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**NEWS RELEASE**

August/September 2011



**From the Desk of Ivan Vesely, Ph.D.**

Dear Colleague,

The countdown to our First-In-Man clinical implant for next month is right on track. All components of our development activities are on schedule and in place for this important moment for ValveXchange. Additional details about our FIM activities are shown below in the first Press Release.

The other big news is reflected in the above graphic. Yes, we are now funded! Please see the various on-line press releases for details ([bizjournal](#), [zacks.yahoo.finance](#)). The full press release can be viewed on our [web site](#) also.

In brief, CryoLife, Inc. (NYSE: [CRY](#)) has invested \$3.5 million in ValveXchange for an equity stake of about 19%. Some of the key terms involve the right to negotiate first for distribution rights in Europe to the exchangeable valve technology once we receive CE Mark approval, and the right of first refusal to acquire VXi. Who will ultimately acquire VXi, of course, will depend on their interest and ability to do so.

Regardless of what the future holds for ValveXchange, the company, we are all excited to have CryoLife as our investment partner and to have weathered the funding drought that the entire medical device industry suffered through over the past 3 years, and which apparently still continues. With this new funding, we are well positioned to complete our First-In-Man study later this summer, and continue with European clinical trials, hopefully leading to our first CE Mark approval in late 2012.

For those new to this Newsletter, ValveXchange is an emerging technology company based in Colorado. We call ourselves "The Lifetime Tissue Valve Company" and are developing the first-of-its-kind "serviceable" bioprosthetic valve. By offering periodic, minimally invasive exchange of the worn-out leaflet set, young and physically active patients can avoid the use of a mechanical valve and the associated Coumadin<sup>®</sup> anticoagulation therapy. By adhering to the time-proven design tenets of conventional bovine pericardial valves, we believe that the ValveXchange system will offer the best combination of least-invasive techniques and greatest valve longevity and durability.

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## **Press Release**

### **ValveXchange "On-Track" for First-In-Man Studies**

**August 18, 2011. Denver** - ValveXchange Inc. rocked the heart valve field early this year by putting a "*Countdown to First-In-Man*" clock on its website. First In Man (FIM) studies represent a major milestone for any heart valve company. They involve a myriad of tests and preparations in the laboratory, animal lab, cadaver lab, and coordination with key physicians, the clinical site and patients. It is almost unheard of for companies to publicly announce their anticipated FIM timing in advance due to the number and complexity of milestones that must come together to make this happen. But ValveXchange has announced in mid-August that the technology, testing, physician team, regulatory authorizations, Contract Research Organization, site and patient selection process are all "on-track" to begin First In Man implants by the end of September. The Company also notes that it has been able to get to this point in a highly capital efficient manner, having expended under \$6 million since its inception to date.

### **ValveXchange Receives "Series A" Investment**

**July 7, 2011. Denver** - ValveXchange Inc. is pleased to announce the receipt of investment capital from CryoLife, Inc. of Atlanta, GA. CryoLife (NYSE: [CRY](#)) is a tissue processing company with its origins in the cryopreservation of cardiovascular tissues, particularly human aortic and [pulmonary valve allografts](#). Indeed, it was the availability of the cryopreserved pulmonary homografts that enabled the Ross procedure to expand into a viable therapeutic option, aided by the training of physicians at the [Ross Summit](#), hosted by CryoLife.



Since its origins in the cryopreserved tissue business, CryoLife has expanded its business activities towards medical devices. In the early 90's CryoLife introduced the O'Brien stentless porcine xenograft, and later, CryoLife expanded its business into surgical adhesives with the [BioGlue](#) product line. Most recently, CryoLife acquired [Cardiogenesis](#), a company that has a system for the application of laser energy for revascularization of the myocardium ([TMR](#)) for the treatment of angina. Cardiogenesis also has developed a combination system, which is designed to combine the intramyocardial delivery of biologic materials with TMR, such as stem cells or growth factors and which has a CE Mark. The acquisition of Cardiogenesis and their biologic delivery system is in line with CryoLife's capabilities in tissue and cell preservation. Their investment in ValveXchange is consistent with their origins in the valve surgery business and their commitment to developing and marketing cardiac valve devices. CryoLife is a surgeon-focused company, as is ValveXchange. The relationship between the two companies is thus one of shared vision and aspirations.



## Reality Check

What is it about News re-broadcasting agencies that makes them always put a spin on everything? Why can't they just report the news as it is? Case in point:



INTERVENTIONAL/SURGERY

### Sapien TAVI device gets resounding thumbs-up from FDA advisors

JULY 20, 2011 | Shelley Wood

**Galthersburg, MD (updated)** - The FDA's Circulatory System Devices Committee has voted overwhelmingly to recommend approval of the **Sapien** transcatheter heart valve (Edwards Lifesciences) at the end of a long day of evidence and testimony.

(click [here](#) for link to article)

A "resounding thumbs-up?"

Committee "voted overwhelmingly to recommend approval of the Sapien valve?"

Have they actually read the minutes of the FDA panel meeting?

Here is what really happened at the [FDA panel meeting](#) on July 20, 2011. First of all, there were three questions on which the panel was asked to vote:

**Question 1:**

Is there reasonable assurance that the Edwards SAPIEN™ Transcatheter Heart Valve is safe for use in patients with severe aortic stenosis who have been determined by a cardiac surgeon to be inoperable for open aortic valve replacement and in whom existing co-morbidities would not preclude the expected benefit from correction of the aortic stenosis?

**Question 2:**

Is there reasonable assurance that the Edwards SAPIEN™ Transcatheter Heart Valve is effective for use in patients with severe aortic stenosis who meet the criteria specified in the proposed indication?

**Question 3:**

Do the benefits of the Edwards SAPIEN™ Transcatheter Heart Valve for use in patients with severe aortic stenosis who meet the criteria specified in the proposed indication outweigh the risks of the Edwards SAPIEN™ Transcatheter Heart Valve for use in patients with severe aortic stenosis who meet the criteria specified in the proposed indication?

And this is how the Panel voted:

**Vote on Question 1:**

The Panel voted 7 to 3 that the data does show that there is reasonable assurance that the Edwards SAPIEN™ Transcatheter Heart Valve is safe for use in patients with severe symptomatic aortic stenosis who meet the criteria specified in the proposed indication.

**Vote on Question 2:**

The Panel voted 9 to 1 that there is reasonable assurance that the Edwards SAPIEN™ Transcatheter Heart Valve is effective for use in patients with severe symptomatic aortic stenosis who meet the criteria specified in the proposed indication.

**Vote on Question 3:**

The Panel voted 9 to 0 (with 1 abstention) that the benefits of the Edwards SAPIEN™ Transcatheter Heart Valve for use in the indicated patient population do outweigh the risks of the Edwards SAPIEN™ Transcatheter Heart Valve for use in the indicated patient population.

Clearly, on what is perhaps the most important question - *"Is the valve safe for the inoperable patient?"* - the vote was not overwhelmingly positive. Three of the 10 panelists thought that the data did NOT show sufficient assurance that the valve is safe. Given that these patients have essentially no options and will die within a few years, concern for safety under the assurance of certain death, should give pause for concern. Indeed, one of

the ten physicians who was not convinced by the data, stated the following:

*"I cannot personally give a vote of reasonable assurance of safety without better morbidity/mortality data on the procedure," Kato said. "I would not be considered to be a good heart surgeon if [my patients] had a mortality rate of 30% and a stroke rate of 8%."*

So even though it led with overly exuberant enthusiasm, the HeartWire article did eventually elaborate on the subtle details of the panel discussion. The problem is that a lot of people don't dig deep in to the details of a web posting and just skim the headlines.

Digging deeper into the details reveals a few more interesting data points.

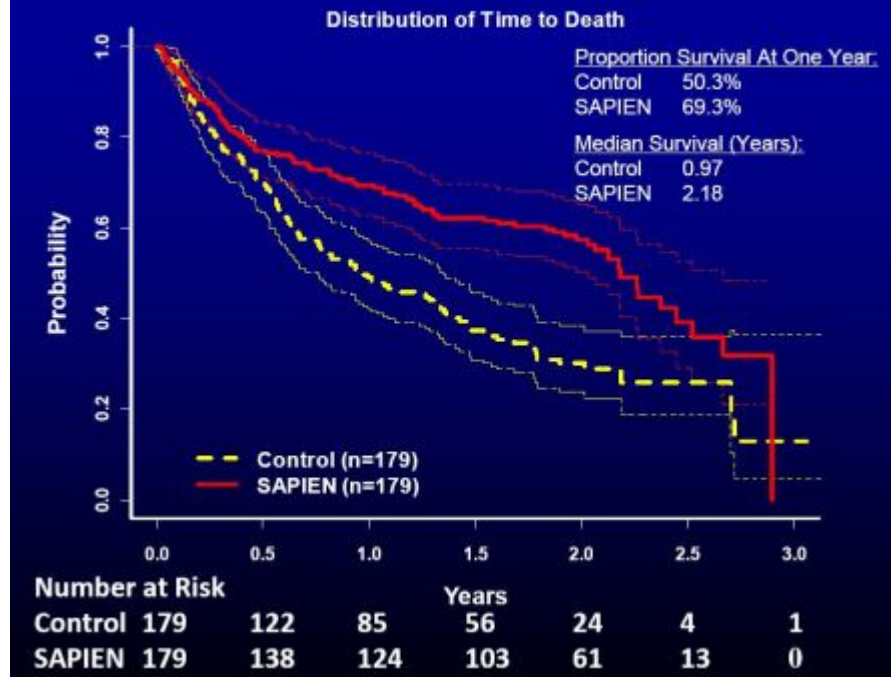
Firstly, the HeartWire article comments that the PARTNER trial had not reported on a sub-group of patients that were labeled as *"continued-access"*. Apparently, the Sapien device continued to be implanted into patients even after the enrollment to the main trial was formally closed. In this group of patients, the mortality was actually higher in those patients that received the device, than in those that did not. Indeed, it was this troubling data that led to the one abstention vote on the final question - *"Do the benefits outweigh the risks?"*

It was the risk of strokes that concerned people the most, with one panel member making the point that elderly, frail patients are much more worried about strokes than they are about death. One patient representative noted that *"We're worried about strokes, but it's really hard to have a stroke if you're dead."*

Personally, I don't know what point is being made by that comment. Is it that death is worse than strokes? Most patients would disagree. Most elderly patients fear strokes more than death, at least according to physicians quoted in the [Spring Newsletter](#) when I elaborated upon the results of the PARTNER A trial.

But it is the freedom of death following TAVI that was touted as the most remarkable outcome of the PARTNER B trial - a 20% reduction in death at 1 year following TAVI. At two years and at three years, that data becomes less impressive. When I looked at the slide deck that was presented at the FDA Panel meeting, that is now [public](#), one slide struck me the most (see image below).

## Primary Safety and Effectiveness Endpoint



This curve, which I've never seen at clinical conferences, shows how the two cohorts fared at two and at three years following implant. Of the 179 patients enrolled in each arm at the outset, only 24 and 61 remain alive in the Control and SAPIEN groups at 2 years, and all of them were dead at 3 years. So the Sapien valve can prolong the life of 2/3 of the really sick patients for two years, but it cannot save anyone beyond 3 years. To me, this is really tragic. The only patients that this device is of any use to are those that face certain death anyway. That lovely, funny, spry old woman that was [brought up on stage at the TCT](#) was indeed an exception and not the rule of what a typical TAVI patient looks like. That lady received her TAVI valve in 2006 and was invited on stage in October of 2010 - 4 years after her procedure. Exactly zero of the patients that were considered candidates for the PARTNER trial survived 4 years. She was an anomaly.

So now that the Sapien valve is likely to be approved, what does the future hold for TAVI? More of the same probably. It is unlikely that the FDA will relax the inclusion criteria used in the PARTNER trial for market release of the device. Indeed, in a [letter written to the FDA](#) by Dr. David Holmes, [President of the American College of Cardiology](#), urged the FDA that "approval for the device be limited to those patients who fit the criteria where positive outcomes were demonstrated in the [PARTNER] trial." That "resounding thumbs up" is actually a cautious nod of approval with the caveat "don't do it any different than what you did in the PARTNER trial" - and that is from Cardiologists - those that have the most to gain from the broad dissemination of this technology.



The advice from surgeons is often quite the opposite. For example, the [testimony from Dr. Steven Greer](#), a surgeon from New York, is far more damning. Dr. Greer begins his testimony by asking the question "*Will History Repeat Itself?*" Will the use of transcatheter valves mimic the history of the drug eluting stents, where only 1 year data led to market approval, usage of stents skyrocketed and then quickly plummeted after "*tens of thousands of Americans have been killed or severely harmed by the first-generation drug eluting stents.*" He also reminds the FDA panel that given the 7% stroke rate, the planned aggressive market roll-out of the Sapien valve could lead to 1,800 strokes per year. I would have loved to be in the room to witness this admonishment myself!

But I'm an optimist. I don't believe that history will repeat itself. I believe that the FDA will indeed curb the dissemination of this technology to only those patients that can truly benefit from it. Nearly every learned physician who knows this technology is advocating caution. First there were the [VARC guidelines](#), and now there are highly placed physician groups that continue to urge caution and collaboration. Most recently, Drs. Holmes (cardiologist), and Mack (surgeon) have partnered to write an [authoritative overview of the position](#) of the American College of Cardiology and the Society of Thoracic Surgeons. In summary, they urge the adoption of (i) a Multidisciplinary Heart Team, (ii) specialized, experienced facilities or "Regional Heart Centers", and (iii) standardized measures for evaluating the safety and efficacy of the technology and the procedures. They restate that "*Adoption of these techniques to populations beyond those studied in these randomized trials, therefore, is not appropriate at the current time.*" Everyone is arguing against opening the flood gates.

I believe that Professional Societies and intelligent, experienced physicians will do the right thing and the FDA will follow. The future of TAVI will be highly regulated and thus highly constrained. The wild projections by [HRI](#) on which I commented in the [January issue](#) of this newsletter are not going to manifest. It is hard to imagine how there could possibly be 30,000 TAVI procedures done in the US by the year 2015. There just aren't that many terminal heart valve patients out there. As stated by André-Michel Ballester, a very smart [Sorin](#) Executive at last year's [Dallas-Leipzig Conference](#), "*The future of heart valve surgery will be .... heart valve surgery*"

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### **Closing:**

In these newsletters, I have focused a lot on questioning the durability of current generation transcatheter valves. With all the design compromises required for tight packaging into catheters, I have argued that there is no way that the majority of these valves will last more than 7 years. The problem with proving that point is that patients with transcatheter valves don't live more than just a few years - 3 years to be exact, for the PARTNER trial population. Those that may live longer because they are less sick and have had their valve implanted in Europe, have not been studied. There simply has not been any report of a patient death or a transcatheter valve explant due to structural failure..... Until now.

And the answer is...**5.5 years**. That is how long a CoreValve lasted in a 92 year old patient. A pre-print of that very interesting paper is available at the Catheterization and Cardiovascular Interventions [web site](#). After less than 6 years in the patients, that valve developed severely calcified, stenotic leaflets. Dr. Eberhard Grube, a master of transcatheter techniques, managed to treat the condition with a valve-in-valve, and he reports that the procedure was very difficult to manage.

But the data are finally starting to come in. Transcatheter valves are not going to last more than 10 years, even in the extremely elderly. And even in those very sick patients, conventional surgery is going to be held up as the procedure of choice for many more years to come. We at ValveXchange thus continue to be very happy with the technology pathway choices we made many years ago.

Sincerely,

Ivan Vesely, Ph.D.  
Founder and Chief Scientific Officer  
ValveXchange Inc.  
[ivesely@valvexchange.com](mailto:ivesely@valvexchange.com)

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## Recent News Releases

**June 26, 2011. Barcelona** - ValveXchange is pleased to announce its attendance at the Society for Heart Valve Disease meeting in Barcelona, Spain. At that meeting, Dr. Vesely, the Founder of ValveXchange and its Chief Scientific Officer, presented two oral presentations - one on the [Vanguard technology](#) and the other on VXi's first [transapical leaflet exchange](#) animal study. The talks were well received and resulted in a large number of follow-on visits to the VXi booth.

**April 2011. Denver** - ValveXchange Inc. is pleased to announce the launch of its First-In-Man Clinical Trial, called "**VITAL**". Through this trial, ValveXchange will demonstrate that the two-part exchangeable valve can be safely implanted into patients that are typically younger, and would otherwise be candidates for mechanical valve prostheses.

**March, 2011. Denver** - ValveXchange Inc. is pleased to announce its first successful two-stage implant of its exchangeable Vitality™ bioprosthetic heart valve in a human cadaveric heart.

**February 14, 2011. Denver** - ValveXchange Inc. is pleased to announce that Mr. Kevin Morningstar has joined the VXi team as Senior Director, Regulatory Affairs and Quality Assurance. [Read More.](#)

**January 17, 2011. Denver** - ValveXchange Inc. is pleased to announce that Mr. Todd Campbell has joined the VXi team as Senior Executive Director of Product Development. [Read More.](#)

**October, 2010. Denver** - ValveXchange Inc. is pleased to announce that Blase Carabello, M.D., has joined the VXi Medical Advisory Board. [Read More.](#)

**October, 2010. Denver** - ValveXchange Inc. is pleased to announce that Bonnie Vivian has joined the VXi Board of Directors. [Read More.](#)

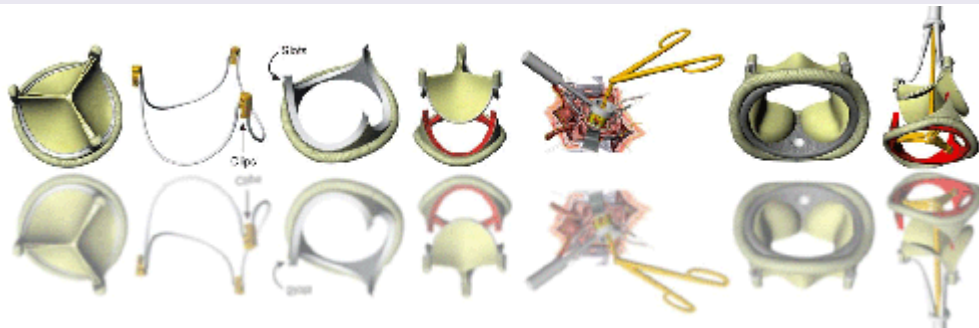
**September, 2010. Denver** - ValveXchange Inc. is pleased to announce that Carlos Ruiz, M.D., Ph.D., has joined the VXi Medical Advisory Board. [Read More.](#)

**August 19, 2010. Denver** - ValveXchange Inc. is pleased to announce the receipt of a \$1.3 million Small Business Innovation Research (SBIR) grant from the National Institutes of Health (NIH) under the Fast Track program. The Fast Track program is reserved for highly innovative and competitive projects with a short time-line to commercialization. This is VXi's 5th NIH SBIR Grant.

**June, 2010. Denver** - ValveXchange Inc. is pleased to announce that Lars G. Svensson, MD, PhD, has joined the VXi Medical Advisory Board. [Read More.](#)

**April 13, 2010. Minneapolis** - Dr. Ivan Vesely, the founder of ValveXchange Inc., presented a review paper entitled "The Three Tenets of Good Valve Design: Where transcatheter Valves Fail", at the 2010 [Design of Medical Devices conference](#) in Minneapolis, Minnesota. Other noted invited speakers were Manny Villafona, the founder of St.Jude Medical, and Dr. Robert Levy, a pioneer in understanding prosthetic valve calcification. Dr. Vesely's presentation can be viewed [here](#).

**January, 2010. Denver** - ValveXchange Inc. is pleased to announce that it has received a \$250,000 grant from the State of Colorado under the Bioscience Discovery Evaluation Grant Program (BDEGP). [Read More.](#)



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