BY DENISE MYSHKO

COMBINATION PRODUCTS
DRUGS AND DEVICES

THE POSSIBILITIES ARE ENDLESS.

EMERGING DRUG-DELIVERY TECHNOLOGIES AND SMARTER DRUG-DEVELOPMENT STRATEGIES ARE PROVIDING A ONE-TWO PUNCH FOR RESEARCHERS AND MARKETERS WHO ENVISION SCIENTIFIC ADVANCEMENTS THAT COULD SPAN MULTIPLE THERAPEUTIC CATEGORIES.

In the broadest sense, pharmaceuticals and their delivery systems, such as asthma inhalers, are considered combination products, but Cordis Corp.'s Cypher stent created an entirely new market that is clearly growing.

U.S. regulatory approval of Cordis' tiny metal mesh tube covered with the drug sirolimus not only changed the interventional cardiology market, but it also created an entirely new way of looking at drugs and devices. The Cypher Sirolimus-eluting Stent, approved in April 2003, was the first U.S.-approved combination drug-device intended to help reduce restenosis of a treated coronary artery.

DRUG-DEVICE COMBINATION PRODUCTS: IMPLICATIONS FOR MARKETING

- Physician education will play a greater role in the marketing of combination drug-device products.
- Surgeons will be become another audience for the sales message.
- Marketers will need to provide self-guided patient tutorials that complement physician-provided information.
- The salesforce will need to be retrained to provide a different type of presentation to physicians, one that relies on product demonstration.
- Payers will take on an increased importance, and marketers will have to build a case for the product's value for reimbursement.

In March 2004, a second drug-eluting stent — Boston Scientific's Taxus Express paclitaxel-eluting coronary stent system — received approval in the United States, and at least four more drug-eluting stents are in development. (See box on page 40.)

According to a report from Millennium Research Group (MRG), drug-eluting stent sales comprised more than 90% of the $3 billion U.S. coronary stent market in 2005.

"Broadly, the framework that's driving the development of drug-device combinations is obviously improvements in health," says John Rhodes, U.S. and global managing partner for pharmaceuticals and life sciences at Deloitte & Touche. "In terms of the changing science, there are magnificent improvements going on where developers can combine technologies. Companies are looking for better ways to deliver products and increase the effectiveness of those products in such areas as cardiovascular."

DRUG-DEVICE COMBINATION PRODUCTS BY GEOGRAPHIC AREA, 2004-2010

	2004	2010
United States	65%	57%
Europe	24%	21%
Japan	7%	15%
Rest of the World	4%	7%

Source: Business Communications Co. Inc.
For more information, visit bccresearch.com.

Device companies are motivated to develop more sophisticated combination products, says Bruce Lehman, CEO of LehmanMillet.

"Devices are really crude mechanisms in a way," he says. "Implants for example, no matter how good they are, are intended to replace a very elegantly engineered structure; and from the moment it is placed in the body, the body is fighting to get rid of it. To optimize performance, the device needs a drug, polymer, or chemical partner."

Interest in drug-device combinations also is being driven by advancing technology, says Jonathan Kahan, a partner and codirector of the food, drug, medical device, and agriculture group at Hogan & Hartson LLP.

"Many scientists and inventors have been figuring out how to use cells and tissues with device components as well as how to integrate delivery hardware with drugs in ways that can have a significant medical benefit," he says. "The drug-eluting stent is an example of a significant advance in technology. Other products are going to have a similar or greater impact."

Device manufacturers are not the only ones looking at opportunities, he says; traditional pharmaceutical companies also are expressing a significant interest.

"Whether traditional pharmaceutical companies will become leaders is hard to know since returns on investment on prescription products are typically higher than on devices," Mr. Kahan says. "But if there is the potential to increase the market for an existing drug product by partnering with a device company, why wouldn't a pharma company pursue the opportunity?"

◀ SUSAN ENO COLLINS

THE MARKETING CHALLENGE WILL BE TO OFFER EDUCATION AND TUTORIALS THAT AREN'T AN ADDED BURDEN TO PHYSICIANS AND TO MAKE SURE THE PROGRAMS COMPLEMENT WHAT THE PHYSICIAN'S TEAM DOES.

◀ MAHESH SINGH

PHARMA AND BIOTECH COMPANIES ARE LOOKING FOR MECHANISMS TO EXTEND THE PATENT LIFE OF THEIR PRODUCTS. ONE AVENUE IS THE ABILITY TO USE A DEVICE FOR A DIFFERENT MECHANISM OF DELIVERY.

◀ BRUCE LEHMAN

WITHIN THE PHARMACEUTICAL INDUSTRY THERE IS GOING TO BE A MOVE TOWARD MORE PERSONALIZED, MORE LOCALIZED MEDICINE; AND DEVICES ARE GOING TO PLAY A ROLE IN THAT TREND.

In the near term, Mr. Lehman says mid-cap and specialty pharmaceutical companies will continue to explore and engage with device companies to search out opportunities.

"As big pharma companies did in the biotech sector, they will keep their finger on the pulse by taking equity positions in device companies or by stepping in when a significant opportunity arises," he says.

One significant factor driving pharma and biotech companies' interest in combination products is as a mechanism to extend the patent life of their products, says Mahesh Singh, a partner with the life-sciences practice at Pittiglio Rabin Todd & McGrath.

"There are several ways to extend patent exclusivity," he says. "One is to investigate new indications for the same medication toward the end of a product's life cycle. Another avenue is the ability to find new mechanisms of delivery with the use of a device."

THE OPPORTUNITIES

The global market for drug-device combinations is expected to increase at an average annual growth rate (AAGR) of 13.6% and reach $11.5 billion in 2010, compared with $5.4 billion in 2004, according to Business Communications Co. Inc. (BCC).

"The drug-eluting stent was an important medical breakthrough," says Stuart Portnoy, M.D., senior director of medical device consulting at PharmaNet Inc. "Both medical device and pharmaceutical companies are looking at possible other opportunities. The entire medical-device industry is looking very carefully at new technologies and how to incorporate drug coatings to obtain a better therapeutic effect. Likewise, the drug industry is looking at various drug-delivery systems."

While the star in the drug-device combination category is drug-eluting stents, some other areas that fall under the combination products umbrella include antimicrobial catheters, antimicrobial wound-care products, bone-graft substitutes and antibiotic bone cements, and photodynamic therapies. According to BCC, with the exception of bone-graft substitutes and antibiotic bone cements, all categories are expected to have double-digit growth.

Analysts from BCC say the United States dominates the market for drug-device combination products, largely because the largest-selling drug-eluting stents, Cordis' Cypher and Boston Scientific's Taxus, have been enthusiastically accepted in this market and have not yet fully penetrated the European market. The first drug-eluting stent was not introduced in Japan until the end of 2004, and therefore Japan held a smaller percentage of the drug-device combination product market than the overall global healthcare product market.

Orthopedics and the spine are areas where there has been interest in the local delivery of drugs through implanted devices, says Deloitte & Touche's Mr. Rhodes.

"Other implantables may move to more biologic types of material, which could interact with drugs in the future," he says. "Spinal and orthopedic products could be a future area of combination use."

DEVELOPMENT CHALLENGES

The development process for combination products may face some hurdles, experts say. Dr. Portnoy points out that the two leading drug-eluting stents use drug compounds that


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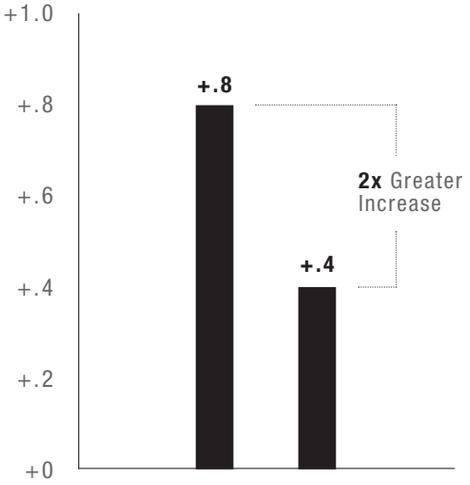

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DR. STUART PORTNOY ▶

WITH THE ADVENT OF DRUG-ELUTING STENTS, THE INDUSTRY ENTERED INTO A WHOLE NEW AREA, NOT ONLY OF MEDICINE BUT ALSO OF HOW PRODUCTS ARE REGULATED BY THE FDA.

◀ JONATHAN KAHAN

IN THE PAST DECADE, SOME BIG PHARMA COMPANIES DIVESTED THEIR DEVICE ASSETS THINKING THEY COULD RECEIVE A HIGHER RETURN BY FOCUSING ON TRADITIONAL DRUG PRODUCTS. BUT THERE HAS BEEN TALK THAT A NUMBER OF THE LARGE PHARMACEUTICAL COMPANIES ARE RETHINKING THAT STRATEGY BASED ON DRUG PIPELINES THAT ARE DRYING UP AND THE PHENOMENAL SUCCESS OF THE DRUG-ELUTING STENTS.

were already market approved, which facilitated timely approval of the new products.

Cordis' product uses sirolimus, which is a naturally occurring substance marketed by Wyeth Pharmaceuticals under the name Rapamune for preventing renal transplant rejection. Cordis has an exclusive worldwide license with Wyeth for the localized delivery of sirolimus in certain fields of use, including delivery via vascular stenting.

In April 2002, the Cypher stent received marketing approval in Europe for treatment of de novo and restenotic coronary artery lesions.

Boston Scientific's product is Taxus Express2, a polymer-based, paclitaxel-eluting stent system that was approved for the U.S. market in March 2004; the product was launched in Europe and other international markets in February 2003. Paclitaxel is a multifunctional microtubular inhibitor that controls platelets, smooth muscle cells, and white blood cells — all of which are believed to contribute to restenosis. Boston Scientific acquired worldwide exclusive rights from Angiotech Pharmaceuticals Inc. to use paclitaxel to coat its coronary stent products and has co-exclusive rights to other vascular and nonvascular products.

Paclitaxel is marketed as Paxol by Bristol-Myers Squibb Co. for the treatment of metastatic breast cancer and metastatic ovarian cancer.

"Interestingly enough, the indications of the drugs used on the stents had nothing to do with cardiac disease," Dr. Portnoy says. "Sirolimus is an immunosuppressant and paclitaxel is used to treat cancer. With an already approved drug, even for a different indication, there was a wealth of safety data to support approval. The only caveat is that those drugs are typically administered intravenously. When the companies put them on a stent as a new way to deliver the drug, they needed to provide the FDA with results from special studies to make sure there wasn't a local toxic effect of the drug on the heart tissue."

He says the development scenario becomes a little more complicated for an unapproved drug being used as a therapeutic coating on a stent. Abbott discovered this with its ZoMaxx drug-eluting stent, which is currently being studied in a large clinical trial.

Abbott's vascular division is developing a stent with a drug specifically designed for that

DRUG-ELUTING STENTS ARE DRIVING THE MARKET

A RECENT REPORT FROM DECISION RESOURCES INC. FINDS THAT DRUG-ELUTING STENTS ARE DRIVING GROWTH IN INTERVENTIONAL CARDIOLOGY, AND BOSTON SCIENTIFIC HAS THE BIGGEST MARKET SHARE (55% IN 2004) DESPITE CORDIS' ONE-YEAR LEAD. BUT THE STENT SEGMENT IS QUITE VOLATILE, AND SALES OFTEN SHIFT RAPIDLY FROM ONE MANUFACTURER TO ANOTHER. AS NEW TECHNOLOGIES ARE INCORPORATED INTO STENT DESIGN, FREQUENT UPHEAVALS IN MARKET LEADERSHIP ARE LIKELY TO OCCUR THROUGH 2007.

DRUG-ELUTING STENT LAUNCHES

Company	2003	2004	2005	2006	2007
CORDIS	*Cypher (US)	Cypher (JP)	—	—	Cypher-Neo (outside US)
GUIDANT	—	—	Vision-E (EU)	Vision-E (US)	—
BOSTON SCIENTIFIC	Taxus Express2 (EU)	Taxus Express2 (US)	Taxus Liberte (EU)	Taxus Liberte (US mid year)	Taxus Express2 (JP)
MEDTRONIC	—	—	Endeavor (EU)	Endeavor (US)	—
SORIN GROUP	—	Janus (EU)	—	Janus (US late 2006)	—
CONNOR MEDSYSTEMS	—	—	Costar (EU)	—	Costar (US)

Source: Decision Resources Inc., Waltham, Mass.
For more information, visit decisionresources.com.
(*Cypher was introduced in Europe in 2002.)

use. The ZoMaxx drug-eluting stent system consists of three key components: a flexible stent platform called TriMaxx; a unique polymer carrier called Pharmacoat intended to enable steady drug elution; and Abbott's patent-protected immunosuppressant drug called ABT-578.

Studies have shown that ABT-578 inhibits inflammation and the proliferation of smooth muscle cells that can lead to artery renarrowing following interventional procedures.

"The approved stent clinical trials each enrolled about 1,000 patients, and that was sufficient for approval," Dr. Portnoy says. "For the Abbott product, because the new drug had not yet been demonstrated to be safe, the number of patients in the study is higher, around 1,670, because the FDA needs more data. There was a reasonable compromise at the FDA, however, and I think this is going to be a benchmark for other companies that have investigational drugs for use on coronary stents."

Medtronic Inc.'s stent, Endeavor, also uses the Abbott compound ABT-578. Endeavor combines the Driver bare-metal stent with a sirolimus-analogue drug — ABT-578 — and a biocompatible polymer, called PC Technology, to treat coronary artery disease.

In October 2005, Medtronic submitted its first premarket application (PMA) module to the FDA for Endeavor. By the time the final PMA module is submitted later this year, Medtronic will have safety and efficacy data on more than 2,000 patients implanted with the Endeavor stent. In clinical follow up of 1,300 patients to date, the Endeavor stent has had no late stent thrombosis (past 30 days), an unmatched achievement.

Medtronic received European approval in July 2005 for its Endeavor stent, which is the first cobalt alloy platform on the drug-eluting stent market and has now been launched in more than 85 countries worldwide.

For device companies, the incorporation of polymers and drugs on stents represents the adoption of new technology onto what have traditionally been metal-based devices, says Josiah N. Wilcox, Ph.D., VP and resident scholar of science and technology at Medtronic Vascular.

"This leap in technology development brings with it a number of new challenges," he says. "Now we have to worry about drug stability. We have to worry about sterility in a different way. It's a wholly different production process, and there's a learning curve on the part of device companies and regulatory bodies. The FDA is learning how to deal with combination therapies that involve drugs and devices while device companies are learning how to deal with drugs. The regulations are becoming clearer as we speak."

Medtronic has made a commitment to look at next-generation opportunities, not only in drugs but in polymers and drug-delivery technology, Dr. Wilcox says.

For these other opportunities, he says, Medtronic will partner with pharmaceutical companies.

"We are not a pharmaceutical company, and we're not consciously developing medicinal chemistry capabilities," Dr. Wilcox says. "Instead, we're looking for partnerships with biotech and pharmaceutical companies, such as the Abbott partnership, to go forward with our next-generation opportunities. Medtronic Vascular has an active drug-screening program that has looked at more than 700-plus compounds for potential product development."

REGULATORY ISSUES

In December 2002, the FDA established the Office of Combination Products (OCP) to streamline the processing of complex drug-device, drug-biologic, and device-biologic combination products. The primary regulatory responsibilities for, and oversight of, specific combination products will remain in one of three product centers — the Center for Drug Evaluation and Research, the Center for Biologics Evaluation and Research, or the Center for Devices and Radiological Health.

"One very positive development at the FDA is the role that the Office of Combination Products is playing in assisting manufacturers to sort out and

arbitrate difficult jurisdictional and FDA review issues," Dr. Portnoy says. "On occasion, the OCP brings all the experts from the various centers into the room at the same time to help moderate the discussions."

Because the regulatory review of combination products is more complicated than either drug or device regulations on their own, the OCP is doing a good job, Dr. Portnoy says.

"Device regulations are typically more straightforward and require a lower burden of proof," he says. "There's a whole world of drug chemistry issues that crop up, and some device companies are caught off guard. They are not familiar with the more stringent drug quality assurance regulations."

This, Dr. Portnoy says, is even true of some of the more sophisticated drug-delivery systems.

"For example, there are companies that are developing novel device technologies to deliver drugs through the skin," he says. "Even more complicated is delivering a drug such as insulin via an inhaler."

The first combination insulin/inhaler product to reach the market is Pfizer's Exubera, which was approved this past January. Exubera allows patients to control their blood-sugar levels by inhaling a fine insulin powder through a flashlight-size device.

"This is a very important new technology, but it also raises legitimate concerns about how to get the clinically required amount of drug into the patient in a consistent manner," Dr. Portnoy says. "Obviously, safety concerns, such as whether the patient may get too much or too little drug, need to be addressed. So there are many new issues that companies have to face with novel drug-delivery systems."

Exubera, a powder form of recombinant human insulin (rDNA), was approved for the treatment of adult patients with Type 1 and Type 2 diabetes. The product was developed through a joint program between Sanofi-Aventis and Pfizer and is inhaled via a proprietary device and powdered insulin formulation developed by Nektar Therapeutics.

MARKETING ISSUES

Mr. Lehman says as more and more combination products enter the market, the differentiation among products may come down to the drug component.

"This suggests that the type of marketing that the pharmaceutical industry is very familiar with is going to become increasingly important to device companies that are marketing a combination product," he says. "As soon as more than one combination product for the same disease is on the market, the challenge becomes providing a differentiation, which could be built on the performance of the drug."

Pricing will be an issue as well. According to a recent Datamonitor report, the single most important driver of price for a combination therapy is whether the company plans to cannibalize or expand the market of the single-agent therapy. Within each strategy, branded-branded combination products do not discount as much as branded-generic combinations. Among cannibalization drugs, branded-generic drugs average a 22% discount and branded-branded only 5.5%. Of expansion strategy products, the average branded-generic has a 5% discount and the branded-branded discount averages 2%.

But the marketing process for combined drug-device combinations is likely to be very different, with a greater focus on education, says Susan Eno Collins, VP of health education at HealthEd.

"These products could lead to a new way of marketing," she says. "We're working with a company now in the area of implants for surgery. Their typical audience is surgeons and hospitals, but the company is starting to do more patient-education programs and trying to drive some consumer pull for the product. In traditional marketing, the company would never have spoken directly to patients because they produce surgical tools. But because consumers are much more involved in making decisions about their healthcare these days, this company is using that pull power from the patients to drive some demand for its surgical products in the office."

Ms. Collins says patient education will be critically important as innovative delivery systems are approved.

"In the case of devices that are drug-delivery systems that the patient will have to use, marketers will need to educate patients on their correct use," she says. "This means much more education will be necessary than a 60-second TV spot and a Website. It means a lot of multimedia work and tutorials to help reinforce skills. Marketing will have to be much more integrated with longer-term educational programming. Additionally, to successfully market these devices, physicians need to be convinced that it is not an added burden to teach their patients to use the devices."✦

PharmaVOICE welcomes comments about this article. E-mail us at feedback@pharmavoice.com.

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