Denise Myshko

The DRUG-DEVICE Conundrum

Combining molecules with devices continues to be an evolving trend, but a lot of uncertainty exists around these combination products.

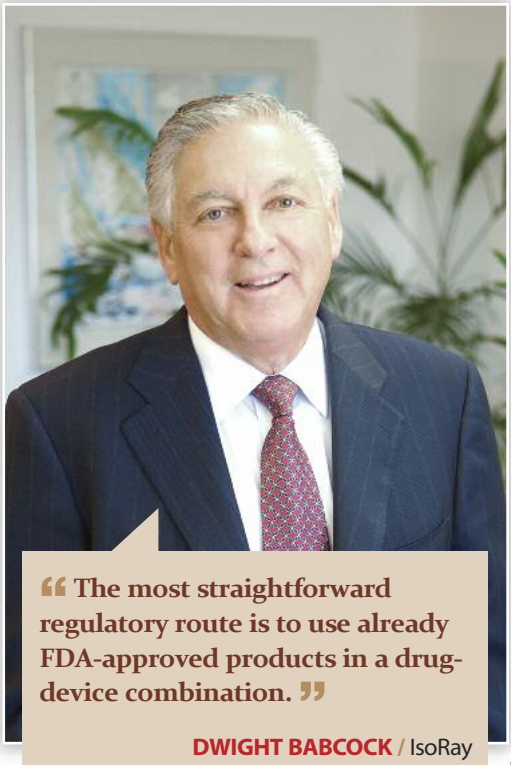
There has been a movement toward convergence of technologies. More and more, drugs are being delivered or used in combination with a device with the intent to reduce side effects and increase efficacy.

One of the best-known drug-device combinations is the drug-eluting stent. Other combinations include antimicrobial catheters, antibiotic-loaded bone cements, drug-eluting beads, and photodynamic therapies. New technologies, such as nanotechnology, molecular diagnostics, and cellular tissue engineering are making these products possible.

"While drug-device combinations is a promising area, regulatory and legal challenges are creating significant barriers to entry," says Robert Nauman, principal, BioPharma Advisors. "Another barrier is cultural, which stems from the short-term focus of the development teams to get their work done first and not complicate their mission with shared sacrifice. Companies need to put their attention to new, small development teams that put these combination products together without interference from the larger single product or device goals. This is getting increasingly difficult to accomplish in today's market-driven funding cycles."

Significant opportunities exist in developing drug-device combinations, and these combination products address unmet patient needs and overall can provide significant value to all stakeholders; this can be seen from a number of case studies, says Dr. Terri Cooper, principal, Deloitte Consulting and national leader, life sciences R&D practice.

"In the example of drug-eluting stents, within two years of introduction, they captured 89% of the U.S. stents market," she says. "They were introduced in 2003 to address the well-defined clinical problem of in-stent restenosis. The clinical outcomes were very favorable, and so providers were willing to come up short learning curves to provide the treatment."



"The most straightforward regulatory route is to use already FDA-approved products in a drug-device combination."

DWIGHT BABCOCK / IsoRay

Experts say, however, there is confusion and uncertainty from a regulatory perspective. The FDA's Office of Combination Products (OCP) was established to coordinate the review process of therapeutic and diagnostic products that combine drugs, devices, or biological products. These products often blur the lines of separation between FDA's medical product centers, which are made up of the Center for Biologics Evaluation and Research (CBER), the Center for Drug Evaluation and Research (CDER), and the Center for Devices and Radiological Health (CDRH).

Our experts say they would like more guidance and more detail about what the agency requires for drug-device combinations.

Robert White, CEO of Tyrx, says while the device path generally requires less data than the drug path, this is changing.

"A lot of change is happening within the FDA, which is making the process much less predictable," he says. "At a minimum, this adds a lot of time to the regulatory approval path. In addition, drug-device product reviews involve multiple arms of the FDA making the approval process even more complicated and burdensome."

This is complicated by the fact that there often are competing interests at the agency and conflicting requests for information.

"The process is not nearly as straightforward as a 510(k) clearance path for a traditional medical device," Mr. White says. "The amount of information requested by the various groups within with the agency can be very significant, and sometimes conflicting."

Mr. White says a lot more information is required now by regulators than in the past. This, he says, has had a significant impact on predictability and timeliness.

"What we think we need to provide the FDA and what regulators ask for after the application is submitted can be very different," he says.

Some companies are addressing the regulatory challenges by using already-approved products, says Dwight Babcock, CEO of IsoRay.

For example, the company's product is Cesium-131, a radioisotope for internal radiation therapy for the treatment of brain, colon, lung, ocular melanoma, prostate, and head and neck cancers as well as cancers throughout the body.

In June 2011, the company acquired GliaSite radiation therapy system, a balloon catheter device used in the treatment of many forms of brain cancer. The company's combination product has been filed for approval with the FDA.

"We place our device in seed or liquid form in a tumor, alongside a tumor, or in the bed where a tumor has been removed," Mr. Babcock says. "This allows the radiation to kill the cancer right at the source and destroy any cancer that may remain after a surgery. This avoids exposure to external radiation."

Tyrx is another company that uses an already approved antibiotic for its combination product.

Tyrx has received 510(k) clearance for the AIGISRx Antibacterial Envelope, which is a small pouch that holds a pacemaker or implantable defibrillator. It releases a combination of antibiotics within a 7 to 10-day period to help reduce the risk of infection following implantation. It is effective against a variety of pathogens, including MRSA.

The mesh envelope contains minocycline and rifampin, and the combination has proven to be very effective, Mr. White says.

"The combination turns out to be highly effective against the pathogens that could be introduced during surgery which is a rapidly growing problem," Mr. White says. "This combination is most effective since the mechanisms of action differ between the two drugs."

AIGISRx has been on the market for more than two years.

The Market

The drug-device combination products market was valued at $8.4 billion in 2009 and is expected to grow at a CAGR of 12.6% from 2009 to 2016, according to a February 2011 report from GBI Research. Drug-eluting stents make up the largest segment within the drug-device combination market, making up 57.1% of the total market in 2009.

Marissa Addalia, VP, management supervisor, at HealthEd, says developing a drug-device provides pharma with the opportunity to consider the full user experience, both functionally from a human factors perspective and emotionally from a brand/product communications perspective.

"We have seen pharma companies work with device companies wholesale where the device company owns development and production of a device," she says. "The benefit is that there is expertise in human factors and engineering; the device is sure to exceed standards for technicality, functionality, and ergonomics. But the opportunities for pharma are often limited in terms of influence over changes to the device. The true opportunity for pharma companies exists when they can couple optimal engineering and dose delivery with what they are trying to accomplish with their market positioning and communications."

FAST FACT

THE DRUG-DEVICE COMBINATION PRODUCT MARKET WAS VALUED AT $8.4 BILLION IN 2009 AND IS EXPECTED TO GROW AT A CAGR OF 12.6% BETWEEN 2007 AND 2016.

Source: GBI Research

Ms. Addalia says marketing the delivery of a product and the product itself can equally influence the brand, so understanding that dynamic is critical.

"Devices, no matter their simplicity, often contribute an additional layer of educational need," she says. "The challenge is to marry this with the drug/product needs and weigh the priorities. This is why understanding the patient audience and insights is important. Due to that balance, there are challenges that can arise internally within a pharma company because different functional areas are coming together toward the same end-goal. Another unique dynamic is navigating the varying perspectives and needs of regulatory, marketing, manufacturing, and clinical development."

Experts say when developing a drug-device combination, compatibility of the drug and the primary containment system is critical.

Dr. Euan Morrison, head of advanced optical and lighting technologies at Sagentia, says it's important to balance the ability to realize innovative new device development against the process that's required to develop that medical device.

"These are often ground breaking treatments," he says. "For example, the Cevira drug-device combination product that we recently worked on with Photocure ASA, a Norwegian specialty pharmaceutical company, is a breakthrough drug-device for precancerous lesions and there is always uncertainty in the early stages of development."

Photocure's Cevira is a photodynamic therapy product that is in Phase II clinical trials across the United States and Europe. The drug-device combination is being developed by Photocure with the help of Sagentia for device development. Cevira delivers a targeted light-activated treatment intended to be used to destroy tissue infected by HPV and treat precancerous lesions on the cervix without damaging healthy tissue.

> "It's important to balance the ability to do innovative new device development against the process that's required to develop that medical device."
>
> **EUAN MORRISON** / Sagentia

"The formulation allows physicians to target the disease or infected cells and leave the healthy cells intact," Dr. Morrison says. "This device uses advanced LED technology to apply light to a very specific point that has been treated with the Photocure drug. In this application, physicians illuminate a patch of skin or tissue but the photodynamic reaction is only occurring in the diseased cells. It's a nonsurgical way of removing diseased or infected tissue, leaving the healthy tissue intact."

Dr. Cooper says combination products typically are more complex, and development and regulatory approval are typically more challenging.

"Also the ability to leverage a well-trained, motivated pool of caregivers who are performing similar procedures is critical, which reduces the learning curve to perform the new procedures," Dr. Cooper says. "The barriers to entry can be relatively high, as both a device

and a drug need to be developed. One approach to lowering the barriers to entry is partnering across medical device and pharmaceutical companies. But there are still challenges that exist, as combination products are typically specialty products and require specific manufacturing capabilities and specialty salesforces. There is no doubt the monetary benefits are present, but significant hurdles exist."

Successful Partnering

GBI Research experts say one of the biggest challenges is the difficulty in having drug and device companies work together to offer the best product possible. This can be challenging because companies need to work not only through the potential cultural differences between their two companies, but also their industries, different practices and mindsets, as well as different business strategies.

Our experts say drug companies should work closely with device manufacturers as early as possible in the process. Additionally, pharma companies need to develop competencies and expertise in the device arena.

"Device manufacturers need to understand the pharmaceutical market and the environment in which the product will be used," Dr. Morrison says. "Pharmaceutical companies meanwhile need to understand the device market and how the product is likely to be used in the field. Each has to have a very strong relationship with the practitioners who will be using the product."

Graham Reynolds, VP of marketing and innovation, pharmaceutical delivery systems, at West Pharmaceutical Services, identifies several additional challenges related to developing drug-device combination products.

"The first challenge is making sure that the primary drug container is appropriate for the drug," he says. "The second is making sure the device-drug combo is appropriate for the end user. The third challenge is making sure that both the device manufacturer and the pharma company take into account the needs of the drug, the container, the delivery device, and the physician and the patient to ensure an effective integrated drug delivery system."

Ms. Addalia agrees that companies have to consider the needs of the patient and provider audiences as they relate to the product, the delivery system, and the payer market.

"For instance, companies need to find ways to clearly describe product risks, benefits, side effect management, and other treatment considerations," she says. "This will help set patients' expectations about their experience with the product. Separately, companies need to consider how patients will learn to operate their new device. For example, will they receive training from their providers? Are there digital or print tools to support and reinforce their ability to use the device? As part of this learning experience, consider the patient's state of mind about using a new device. What does this mean in terms of disease progression? What fears or motivators do patients have in adopting the device? The strongest strategy is for marketers to understand key patient and provider questions about the product and the device and determine the best mix of educational and marketing channels to respond to those questions." PV

> "The combination of a drug package and a device is a growing trend, and the FDA is looking closely at the requirements for combination products."
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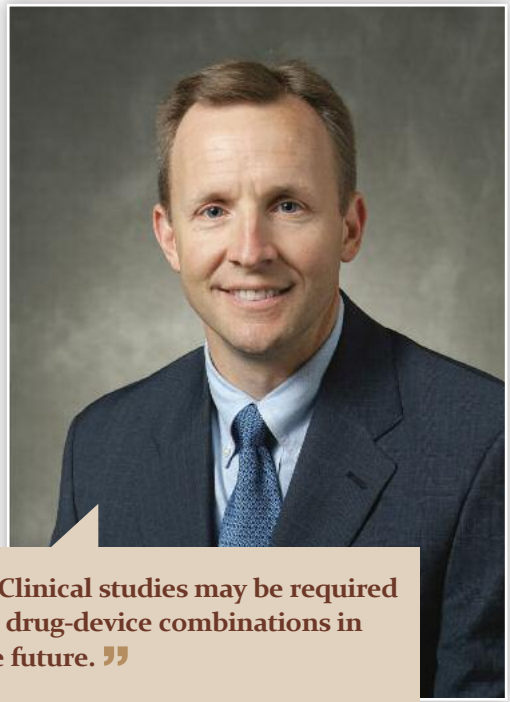
> **GRAHAM REYNOLDS**
> West Pharmaceutical Services



> "Clinical studies may be required for drug-device combinations in the future."
>
> **ROBERT WHITE** / Tyrx

EXPERTS

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