The agency indicated that due to lack of correlation between surrogate endpoints and mortality in several other sepsis studies (not related to CTSO) that, essentially, it was not in CytoSorb's best interest to pursue the EAP route and 28-day all-cause mortality needs to be the primary endpoint.

As a reminder, in the spring of this year CTSO announced that that they were investigating the EAP pathway as a means to speed time to market of CytoSorb in the treatment of sepsis (and/or other critical care illnesses). This would also be less costly upfront as compared to the traditional IDE/PMA route and allow for much of the pivotal data collection (i.e. – to demonstrate 28-day all-cause mortality) to happen during commercialization. And while proof of safety and efficacy would still need to be demonstrated in clinical studies prior to commercialization, the use of surrogate endpoints such as reduction of certain key biomarkers (which has been demonstrated in published studies) were hurdles that were likely relatively easy to clear. The thinking at the time was that if EAP for sepsis was eventually deemed not to be viable that the company would then seek FDA approval via a cardiac surgery indication and, once cleared for sale in the U.S., then look to expand the label once to include critical care illnesses such as sepsis.

While CTSO's Dec 21 press release did not definitely state that they will pursue the IDE/PMA route, it is strongly suggested that they will. Timing is also uncertain. First steps would include outlining trial design and protocol through additional consultations with FDA – plans for which we may hear more about in the near future.

So while we don't know exactly what a CytoSorb IDE sepsis study would entail, it certainly is not a trivial undertaking. Obviously management has looked at other companies' device and drug sepsis clinical trials and has an idea of what to expect. The many-year and many millions of dollars that is likely to be consumed in an IDE study is what was hoped could have been avoided – or more accurately, somewhat delayed after commercialization. This was the impetus in exploring the EAP pathway. To be clear, CTSO still would have had to undergo a pivotal sepsis study – the only difference now is that this will have to happen prior to obtaining U.S. marketing clearance.

But while the EAP pathway would have allowed CTSO to test the water with their toe, IDE means jumping in with both feet. Sepsis is incredibly difficult to control, has a mortality rate of 30%+ and can be instigated by a variety of underlying conditions. This can cause challenges to trial design, patient selection, enrollment and data analysis – which adds to the uncertainty of timelines, cost and, ultimately, quality of the data. This is part of the reason that there are no approved sepsis therapies in the U.S. As such, we expect management will be taking a hard look at this – including waiting for more data from ongoing OUS sepsis studies, and of course, guidance from FDA – before fully committing.

They are also certainly well-versed on sepsis candidates of other companies. Eli Lilly actually did get a drug approved in the U.S. in 2001 for the treatment of sepsis. **Xigris**, a recombinant form of human activated protein C, met the 28-day all-cause mortality endpoint. The pivotal study showed mortality of Xigris patients (24.7%) was statistically lower than those treated with placebo (30.8%) – an absolute reduction of 6.1%. However, a requisite post-marketing study did not confirm Xigris' efficacy, prompting the drug to be removed from the market in 2011.

Spectral Medical's experience may provide the most insight into what CytoSorb may expect if and when they pursue an IDE study. Spectral's extracorporeal **Toraymyxin** column is designed to treat sepsis by removing endotoxins from the blood. While obviously a different target than CytoSorb, Spectral is pursuing a treatment of sepsis indication with the "standard" 28-day all-cause mortality endpoint.

Spectral initiated pursuit of FDA approval following commercialization in Europe and Japan for sepsis. The device has demonstrated a dose-response between endotoxin levels in sepsis patients and certain adverse outcomes including organ failure and death. And in small, open-label studies has shown a survival benefit. Similarly, CytoSorb showed a survival benefit in a small European sepsis study.

EUPHRATES is Spectral's pivotal study which began in mid-2010 and is still ongoing. It is double-blind, placebo-controlled and being conducted at approximately several sites across the U.S. Primary endpoint is 28-day all-cause mortality. Secondary measures are mortality at 90 days, 6 months and 12 months following treatment. Initial enrollment was expected to be 360 patients but the trial's DSMB, following a planned interim analysis (April 2014), recommended enrollment be increased to 650. An additional exclusion criteria was also added – allowing

only severely ill patients (MODS score >9) to enter the study. The criteria was added as earlier studies showed that Toraymyxin demonstrated a more obvious benefit on very sick patients.

Spectral received IDE approval in February 2010. Enrollment size has been recalculated throughout the study, increasing it from the original 360 in order to provide a better chance of meeting statistical significance on the primary endpoint. In addition and as noted, inclusion/exclusion enrollment criteria were updated to only allow very sick patients to enter the study – again to attempt to increase the odds of success. In September 2015 enrollment size was recalculated to 446 patients, 65 of which still have yet to enroll. Based on current enrollment rates, it is anticipated that the trial should complete by June 2016.

Total cost of the study is estimated at approximately $35M. Spectral is using a modular filing. Three of the four modules have been submitted with the fourth expected to be filed in Q4 2016. Assuming they hit that timeline, the study will have spanned almost 6 years since receiving IDE approval.

The need to substantially increase the size of study and difficulty in patient selection (i.e. – meeting inclusion and exclusion criteria) and enrollment is what have been the main reasons why the study has dragged on so long. This has also added to the cost. EUPHRATES' screen-to-enroll rate has averaged 2% or less (i.e. – for every 100 patients screened, only 2 meet the criteria and are enrolled) and, given that these are very sick patients, some will die prior to completion of the 28-day treatment period.

This highlights the need for a well thought out and scientifically sound clinical trial design.

Valuation:
Our DCF model incorporated a risk-adjusted probability that CytoSorb would enter the U.S. market for critical care use prior to 2018. With EAP now off of the table, that is very unlikely to happen, prompting update to our risk-adjustment from 50% to 0%. While the update does impact our calculated valuation, we had allocated relatively minimal sales to CytoSorb in the U.S. for a "generic" critical care indication.

Under EAP CTSO would have eventually had to demonstrate benefit in 28-day all-cause mortality in clinical studies for a sepsis indication – the only difference now being that CytoSorbents will have to show that prior to marketing approval. This data is what we had always modeled to support demand (i.e. – U.S. revenue related to sepsis). The update to our model has moved our DCF-generated price target from $12.50 to $11.50/share. The stock trades well below this. We are maintaining our Buy recommendation.

FINANCIAL MODEL

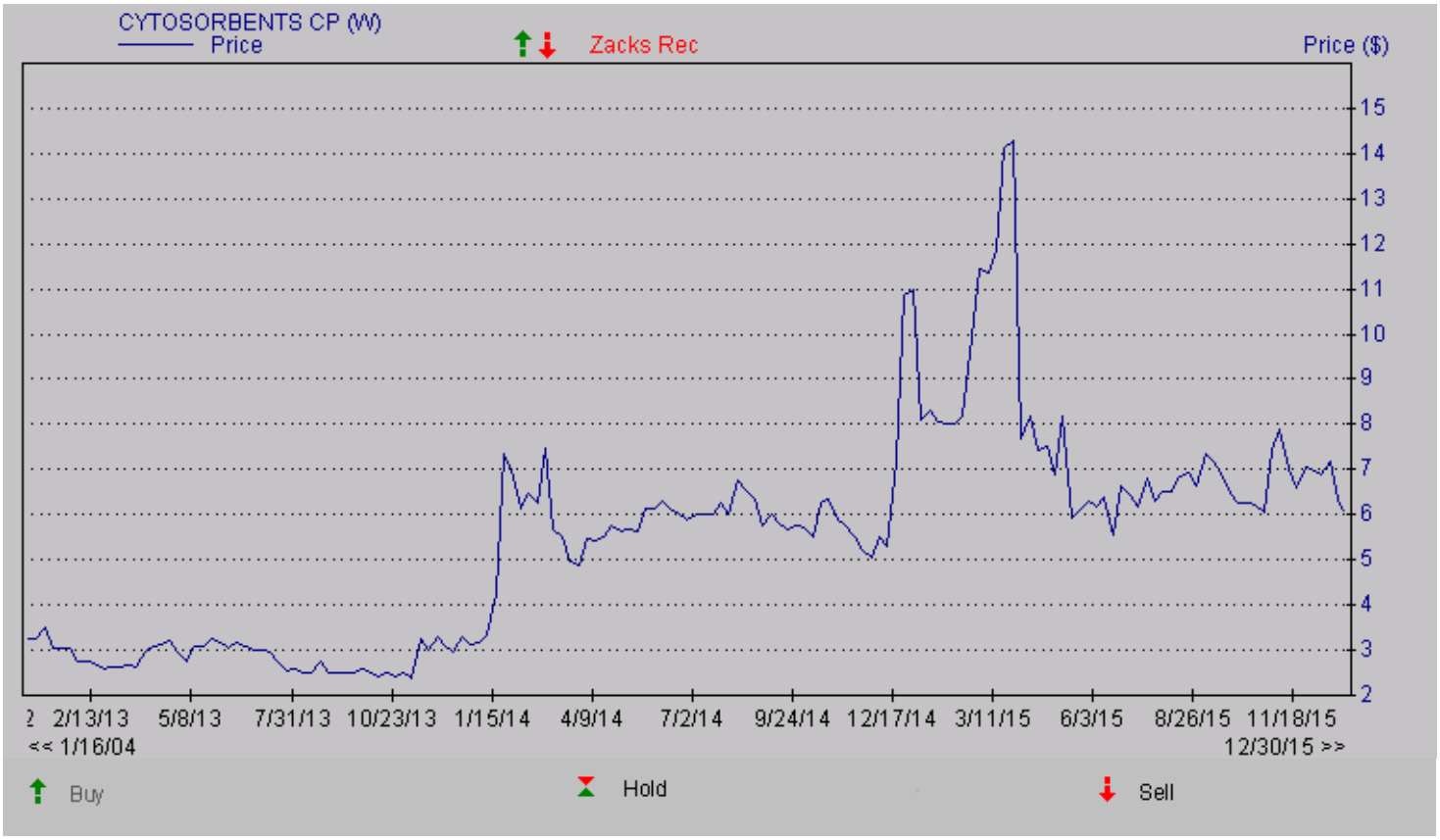
CytoSorbents Inc.

	2014 A	Q1A	Q2A	Q3A	Q4E	2015 E	2016 E	2017 E	2018 E
CytoSorb Sales	$3,135.4	$703.7	$773.1	$1,071.5	$1,242.7	$3,790.9	$11,030.0	$19,580.0	$28,010.0
y-o-y growth	*281.5%*	*23.6%*	*16.6%*	*3.8%*	*42.6%*	*20.9%*	*191.0%*	*77.5%*	*43.1%*
Total Royalties/Grants/Other	$987.5	$19.4	$190.8	$272.2	$211.1	$693.5	$1,181.8	$665.0	$0.0
y-o-y growth	*-38.3%*	*-96.1%*	*-47.2%*	*108.4%*	*8217.6%*	*-29.8%*	*70.4%*	*-43.7%*	*-100.0%*
Revenue	$4,122.9	$723.1	$963.9	$1,343.6	$1,453.8	$4,484.4	$12,211.8	$20,245.0	$28,010.0
YOY Growth	*70.2%*	*-31.9%*	*-5.9%*	*15.6%*	*66.4%*	*8.8%*	*172.3%*	*65.8%*	*38.4%*
Cost of Goods Sold	$2,133.9	$304.5	$465.4	$638.8	$667.6	$2,076.3	$5,225.4	$8,005.7	$10,643.8
Gross Income	$1,989.0	$418.6	$498.5	$704.8	$786.2	$2,408.1	$6,986.4	$12,239.4	$17,366.2
Gross Margin	*48.2%*	*57.9%*	*51.7%*	*52.5%*	*54.1%*	*53.7%*	*57.2%*	*60.5%*	*62.0%*
SG&A	$6,836.2	$2,179.2	$1,924.3	$1,988.8	$2,334.0	$8,426.3	$9,654.0	$13,237.0	$14,341.1
% SG&A	*165.8%*	*301.4%*	*199.6%*	*148.0%*	*160.5%*	*187.9%*	*79.1%*	*65.4%*	*51.2%*
R&D	$2,431.7	$951.0	$801.7	$866.3	$1,035.0	$3,654.0	$4,694.0	$4,902.0	$4,915.0
% R&D	*59.0%*	*131.5%*	*83.2%*	*64.5%*	*71.2%*	*81.5%*	*38.4%*	*24.2%*	*17.5%*
Operating Income	($7,278.9)	($2,711.6)	($2,227.5)	($2,150.3)	($2,582.8)	($9,672.2)	($7,361.6)	($5,899.7)	($1,889.9)
Operating Margin	-	-	-	-	-	-	-	-	-
Total Other Expense	$2,428.5	$2,005.3	($3,661.8)	$697.1	($3.0)	($962.3)	$0.0	$0.0	$0.0
Pre-Tax Income	($9,707.4)	($4,716.9)	$1,434.3	($2,847.4)	($2,579.8)	($8,709.8)	($7,361.6)	($5,899.7)	($1,889.9)
Taxes (benefit)	($385.6)	$0.0	$0.0	$0.0	$0.0	$0.0	$0.0	$0.0	$0.0
Tax Rate	*4.0%*	*0.0%*	*0.0%*	*0.0%*	*0.0%*	*0.0%*	*0.0%*	*0.0%*	*0.0%*
Preferred Dividend	$9,266.7	$0.0	$0.0	$0.0	$0.0	$0.0	$0.0	$0.0	$0.0
Net Income	($18,588.4)	($4,716.9)	$1,434.3	($2,847.4)	($2,579.8)	($8,709.8)	($7,361.6)	($5,899.7)	($1,889.9)
Net Margin	-	*-652.3%*	*148.8%*	*-211.9%*	*-177.4%*	*-194.2%*	*-60.3%*	*-29.1%*	*-6.7%*
EPS	($1.29)	($0.19)	$0.06	($0.11)	($0.10)	($0.35)	($0.27)	($0.21)	($0.07)
YOY Growth	-	-	-	-	-	-			
Diluted Shares O/S	14,441	24,394	24,769	25,038	25,350	24,888	27,000	27,700	28,200

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