



## Surviving as a Stent Startup

***To succeed in the nascent drug-coated stent industry, startups are finding niche markets and cozying up to industry giants.***

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The medical device industry rarely sees an overnight success. But in April 2003, when Johnson & Johnson first introduced the United States to a revolutionary heart disease treatment—a drug-coated version of the stents commonly used to prop open blocked arteries after they’ve been cleared—doctors jumped at the opportunity and quickly opted for the newer products.

In less than three years, the global market for these drug-eluting stents has grown to \$5.5 billion, according to Hoovers, and Medtech Ventures expects it to reach \$6.5 billion in 2010. With an eye on the potential profits, ambitious startups are trying to carve out a lucrative space by improving on the limitations of current stent technology. But deep-pocketed heavyweights have left little room for smaller entrants—especially in the U.S., which accounts for 70 percent of the global market for drug-eluting stents.

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**Boston Scientific**, with a market cap of about \$21 billion, introduced its own stent to the U.S. in March 2004 and now controls 53 percent of the U.S. market, according to the Millennium Research Group. J&J, a mammoth multi-industry company with a market cap of \$186 billion, accounts for 47 percent.

The story is much the same abroad. In Europe, Boston Scientific leads with 47.5 percent, followed by J&J with 40 percent, and 10.5 percent for medical device giant **Medtronic**, which has marketed its medicinal heart stent internationally since August 2005. Other companies account for only 3 percent of the European market. If Medtronic, with a hefty \$71-billion market cap, passes U.S. regulatory muster as expected in 2007, it has a fighting chance of chipping away at the U.S. duopoly.

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Startups, on the other hand, need more than favorable clinical trials to stand a chance. Getting a drug-eluting stent to market isn't cheap—Boston Scientific's Vice President of Cardiology Marketing Eric Simso estimates the company has spent \$500 million to bring its product to market. And the combination of a drug and device means increased regulatory hurdles and longer clinical trials. Even for cash-rich players, it's no easy task. "It's a marketplace that most people underestimate," says Mr. Simso. "It's much more difficult to get a product to market than anyone dreams, including us."

To break into the drug-eluting stent space, smaller firms—including Xtent, Devax, and REVA Medical, among others— need technology and a business plan that will allow for their survival, or an acquisition by a larger company.

If they're determined to go it alone, these fledgling companies can help feed larger multinationals' R&D pipelines through technology licensing, says Ahmed Sheikh, an analyst at Belgium-based research firm Medtech Ventures.

But their best move may be an acquisition. The big companies are looking: So far, Boston Scientific has acquired or is negotiating deals with about six companies in the drug-eluting stent space, according to Mr. Simso.

If these startups combine the right innovations with the right business relationships, their targeted markets could eventually lead to a hefty payday.

### **Inlets to the Market**

Bare metal stents have long been implanted into the arteries of heart disease patients to keep them from re-narrowing. But coating them with a drug reduces the chances of artery re-narrowing from as high as 30 percent to under 9 percent.

Current drug-eluting stents on the U.S. market are made of an expandable, metal scaffold, which is inserted into a vessel via a catheter after heart surgery and expanded to keep blood flowing properly (see diagram). Once implanted, the stent releases controlled amounts of medicine over an average of two to four weeks to reduce the overgrowth of scar tissue that can result in the artery re-narrowing in reaction to the device.

But stents are not perfect. They have a fixed length, "crimped on a fixed-length balloon" for placement, says Brian Walsh, vice president of sales and marketing at Xtent, a Menlo Park, California-based startup that's developing a customizable stent. The problem with stents, he says, is that only one can be delivered at a time, although doctors are more frequently using stents to treat patients having multiple blockages, often in several blood vessels.

Xtent's system will allow cardiologists to customize the length of each stent and lay down two or three in multiple vessels using a single catheter insertion, thereby improving efficiency and lowering procedure times and costs compared to implanting one stent at a time.

Xtent was founded in 2002 by Menlo Park-based medical device incubator firm The Foundry. The company has since secured \$45 million in three rounds of venture capital funding from Morgenthaler Ventures, Advanced Technology Ventures, Split Rock Partners, and Latterell Venture Partners. In June, Xtent began clinical trials in Europe for its technology; it hopes to launch its product by early 2007 in Europe and 2009 in the U.S.

Mr. Walsh says Xtent isn't relying on a single exit strategy. "We're prepared to take it all the way," he says. Although they need to raise another round of funding to get the product on the market, Xtent executives believe the company has what it takes to go after the lion's share of the drug-eluting stent market. "We have an opportunity to change the basis of competition," says Mr. Walsh, who claims that 70 percent of all drug-eluting stents are used in multi-stent cases. Still, he doesn't rule out the possibility of a favorable acquisition. But if any potential buyers have come knocking, he won't say.

### **A Branching Opportunity**

Irvine, California-based Devax is focusing on another limitation of today's stents. In places where a single heart vessel branches into two, stenting becomes problematic and risky. Cardiologists then have to alter a medicated stent's shape to fit the angle of the vessel, by using multiple stents that often overlap one another to cover the lesion. This can sometimes cause abnormal blood flow in treated

arteries and potential gaps that lead to higher rates of re-narrowing.

Devax, originally founded in 1999 to develop a bare metal stent, is now developing one designed specifically for deviating vessels. "For us to be successful, we had to go after a niche," admits Devax CEO Jeff Thiel. But in a multibillion-dollar market, niches can be quite large. The company hopes to tap a market that it says is worth more than \$1 billion with its self-expanding, cone-shaped stent that conforms to split vessels.

In October, Devax released positive results for its first European clinical study, which was also designed to serve as an early-stage U.S. clinical trial. The company hopes to have European approval and submit for U.S. regulatory approval in early 2006.

Devax will have to prove that its approach is better than that of Advanced Stent Technologies, which Boston Scientific acquired in March 2005 for \$120 million in stock. The deal also left room for possible future payments. Despite playing odds against Devax, Boston Scientific has been impressed with the company. "They've done what a small company should to be successful: stay focused and move fast," says Mr. Simso.

Devax has raised four rounds of venture capital, including \$3 million in its last round, which closed in November. Investors include HBM Partners, Rock Creek Partners Capital, MedFocus Fund, InterWest Partners, and US Venture Partners.

In the face of increasing competition, Devax could get scooped up by a Boston Scientific competitor to keep pace. When asked whether Devax is open to an acquisition, Mr. Thiel would only say: "We are running the business to do the clinical studies and bring the product to market, however that might happen."

#### **Disappearing Act**

REVA Medical is going after more radical change. The San Diego-based company is trying to make drug-eluting stents disappear—or at least, get absorbed into the body. Once a stent is implanted and the vessel repaired, REVA's stent—made of a strong plastic that weakens when exposed to moisture in the body—is gradually absorbed (within two years) into the arterial wall. "The metal stent doesn't have to be around forever," says Robert Schultz, REVA's president and COO. "The stent needs to perform its acute function, and then it can go away and leave the natural vessel behind."

Such an absorbable stent would give doctors more freedom to treat a single patient with severe heart disease without putting too much metal into a patient's coronary artery. It would also allow for the vessel to be re-treated; if the patient needs to undergo a more invasive procedure, such as bypass surgery, excess metal won't reduce the area that the cardiologist can treat.

REVA also has a different structural approach. "You can't take a standard metal stent and make it out of plastic," says Mr. Schultz. Unlike traditional stent designs that deform or bend into position, REVA uses a slide-and-lock technology. Like an extension ladder that locks into place as it expands, the technology allows the stent to expand without deforming the device. The company is currently gearing up for its first-in-man human trials by mid-2006.

REVA's technology has already piqued the interest of Boston Scientific, which invested in the company in November 2004 and at the same time signed an exclusive option to purchase the company. As to whether REVA will actually be able to pull it off, "that's in the 'to-be-determined' category," says Boston Scientific's Mr. Simso.

The deal is a major win for REVA, considering that the company completely shifted its focus and downsized from 48 employees to 18 in January 2003. "It was the nuclear winter of venture capital," says Mr. Schultz, and REVA decided to move away from its founding idea of building the world's thinnest metal stent for small vessels. Instead, the company bet that its already-developed slide-and-lock design, coupled with the right material, could bring about a bioabsorbable drug-eluting stent.

REVA's early funding came mostly from small seed capital and venture firms including Group Outcome and Domain Associates. Later funding came through the company's partnership with Boston Scientific.

#### **Payday**

The success of many drug-eluting stent startups will depend on large companies' appetite for new

technology.

In addition to purchasing several companies, Boston Scientific has acquired technologies outright or through licensing. “[Boston Scientific] has been active in acquiring both companies and technologies and will continue to do so,” says Mr. Simso.

At press time, Boston Scientific was trying to overpower J&J’s agreed-upon \$21.5-billion acquisition of **Guidant** with a higher bid of \$25 billion. Guidant, which is a leader in heart rhythm management devices like pacemakers and defibrillators, also has a drug-eluting stent program in the works.

J&J won’t discuss its acquisition or licensing strategies. But in December 2003, Advanced Bio Prosthetic Surfaces said it entered into an exclusive licensing deal with J&J. Advanced Bio is working on a nickel-titanium alloy stent that allows drug delivery.

Medtronic has acquired at least one stent company, Arterial Vascular Engineering (purchased in 1999 for \$4.2 billion), which led to the evolution of Medtronic’s drug-eluting version. Medtronic remains tight-lipped about its acquisition tactics, but the company says it’s always looking at different technologies and their accompanying businesses.

No matter how good the technology, these companies will have to stay one step ahead of young competitors, as well as multinationals that could easily develop the same—or better—innovations in-house.

Says Medtech Ventures’ Mr. Sheikh: these are all unique, “but similar products can be developed at larger companies.” REVA, for instance, has to worry about Guidant’s subsidiary Bioabsorbable **Vascular Solutions**, which is also cultivating a completely bioabsorbable stent. Xtent will have to show that it’s a worthy alternative to current stenting systems like Boston Scientific’s and J&J’s, both of which lay one stent during a single procedural insertion.

Of course, many other startups are vying for different pieces of the same market. Lake Forest, California-based Allvivo Vascular, for instance, is developing a next-generation coating for stents to further reduce the chances of artery re-narrowing.

If they are truly innovative, many of these smaller companies will feed bigger companies’ R&D pipelines. But few, if any, will be able to bring their product to market on their own, says Mr. Sheikh. “They are primordial soup. Some of them will grow, some will die, and some will be absorbed.” In this industry, being absorbed doesn’t sound like such a bad idea.

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