Executive Summary

After exploring a number of new product markets to drive growth in the decade since its spin-off from Baxter, Edwards has found its sweet spot in its own backyard: heart valves. Through an aggressive early acquisition, the company has emerged as the leader in what looks to be the next major device product market: transcatheter valves. But in building a transcatheter valve business, Edwards must maintain its surgical customers while also selling to new physician customers: interventionalist cardiologists - a clinical specialty with a history of competing with surgery.

Edwards appears to have found its growth driver in the hottest segment of the valve market: transcatheter valves, which look to be the next major area of device growth.

When Edwards spun out of Baxter 10 years ago, the new company found that many of its existing businesses, particularly its surgical heart valve franchise, were in slow-growth sectors.

To drive growth, the company aggressively explored a number of potential new product markets outside of its core areas without success.
In building a transcatheter valve business, Edwards must maintain its surgical customers while also selling to new physician customers: interventionalist cardiologists - a clinical specialty with a history as competitors to surgery.

Perhaps the company's biggest challenge is that transcatheter valves places them directly in the competitive interventional cardiology market, an area the company has previously been able to avoid.

Change is an inevitable part of business and it is often true that companies that resist change generally come to regret it. The key is recognizing impending change and responding to it effectively, whether you seek out a new direction or have it thrust upon you. Edwards Lifesciences Corp, was looking for new product markets outside of the company's slow-growth traditional core areas to drive expansion. Ultimately, however, Edwards realized that its best opportunity for future growth was in extending its historic leadership in surgical tissue heart valves into the emerging area of transcatheter valves. Through an aggressive early acquisition, the company has emerged as the leader in what looks to be the next major device product market.

The decision to embark on this strategy was not without significant risks: commercial, clinical, and competitive. Commercially, Edwards risked alienating its traditional customer base, surgeons, because the move into transcatheter valves meant marketing to a new and - as perceived by some surgeons - competitive clinical specialty, interventional cardiology. The strategy appears to be paying off with the company selling successfully to both clinical specialties in Europe, where it is the leader in this new area along with Medtronic CoreValve LLC, a division of Medtronic Inc. Clinically, Edwards is also ahead in the race to enter the US transcatheter valve market, having recently successfully completed the first of its US clinical trials, the PARTNER study, whereas Medtronic CoreValve has just initiated its US study.

Ultimately, Edwards' biggest risk may be competitive. Even though the company did not decide to change product markets per se, the decision to build a transcatheter valve business puts Edwards squarely into the competitive and volatile interventional cardiology market. As a result, Edwards is likely to face significant competitive challenges that it has been able to avoid by virtue of its previous product mix.

As a result of its early success and the future promise of the transcatheter valve market, Edwards has dramatically changed the course of its corporate development strategy. Instead of looking to invest in clinical areas outside of its core competencies to drive future growth, such as in abdominal aortic aneurysms (AAAs) and peripheral artery disease (PAD), the company has been divesting many of those non-core technologies to focus on valves and critical care products, the two areas in which the company was the market leader in April 2000, when it emerged as the publicly traded spin-off of Baxter International Inc.'s cardiovascular group. For all of Edwards' efforts to find new product markets to drive growth, actually, the more things have changed in valves, the more they have been the same for the company. However, as the commercial development of these new valves ramps up, Edwards is likely to find that the changes have just begun.

Looking For A Focus

For all of the early success that Edwards has had in transcatheter valves, Michael Mussallem, the company's chairman and CEO, admits that, at the time of the spin-off, Edwards did not envision the prospect of an interventional valve
market emerging. However, soon thereafter, as viable new percutaneous
technologies emerged, the company launched an internal R&D program
focused on transcatheter valves. In pursuing the percutaneous opportunity,
Edwards executives faced the classic innovator's dilemma. The company could
either continue to focus exclusively on surgical valves and maintain its market
leadership by developing next-generation minimally invasive surgical (MIS)
products, or it could turn its attention to what could be the next major device
innovation, transcatheter valves - hoping of course to maintain its position in
surgical valves. Adopting the latter strategy would also mean expanding to sell
to a new customer group: interventional cardiologists, and running the risk of
rendering obsolete at least a segment of the company's current product line and
perhaps alienating its core customers - surgeons - in the process. Mussallem
notes that Edwards officials became close readers of Clayton Christensen's *The
Innovator's Dilemma*, which argues that market leaders generally have a hard
time rendering their own technology obsolete. "We knew from the beginning
that this potentially could be a big obstacle for us with transcatheter valves, but
we were determined not to let that traditional wisdom stand in our way," he
says.

A major factor for Edwards in its push into transcatheter valves: the markets for
the company's leading products, which the company generally referred to under
the umbrella of late-stage heart disease (largely because the conditions that
label covered were generally the province of surgeons, who were Edwards' primary customers), had slowed significantly. Mike Mussallem recalls, "The core
markets in which we participated weren't growing very fast, and we recognized
early on that we needed to find other areas to get into if we were going to
stimulate growth." The tissue valve market - the segment in which Edwards is
the leader - was growing at around 10%, but the overall surgical valve market
was averaging annual growth of only 5%, dominated by mechanical valves in
which Edwards is not the market leader. Similarly, the cardiovascular MIS
market, another important area for the company, was developing at a slower
rate than many had predicted. As a result, Edwards was looking for products
that could generate more rapid growth rates and help drive future company
expansion.

In looking to broaden its product portfolio to more rapidly drive growth, Edwards
considered a number of product markets. This led to product development
efforts in several new and different areas over the past 10 years, many of which
were later divested when the company decided ultimately to focus on the
structural heart (primarily heart valves, both surgical and transcatheter) and
critical care markets. Thus, the company undertook projects in peripheral
vascular disease, launching the *LifeStent* (which it eventually sold to *CR Bard Inc.*); AAA repair, with its *Lifespan* stent graft (which was sold to *Angiotech Pharmaceuticals Inc.*); atrial fibrillation therapy; heart failure; and
transmyocardial revascularization (TMR). [See Deal] [See Deal] In the course of
narrowing its product focus by shedding some more recent acquisitions,
Edwards also divested its perfusion and ventricular-assist businesses, both
carryovers from Baxter. [See Deal] The result is that, despite these expansion
efforts, the company's current product mix nearly mirrors what Edwards' portfolio looked like at the time of the spin-out 10 years ago, with heart valves and critical care products composing 80% of its revenue.

But one important difference between Edwards now and when the company
spun out of Baxter is the expansion of its customer base, moving from an
almost exclusive focus on selling to surgeons to a future in which interventional
cardiologists will be an important part of the customer mix, driven largely by
transcatheter valves. Edwards officials are aware that some surgeons might
take issue with the company’s sudden outreach to interventionalists, who all but took revascularization procedures away from surgeons and now threaten to do the same with valve repair and replacement. Yet, the company’s strategy has never been customer-focused. According to Mike Mussallem, “We decided early on that we were not going to be purely focused on any particular customer because we knew that since the physician specialty treating any disease may change over time, a strategy focused purely on customers could be fragile.” In his view, the same is true of a corporate strategy focused on one specific technology or group of technologies, because technology changes. “We decided that our most robust strategy was to focus on the disease and the patients,” he says. “Wherever that approach took us was going to be the best way to go.”

In the early years following the spin-out, Edwards’ approach evolved to a disease-focused strategy that the company initially termed late-stage heart disease. Since these conditions were synonymous with surgical treatments, Edwards became known as a company whose primary customers were surgeons. Indeed, until its involvement in the peripheral vascular market several years later, Edwards focused almost exclusively on selling to surgeons, having very little to offer interventionalists, a strategy driven by both the company’s focus on late-stage disease - because interventionalists generally don’t treat these patients - and by the competitive landscape. “At that time, interventionalists were almost exclusively treating coronary artery disease, and for us to try to compete in that market against successful major players without having a very novel technology would have been foolish,” Mussallem notes. “The world didn’t need another drug-eluting stent when the market was being so well served by the companies in the market.”

**Grow It Or Buy It?**

Mussallem acknowledges that the focus of the late-stage heart disease strategy was unclear for the first several years following the spin-out. That is because, as noted, the company did not believe that its initial product mix could generate the growth needed to drive future expansion and so Edwards was actively searching for new technologies to fuel its growth. And transcatheter valves were not on anyone’s radar screen as a technology that could eventually provide significant growth. While the company had launched an internal transcatheter valve program called Patriot shortly after the spin-out, the project remained nascent for several years, not attracting a significant portion of Edwards' overall R&D budget.

The company’s interest in transcatheter valves picked up, however, in May of 2002 when Alain Cribier, MD, an interventional cardiologist from the University of Rouen, Hospital Charles-Nicole, performed the first transcatheter aortic valve replacement during a live case at that year’s EuroPCR conference, using a device developed by a then little-known Israeli start-up called Percutaneous Valve Technologies (PVT). “We were aware of PVT, but that case really got our attention and we started looking at them more closely,” notes Mussallem. “And we found that they had some very interesting intellectual property concerning transcatheter valves, in addition to their valuable early clinical experience.”

In fact, Edwards had first become aware of PVT several years earlier, but in the context of AAA devices, not valves. The start-up company had not yet focused on structural heart disease and was considering a number of potential applications for its basic technology. At the time, it was attempting to convince Edwards that PVT’s underlying technology could have applications for AAA repair. The two companies weren’t able to work out a deal in AAA, and PVT continued to develop its technology, eventually focusing on percutaneous heart
PVT's breakthrough was made even more dramatic because it transformed a procedure that had been the sole province of surgeons into an exclusively percutaneous approach, not the hybrid approaches currently being developed for either transapical (TA) or transfemoral (TF) delivery. That isn't surprising because PVT was a company with a purely interventional pedigree, co-founded by leading interventional cardiologists Alain Cribier and Martin F. Leon, MD, of New York-Presbyterian Hospital/Columbia University Medical Center, and Stan Rowe and Stan Rabinovitch, two industry veterans who helped bring the Palmaz-Schatz coronary stent to market for Johnson & Johnson and then worked together at Datascope Corp., manufacturer of intra-aortic balloon pumps and vascular closure devices.

While doing some work for J&J on stents at the Thoraxcentre in Rotterdam, The Netherlands, in the mid-1990s, Rowe came across the work of Henning Rud Andersen, MD, a Danish cardiologist. Andersen was doing early work percutaneously implanting heart valves into pigs, and he had authored several seminal patents in this area. The patents were acquired by Heartport Inc., which ultimately went in a different direction, focusing on minimally invasive cardiac surgery. J&J eventually acquired Heartport, and in December 2000 PVT acquired an exclusive license for all of the Andersen patents. [See Deal] [See Deal]

PVT used that IP to develop a device that mounted a bioprosthetic heart valve on a balloon-expandable stent, deploying the valve inside the patient's native valve. The company used an approach and tools, such as stents, balloons, and catheters, with which interventionalists were already comfortable. The interventionalist inflated the balloon to pre-dilate the valve opening so that the prosthetic valve could be implanted inside the native valve without having to excise the existing valve. The procedure is performed on a beating heart, thereby obviating the need to place a patient on cardiopulmonary bypass, avoiding the potential neurological risks that accompany bypass during surgical procedures.

Cribier's breakthrough with the PVT device at EuroPCR triggered an internal debate within Edwards as to which was the better transcatheter aortic technology: PVT's or Edwards' internal project, Patriot. Not surprisingly, many Edwards officials felt that although PVT was first in implanting a transcatheter valve, Edwards' technology was better. What was clear was that PVT had gained an important advantage: the fact that it had achieved a successful first-in-man implant meant it was well ahead of Edwards and closer to commercialization - even Mussallem estimates PVT had about a one-year lead.

In the end, Edwards decided that the answer to the question as to whether it was better to be first or best was, in Mussallem's words, "Let's be both." The result: Edwards entered into serious discussions to acquire PVT. [See Deal]

These negotiations were, however, far from your run-of-the-mill M&A discussions. Edwards was not the only - or the largest - company interested in PVT. Johnson & Johnson, Boston Scientific Corp., and Medtronic all were investors in PVT and held board seats. Edwards was the last of these companies to express interest in the start-up and was also the only one that did not have any significant presence in the interventional market.

Edwards entered these negotiations with a two-tiered strategy, says Mussallem. First, the company wanted to make it clear to PVT that Edwards was serious
about doing a deal. "We didn't want to be seen as a stalking horse for any of the other companies," he explains. Second, Edwards was prepared to close the deal quickly. "We had built enough internal conviction to enable us to put our cards on the table and give PVT only a short period of time to either make a deal with us or we were prepared to move on," he adds. In Mussallem's view, J&J, Boston Scientific, and Medtronic were all interested in PVT but they wanted to see the technology mature, so that more risk was removed from the transaction before they were ready to make a deal. Edwards, on the other hand, was comfortable assuming what was, at that point in PVT's development, a significant level of risk on all fronts: technology, clinical, and commercial.

Some have criticized Edwards for its risky deal, arguing that the company should have hedged its bet by paying less up front and structuring the acquisition based on milestones achieved. Edwards officials disagree. Not only would such a deal structure have been much less desirable for PVT and much easier for one of the start-up's existing large investors to match, Mussallem says, but also those kinds of deals work best for buying products, not companies, and for Edwards, PVT clearly was a strategic acquisition.

Each of the other companies, by virtue of their investments in the start-up, also had various preferential rights they could exercise prior to any sale that would have placed them ahead of Edwards. To Edwards' advantage, however, the timeframe in which those rights had to be exercised was short, and knowing that, Edwards made what Mussallem calls "a compelling enough offer" designed to convince PVT to accept the Edwards bid and discourage competing offers.

Edwards' strategy proved successful on both counts, winning PVT's acceptance without prompting any competing bids, and the deal closed in early 2004. Indeed, the offer of $125 million in cash plus an additional $30 million earn-out for an early-stage company in an early-stage technology area prompted significant criticism of Edwards, charging that the company dramatically overpaid for PVT. Mike Mussallem says the criticism was understandable. "Our motivation was clear: we had made our mind up that we wanted to acquire this company, and we knew there was significant risk associated with this acquisition," he acknowledges. "This was either going to be seen someday as a really bright move or a really terrible move - there probably wasn't going to be a lot of gray in between."

![Exhibit 1: Global THV Market Opportunity](image)

- 30-60% of patients with severe aortic stenosis go untreated
- Transcatheter valve market opportunity expected to exceed $2 billion in 4 to 5 years
Leading The Way

According to Mussallem, Edwards was looking to become the leaders in the valve space by "focusing on delivering the best heart valve therapy for the patient. We were agnostic when it came to the physician customer or the type of procedure. We thought the transcatheter opportunity was the future of this market, and we weren't going to walk away from what could be a transformational opportunity in order to protect our base business. If the heart valve business was going to change, we wanted to lead that effort."

Because the PVT acquisition was really the first major deal in such a nascent product market, Mussallem also acknowledges that this was a very difficult transaction to value. "On the one hand, it wasn't difficult to talk ourselves into believing that transcatheter valves looked to be a very large market opportunity, but objectively we also had to consider that the risks remained very high," he explains. And for Edwards, there was also a strategic value to the deal. "We played out various scenarios, including whether PVT was acquired by a heart valve competitor or an interventional competitor gaining the first mover advantage," Mussallem recalls, "and we didn't like the way either one shaped up, which also helped motivate us to take this big step."

Larry Wood, who is now corporate VP of transcatheter valve replacement and was then VP, strategic marketing, suggests that, "For us, the risk of not doing something was far greater than the risk of doing a deal that didn't work." He argues that, even if the PVT device didn't pan out, the worst case scenario for Edwards was that its surgical valve franchise would remain strong for an even longer period of time because there would be less of a chance that a new disruptive technology would emerge. The bigger risk to Edwards would have been if a competitor had acquired PVT and the technology proved successful.

Transcatheter valves are a particularly attractive opportunity for Edwards because they won't replace surgical valves in the current patient population but could significantly expand the valve market. Indeed, the first clinical applications for transcatheter valves are to treat a large group of high-risk patients who are not surgical candidates due to the frailty of their health, including serious other co-morbidities, and thus are currently left without any viable treatment options. This clinical approach had implications for Edwards' early regulatory strategies since most important cardiovascular devices - coronary stents, for example - are targeted at and tested on moderately diseased patients, not on the sickest ones.

This initial focus on higher-acuity patients has caused some valve company experts to speculate that, had stents been subjected to the same regulatory protocols as valves, they would not have gained the same level of rapid adoption and become blockbuster devices. Although no one is predicting that transcatheter valves will spark that level of growth in the overall valve market, there are estimates that these new valves have the potential to turn what traditionally has been a slow-growth market into a rapidly accelerating area, akin to what cardiac resynchronization therapy (CRT) did for the implantable cardioverter defibrillator (ICD) market in the early to mid-2000s.

While the PVT acquisition provided the foundation for Edwards' burgeoning transcatheter program, it was far from the company's only move in the space.
Not only had Edwards, as noted, been working on its own internal program, but the company had also completed another deal several months earlier, adding to its expertise in this area by acquiring Jomed's percutaneous mitral valve program for $20 million. [See Deal] (Edwards was pursuing internal programs on both aortic and mitral valve transcatheter devices.) The Jomed deal was a result of Edwards aggressively tracking many of the companies with transcatheter programs. "We surprised a lot of people with that deal," remarks Donald E. Bobo, Jr., VP, general manager, heart valve therapy, "but we had been following Jomed for about a year so that when they ran into their problems and ended up in bankruptcy, we knew the value of their IP and were able to put an offer in front of the trustees within a couple of days that landed the deal. That was definitely a case where fortune favored the prepared."

Integration: The Real Innovator's Dilemma

Having completed these deals to acquire external transcatheter technology, Edwards' next challenge was integrating these with its internal programs to build a cohesive business unit. For Edwards, the integration was made more difficult by the fact that PVT was co-located in both Israel and New Jersey, creating geographical challenges to match the cultural challenges that come from merging a small start-up with a company as large as Edwards. Mike Mussallem notes that, rather than forcing PVT to become more like Edwards, company officials knew they needed to retain the energy and creativity of the start-up.

But there was a bigger, more strategic challenge for Edwards. Having moved aggressively into percutaneous valves, the company was faced with competing missions: true, Edwards sought eagerly to develop this new technology, but it was also intent on protecting its existing market-leading position in tissue valves. PVT, on the other hand, had nothing to lose in focusing exclusively on transcatheter valves, creating a contrast in risk profiles. "We wanted to transplant the energy, the single-mindedness, and maybe some of that start-up risk profile from PVT into Edwards," Mussallem explains. The company attempted to accomplish that by creating a separate organization encompassing all of the company's transcatheter valve research under the leadership of Stan Rowe, who previously headed PVT.

"One of the things that impressed me is the way Edwards, as a company, embraced a disruptive technology," Rowe previously told IN VIVO. (See "Edwards: Battling the Innovator's Dilemma," IN VIVO, December 2005 "Edwards: Battling the Innovator's Dilemma" - IN VIVO, December 2005.) "Many companies do an acquisition, rip out the technology they really were after, and bring that in-house, or they put up a wall between competing technologies and say, 'We're going to fight this out.' But Edwards' goal has always been to integrate the two companies."

Mussallem echoes that view. "With PVT, we weren't just buying a product design. We wanted their team to become an integral part of Edwards, so a successful integration was critical to making the deal work," he says.

In addition to cultural and geographic issues, there were other major differences between Edwards and PVT that would make integration challenging. For example, "We didn't really have any significant interventional expertise in-house," notes Larry Wood, and while PVT brought a wealth of percutaneous experience, blending that with the largely surgical orientation within Edwards took some doing. There was also the matter of scale. "We went from having a small internal transcatheter program to creating an organization that, by comparison, was huge, and we did it so quickly that it felt like it happened
overnight," Wood recalls.

Edwards also faced a significant product development issue because PVT had focused its efforts exclusively on developing a valve and a stent. To implant the device, the start-up relied on a delivery system comprising various off-the-shelf items including valvuloplasty balloons and introducers. The result was a clunky system that necessitated a difficult, trans-septal procedure, which ultimately proved too complex. Following the acquisition, Edwards' engineers eventually developed a transfemoral delivery system. The irony, Larry Wood points out, is that "the valve company built the delivery system and the interventional company built the valve."

The biggest difference between surgical valves, which Edwards has been producing for 50 years, and transcatheter valves such as PVT's is the need to compress the valve to be delivered through a catheter and then expand it for implantation without damaging the valve (surgical valves are implanted fully formed). While Edwards employed PVT's basic valve design, the company was able to apply its valve expertise to quickly improve that original design through processes such as anti-calcification treatments. The result was that Edwards' new transcatheter valve group was able to leverage the combined expertise of the two companies to dramatically shorten the time it would have taken either company on its own to develop the first commercially available transcatheter aortic valve, Sapien.

One irony in this process is that Edwards' internal transcatheter valve was self-expanding; the company elected to go with a balloon-expandable design following the PVT acquisition. Edwards' primary competition, the ReValving system from Medtronic CoreValve, employs a self-expanding design, providing a point of differentiation that wouldn't have existed had Edwards gone with the Patriot device. The difference is largely a matter of size. The balloon-expandable design generally requires a larger diameter sized device - the initial Sapien system was first 24 and then 21 French - because of the need to mount a balloon along with the valve and stent on the catheter, compared with self-expanding systems. In its current ongoing clinical trial, Edwards is employing a smaller-sized (18 French) device, the Sapien XT, in which the stent is placed on the balloon while in the patient's vessel, thereby enabling the use of smaller-diameter devices, but also requiring an additional procedural step.

Whether a transcatheter valve system is balloon-expandable or self-expanding, however, turns out to be less important than the procedure through which the valve is delivered. The ultimate success of a transcatheter system lies in a device that can be used by both surgeons and interventionalists. The best way to ensure adoption by both clinical specialties is through a device that can be delivered both transfemorally (TF) and transapically (TA), the latter being an approach more naturally suited to surgeons because it requires both surgical and catheter skills. (In a smaller number of patients, transcatheter valves can also be delivered using a transaxillary approach.) Performing the TA procedure requires a small incision or mini-thoracotomy between the fifth and sixth ribs, giving the physician access to the apex of the heart through which the catheter is placed. As a result, a transapical device is much shorter - around 20 inches in length - and easier to steer because of the shorter distance covered, than a transfemoral device - around four feet long - which is inserted in the groin through the femoral artery, much like most other interventional devices, and steered up to the heart.

Early percutaneous valve companies like PVT most often adopted a transfemoral approach since it relies primarily on interventional/catheter-based skills. Indeed, the only role required for surgeons in this procedure is making
and closing the incision needed to introduce these devices, which is larger than
that typically used for PCIs (percutaneous coronary interventions) and thus
requires surgical incision rather than venous puncture.

The fact that early transcatheter approaches favored transfemoral delivery only
served to further alienate surgeons, who saw this as another procedure where
they would be disenfranchised by interventionalists. And the TF approach was
also not ideal for all patients, particularly those with peripheral vascular disease
(PVD) - a common co-morbidity of elderly aortic stenosis patients - for whom
access through the femoral vein or artery is often risky or not possible. To better
treat PVD patients and to make the procedure easier for surgeons to perform, in
2005 Edwards pioneered the transapical delivery technique by introducing a
new system. According to Larry Wood, "Developing the transapical approach
was critically important to this field because it really brought the surgeons to the
table since it gave them a procedure that they could take the lead on, and that
started to solidify the partnership between surgeons and cardiologists by
facilitating some significant knowledge transfer on how to best treat patients."
(Medtronic CoreValve's device can only be delivered transfemorally, primarily
because of its length. Medtronic's acquisition of Ventor Technologies Ltd. for
$325 million provided the company with transapical technology.) [See Deal]

Edwards' transapical strategy was criticized by some interventionalists as a step
back from furthering the development of percutaneous technology and an
approach designed primarily to appease surgeons; company executives point to
patients with PVD and other similar limitations as examples of the unmet clinical
needs served by this approach.

Avoiding A Turf Battle

Perhaps the most difficult challenge, however, for Edwards in launching its
transcatheter valve business, particularly PVT's TF approach, did not involve
technology; rather, it was convincing surgeons, who were the company's
longstanding valve customers, that Edwards was not forsaking them for
interventional cardiologists in developing this new technology. For surgeons,
percutaneous valves recalled their early experience in re-vascularization, where
angioplasty dramatically reduced the number of CABGs performed. PVD, too,
soon lent itself to percutaneous technology. For most surgeons, heart valve
repair and replacement was the last bastion of a surgical approach. Now, even
valve procedures were being taken over by interventionalists - and Edwards
was leading the way.

Edwards has tried to balance the interests of both surgeons and
interventionalists by taking a leadership role in bringing the two together around
transthecatheter valves. Perhaps most notable was the company's sponsoring of
an historic course on valvular heart disease in Chicago in September 2005, that
brought together cardiac surgeons - through Delos "Toby" Cosgrove, MD, of
the Cleveland Clinic Foundation and the American Association for Thoracic
Surgery (AATS) - and interventional cardiologists - through Marty Leon and the
Cardiovascular Research Foundation (CRF) - to discuss the future of heart
valve therapy, with a focus on transcatheter techniques. (See "Cardiologists
and Surgeons Meet for Heart Valve Summit," IN VIVO, October 2005
"Cardiologists and Surgeons Meet for Heart Valve Summit" - IN VIVO.
October 2005.) The scope of the challenge inherent in bringing these two
groups together was reflected both in the direct and occasionally heated nature
of the debate at the conference, and by the fact that the meeting has not been
repeated.

Given its long-standing relationships with surgeons, Edwards executives believe
that they are actually in the best position to promote transcatheter valves in the
least threatening manner for surgeons and to lessen the historic antipathy between surgeons and interventionalists. "Having Edwards acquire PVT's percutaneous system was the best thing to happen for the technology as a whole because we were committed to engaging surgeons and bringing them to the table," says Larry Wood. He points to the evolution of other percutaneous therapies, including coronary and carotid stenting, as examples that spawned significant turf battles between the specialties to the detriment of patients and, particularly in carotids, significantly slowed technology adoption.

Wood admits that the idea of attempting to bring surgeons and interventionalists together sparked significant debate within Edwards. "We believed this was the right approach both for patients and for the technology, and we knew that if we could accomplish bringing both groups together, it would be a powerful means of driving adoption. But we also knew that it was a big 'if' to get some of these doctors to put their egos aside and work together," he says. "And while it has taken a while and remains a work in progress, the strategy appears to be working."

Some would argue that, for surgeons, the idea of fighting, rather than switching, was not a viable option, that a switch to transcatheter approaches is inevitable once the technology works, given the advantages of percutaneous technologies to patients, payors, and health care providers. Indeed, the benefits of percutaneous technologies for certain patients are so obvious that, once the clinical data demonstrate the safety and effectiveness of these new techniques and devices, resisting their adoption is futile and risks having the non-adopters become irrelevant.

Not Ready For Prime Time

By the mid-2000s, notwithstanding the tone of some of the rhetoric at the 2005 Chicago conference, the tide was clearly changing in terms of surgeons’ attitudes toward transcatheter aortic valve implantation (TAVI). Although pockets of resistance remained in the surgical community, particularly among
older-generation surgeons, there was a consensus emerging that the advantages of transcatheter valve procedures were compelling enough and were being supported by increasing quantities of clinical data, so as to make transcatheter approaches the standard of care at least for certain patient populations, especially high-risk, non-surgical candidates with aortic stenosis. Further resistance by surgeons would be futile, and many realized they'd be better off learning catheter skills. Indeed, at around that time, the first hybrid operating room/cath lab suites, staffed by both surgeons and interventionalists, started to be formed primarily at major academic medical centers.

Not that there weren't bumps in the road for Edwards. Indeed, 2004 saw the company survive what could have been a serious setback to its transcatheter valve program. In September of that year at the Transcatheter Cardiovascular Therapeutics (TCT) conference in Washington, DC, the leading international interventional cardiology conference, a Sapien valve was implanted in a severely ill elderly patient during a live case performed in Milan that was transmitted to the conference; during the procedure, the patient suffered major complications. Shortly thereafter, conference attendees watched in shock as the patient's heart failed and the attending team of cardiologists unsuccessfully tried to resuscitate him before the case transmission was abruptly ended. The patient died later that day.

The event cast a pall over the conference, and even though the patient was elderly and severely ill with significant co-morbidities - a patient who truly had no other options and was not a candidate for traditional open surgery - the case raised questions about this emerging transcatheter approach. "There was a lot of enthusiasm surrounding the procedure coming into this conference, and while much of that enthusiasm continued even after the conference, this case also sent a signal that the procedure was not ready for prime time," Mussallem recalls. "Something like this happening at a major meeting suggested the immaturity of this approach."

The case also drew attention to the inherent difficulty of performing the TAVI procedure using the first-generation delivery system that, as noted, was composed of off-the-shelf components. At that time, implanting the Sapien valve still required a complex antegrade approach that involved threading a catheter transvenously through the femoral vein, making a trans-septal puncture - a procedure many interventionalists aren't used to performing and are not comfortable with - from the right to the left atrium, dilating the atrial septum and crossing through the mitral valve and the ventricle before reaching the aortic valve. As Larry Wood explains, "It was like playing a symphony: one instrument playing one note isn't hard, but getting a group of musicians to play all the notes in the right order gets challenging. No single step in this procedure was all that difficult, but performing all the necessary steps in one procedure was hard."

For Edwards, the problem was compounded by the fact that it had begun its initial US trial using this antegrade approach. The first case went very well and attracted a lot of attention, including an article in The New York Times, primarily because of the rapid improvement that occurs following implantation. Patients with severe aortic stenosis who otherwise have no treatment options frequently say they feel as if they are drowning. Yet, unlike other device implants where it takes a while for a patient's condition to improve, aortic stenosis patients generally feel dramatically better immediately following a TAVI procedure.

Despite the positive outcome of the first case in the study, subsequent cases encountered problems. "It wasn't any one thing," says Larry Wood. "We had a series of complications in the next few cases, including death, which led us to realize that this antegrade approach would not be commercially viable."
At the same time, Edwards was also working with John G. Webb, MD, a leading interventional cardiologist at St. Paul's Hospital in Vancouver, British Columbia, on developing a retrograde delivery approach that delivered the valve transarterially - as opposed to going through the venous system - through the femoral artery and then across the stenosed aortic valve. This approach had the advantages of being easier to perform and being more easily able to accommodate a larger device such as the 24 and 21 French systems Edwards was offering at that time.

Initially, the retrograde delivery, too, ran into problems, but the more cases Webb did, the more it became clear that this approach could significantly simplify the procedure, making it more commercially viable than the antegrade delivery. Edwards stopped the trial and went to the FDA with this new data, proposing that the study employ a retrograde approach using a new delivery system, and the agency agreed to revise the study's protocol. "That experience probably set us back a year," says Larry Wood, "but it was the right decision, and when we started the trial back up again using the retrograde approach, it made a huge difference."

Forging A Partnership Through A Clinical Trial
The leadership that Edwards has tried to exert in bringing surgeons and interventionalists together around transcatheter valves extends far beyond simply sponsoring educational events and conferences such as the 2005 AATS/CRF meeting. The most notable example of this strategy lies in the company's groundbreaking PARTNER clinical trial, which was the big news of this year's TCT conference in September in Washington.

The clinical trial's acronym reflects the study's protocol, which required representatives from each of the two clinical specialties to assess patients recruited for the trial and agree on which patients would be accepted. In Mike Mussallem's view, much progress has been made already in terms of getting surgeons and interventionalists to work together to treat these patients. He acknowledges that it wasn't that long ago that the debate was framed in a much more confrontational, rather than collegial manner, with cardiologists aggressively talking about taking patients away from surgeons, while surgeons discounted the safety and efficacy of transcatheter technology. "Now our approach sounds logical and reasonable, but just a few years ago, many people said that it was highly unlikely that a company of our size, not being the biggest player, and focusing on a single product innovation would be able to get these specialties to work together productively," he says. "We never wanted this to become another battle in the war between specialties - that wasn't going to be good for patients or good for the advancement of what this technology could do. We always fought to try and stay above that, but not always successfully."

Edwards' perspective was that surgeons knew the most about valvular disease because they treated these patients every day, and that interventionalists had the skill set from working with catheter-based technologies to best employ these newly emerging devices, and that it would take both skill sets to truly master the transcatheter valve procedures. Mussallem sums up Edwards' strategy this way: "We believed it wasn't about developing one approach that surgeons would use and another approach for interventionalists, but rather that if they would work together, they could achieve much better success, and the clinical trial has shown that to be true."

The executive committee for the PARTNER trial is split equally between surgeons and interventionalists. Every patient enrolled in the study has to be
screened and approved by a specialist from each group. Mussallem describes the procedure for treating the patients as a pilot/co-pilot arrangement: during a transfemoral case, the cardiologist is generally the pilot and the surgeon is the co-pilot, whereas in a transapical case, the roles are usually reversed.

The real benefit of this approach is that by forcing the two specialties to work together on these cases, they can see the other specialty's expertise, particularly when a complication arises. For example, among the most common TF complications are those involving the iliac artery, which is an area surgeons know well; similarly, a surgeon may have a problem in a TA case handling a wire or catheter, which is a situation familiar to interventionalists. "When they see their colleague bail them out of a jam, that's when it becomes meaningful to be working together, and it usually only takes one such case to convince both doctors that this is the right way to go," Larry Wood points out.

Donald Bobo, who manages Edwards' surgical valve program, notes that surgeons' attitudes change as they are able to employ the device in their practice. Thus, European surgeons, where Sapien is commercially available, generally see the benefit of providing a treatment option for patients who currently often have no other available therapy. "These surgeons generally appreciate that they can now do something for patients they couldn't treat before, and they like having a seat at the table with cardiologists to influence the process of developing the best treatment options," he explains.

In the US, however, where surgeons cannot yet use Sapien except as part of the PARTNER trial, Bobo says their attitudes are different. "Here, surgeons still see transcatheter valves as more of a threat and talk about the need to develop these skills so that they can continue to earn a living - 'I have to learn this or I'll become irrelevant,'" he says. Even in the US, though, Edwards has seen surgeons' attitudes evolve over the past few years, driven largely by the increasing amounts of data being generated that reflect the safety and efficacy of these devices. Bobo admits that as recently as three years ago, some surgeons who had been longtime Edwards customers took their business to competitors because they saw the company's move into transcatheter valves as a threat to their livelihoods.

The interest in the PARTNER study has also been high because it is the first randomized controlled trial in the history of valve surgery. In keeping with the study's protocol, PARTNER has two principal investigators: a cardiologist, Marty Leon, and a surgeon, Craig Smith, MD, also from New York-Presbyterian Hospital/Columbia University Medical Center. (Leon has apparently gone to great lengths to remove any conflicts of interest to participate in this study. As one of PVT's co-founders, Leon reportedly collected around $6 million when Edwards acquired the company. Along with other PVT shareholders, he also was scheduled to share in three $10 million milestone payments upon reaching three goals: successfully treating 50 patients, regulatory approval in Europe, and limited approval in the US. Two of those milestones have already been reached. To participate in the PARTNER trial, Leon has said that he donated his proceeds from the Edwards milestone payments and rights to future such payments to an unnamed school in Manhattan.)

The study also has two cohorts: Cohort B, which compares Sapien using the TF approach with medical therapy, results for which were presented by Leon at this year's TCT meeting, and Cohort A, which compares Sapien using the TF and TA approaches with surgical aortic valve replacement, the results for which are expected to be released in the first half of 2011, possibly at the American College of Cardiology meeting in April in New Orleans. The Cohort B data included 358 patients randomized between Sapien and medical therapy (21
centers, 17 in the US) with a primary endpoint of all-cause mortality at one year follow-up. The results demonstrated a statistically significant 20-point absolute reduction in all-cause mortality in the Sapien arm, causing Leon, on behalf of the study's authors, to conclude, "Balloon-expandable TAVI should be the new standard of care for patients with aortic stenosis who are not suitable candidates for surgery." Sapien patients did experience high - although not statistically significant - major stroke rates at 30 days (5% vs. 1.1%) and at one year (7.8% vs. 3.9%), which the authors called a "troublesome adverse effect." Edwards will soon begin enrolling patients in the PARTNER II trial in the US, which will feature a two-to-one randomization rate. Despite the study's success, Leon cautioned that long-term follow-up out to 10 or 15 years was needed to assess valve durability, pointing out that median follow-up in PARTNER to that point was only 1.6 years.

Certainly, the PARTNER data support the increased attention focused on transcatheter valves at cardiology conferences like TCT and EuroPCR. Indeed, until the last few years, Edwards had only a minor presence at TCT and did not attend EuroPCR; now the company is prominently featured both on the programs and in the exhibit halls. For the last several years, TCT, for example, has been offering separate surgeon tracks, which include training components. Mike Mussallem points out that a similar phenomenon is underway at many US medical schools, where surgeons are going through rotations in the cath lab. "In the same way we're seeing hybrid operating rooms/cath labs, we are also witnessing the beginning of an evolution in training hybrid clinicians," he says.

Growing The Market

The success of the PARTNER trial, combined with the launch of the smaller Sapien XT device, have fueled a more rapid level of growth in Edwards' European sales than had been expected, particularly for transfemoral procedures using the smaller system. Donald Bobo says the company had expected the XT to increase TF procedures, but didn't know if that would come at the expense of transapical cases. Before the XT was available, Edwards was doing around two-thirds TA cases and one-third TF cases. Now, Bobo estimates the split to be around 50-50, but in an overall larger market.

On a competitive basis, one industry executive familiar with this market estimates that Medtronic CoreValve has approximately two-thirds of the European TF market and Edwards has one-third, but that the overall European transcatheter valve market is pretty evenly divided between the two. (Both companies received CE Mark approval and entered the market in 2007.) Edwards executives declined to provide a competitive breakdown of the European market. Larry Wood notes that, when Edwards launched the XT, the product went mostly to its existing customers, not institutions where the two companies were competing head-to-head. Even with this limited rollout of the Sapien XT, Wood claims Edwards is seeing a large expansion of the market. Timothy J. Lee, a senior research analyst at Piper Jaffray who follows Edwards, notes, "One of the most striking points about the PARTNER trial were the bad outcomes in the control arm. Despite having patients receiving the best care possible, half of them had died at the end of 12 months, showing the large unmet clinical need that this device is addressing."

The company is also seeing the introduction of transcatheter valves increasing the number of surgical valve patients in the US at the PARTNER trial sites. According to Wood, patients who previously thought they were not surgical candidates often wouldn't bother consulting a surgeon. Now, they're hearing about the study and undergoing consultations with surgeons. The result: while these patients are often not candidates for the PARTNER trial, they frequently
turn out to be surgical candidates, which is accounting for this overall increase in valve surgeries.

Edwards expects the data from the two cohorts of the PARTNER study to support its PMA submission to the FDA. The company's hope is that it can enter the US market by the end of 2011 or the beginning of 2012. Mike Mussallem expects, with that timeframe, that Edwards will have the US market to itself for two to three years, as Medtronic CoreValve has just begun enrolling its initial US clinical trial. Between now and the time it receives FDA approval, Tim Lee suggests that Edwards' biggest challenge will be expanding its US sales and marketing infrastructure to hit the ground running in support of Sapien. According to Lee, the company plans to build a separate salesforce to handle Sapien.

The positive PARTNER data, coupled with the successful early sales results from the XT device combine to increase the talk that Edwards is attracting more attention as an acquisition target. With Medtronic having already completed major deals in this space and St. Jude Medical Inc. having just announced its acquisition of AGA Medical Holdings Inc. and its structural heart business for $1.3 billion to add to SJM's existing valve group, the number of potential large companies that could afford Edwards is dwindling. The leading candidate over the past year or so has been Johnson & Johnson, which reportedly is working on its own internal percutaneous valve program. And the latest speculation has J&J joined by Abbott Laboratories Inc., whose Abbott Vascular Devices division acquired Evalve and its mitral valve program for $410 million to serve as the foundation for a growing structural heart business that currently lacks any significant aortic technology, which represents the largest segment of the valve market. [See Deal] [See Deal]

Mike Mussallem declines to speculate on Edwards' future, other than to focus on the business at hand. Since doing the PVT deal, Edwards has been relatively quiet on the dealmaking front, despite the flurry of recent transcatheter valve deals. Mussallem says the company continues to follow all of the start-ups that are active in transcatheter valves and in the broader structural heart disease area. He claims Edwards will not hesitate to do what it considers to be the right deal to acquire additional technology in this space. "We continue to take the attitude that we must be the leaders in the valve market and if a good potential acquisition comes along, we have the balance sheet and the will to do another deal," he says.

But Edwards has also gone through the acquisition process previously in other sectors only to find out that the company's best opportunities existed in its core markets: valves and critical care monitoring. "As things played out in those other product segments, we found that we didn't have the big winners and the important therapeutic options that we were bringing to the table in our core areas," Mussallem admits.

In the end, Edwards found that its initial strategy of having to diversify to find growth turned out not to be the case. "What is ironic is that, after all of our looking around and doing deals in different areas, we found that our two anchor businesses - structural heart disease and critical care medicine - both have really interesting growth profiles that have thrived through our increased focus," Mike Mussallem explains. "That gives us a wonderful opportunity on a lower risk and more narrow focus profile to go after growth close to home."

Along with that opportunity, however, come the risks that accompany any emerging market, and although Edwards appears to be successfully navigating
the initial clinical and commercial challenges (pending, of course, US commercialization), the company's biggest challenge may be the competitive landscape that lies ahead. As Mike Mussallem noted previously, to this point, the company has avoided the hyper-competitive interventional cardiology market, choosing to play in other, slower-growth cardiovascular product segments. When it comes to transcatheter valves, that all is about to change for Edwards as it lands squarely in the volatile interventional space.

While the company appears well-positioned to succeed in what looks to be the next major emerging CV market, that success may well present Edwards with its biggest test: can the company be a leader in transcatheter valves and still remain an independent company? Edwards is already rumored to be a hot takeover target and that is even before US commercialization. The real question for Edwards may be whether the company turns out to be a victim of its own success.

Exhibit 3

**Cardiologists’ Views On Transcatheter Valves**

These questions and responses are from a survey of US and European interventional cardiologists on transcatheter valves conducted for **IN VIVO** by Gerson Lehrman Group.

**How many transcatheter valves do you implant in a typical 30-day period?**

<table>
<thead>
<tr>
<th></th>
<th>Mean Value</th>
<th>Median Value</th>
<th>High Value</th>
<th>Low Value</th>
<th>Standard Deviation</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>5.67</td>
<td>4.00</td>
<td>12.00</td>
<td>1.00</td>
<td>4.29</td>
</tr>
</tbody>
</table>

**Please estimate the total number of transcatheter valve procedures performed at your institution using each method during 2010 and 2011.**

<table>
<thead>
<tr>
<th></th>
<th>Transapical</th>
<th>Transfemoral</th>
<th>Trans-subclavian/Trans-axillary</th>
<th>Traditional Open Surgery</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>2010</strong></td>
<td>18</td>
<td>40</td>
<td>1</td>
<td>123</td>
</tr>
<tr>
<td><strong>2011</strong></td>
<td>18</td>
<td>51</td>
<td>2</td>
<td>112</td>
</tr>
</tbody>
</table>

**Please estimate the % market share for the following transcatheter valves during the follow years:**

<table>
<thead>
<tr>
<th></th>
<th>Edwards Sapien</th>
<th>Edwards Sapien XT</th>
<th>Medtronic CoreValve</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>2010</strong></td>
<td>18.44%</td>
<td>30.00%</td>
<td>51.56%</td>
</tr>
<tr>
<td><strong>2011</strong></td>
<td>7.22%</td>
<td>42.56%</td>
<td>48.56%</td>
</tr>
<tr>
<td><strong>2012</strong></td>
<td>3.33%</td>
<td>47.78%</td>
<td>41.67%</td>
</tr>
</tbody>
</table>

**Would you consider performing the transapical procedure?**

| Yes | 69% |
| No  | 31% |

**Do you currently participate in a hybrid treatment (with surgeons) team to treat valve patients?**

| Yes  | 59% |
No
0

No, but I do consult with my (surgeon) colleagues prior to a transcatheter procedure.  26

No, but I intend to consult with my (surgeon) colleagues to determine whether a patient is appropriate for either a transcatheter or surgical procedure.  15

SOURCE: Gerson Lehrman Group
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Percutaneous Valve Technologies licenses Heartport’s patents

Edwards acquires Percutaneous Valve Technologies

Edwards gets Jomed percutaneous valve program for $20mm

Medtronic buys Ventor Technologies for $325mm

St. Jude Medical acquires AGA Medical for $1.3bn

Abbott buys rest of Evalve for $320mm plus earn-outs