

Innovation Through DRUG DELIVERY

The increasing demand for effective delivery mechanisms of novel biopharmaceuticals is driving the growth of the drug delivery market.

W

ith formulation playing such a key role in the making of a successful product, the right delivery platform, partnership sourcing, and management of collaborations are crucial to success. Experts say one major trend is the increase in the number of devices and systems that are being used to deliver drugs. This is coupled with the increasing shift to have patients self-administer their medications. Companies are pushing the envelope, using newer technologies to enable easier patient administration and to reposition products that may have failed in trials or that may have been too toxic.

"Having a more thorough understanding of user needs and incorporating this information into the design of new drug delivery systems is becoming more critical to success," says Graham Reynolds, VP, marketing and innovation, at West Pharmaceutical Services. "Understanding patient needs and how a drug is administered and making this as easy as possible are critical."

Changing a drug's delivery method is important in life-cycle management and can differentiate the drug and extend its life, says Ingrid Blair, VP, MTS/TDD Business, 3M Drug Delivery Systems.

"This approach can also be incorporated at

FAST FACT

U.S. DEMAND FOR DRUG DELIVERY PRODUCTS WILL EXPAND 7.2% ANNUALLY TO \$133 BILLION IN 2015.

Source: Freedonia Group

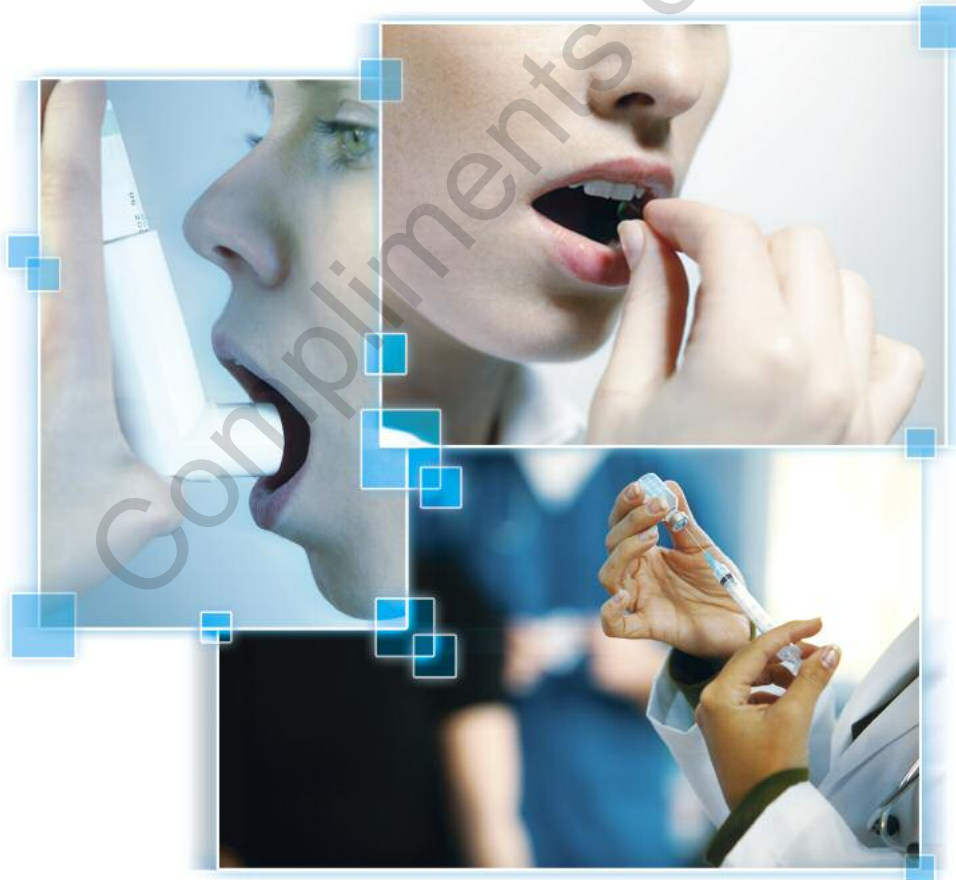
the very beginning of development in order to give a drug a competitive edge in a marketplace that is increasingly patient-driven," she says. "For example, because a microstructured transdermal system, which is designed for intradermal delivery of biologics, has the potential to improve compliance and be easier to administer for both patients and caregivers, companies are exploring how to use the technology to treat chronic conditions such as rheumatoid arthritis and multiple sclerosis."

Alan Touch, O.D., principal strategist, medical devices and diagnostics, at INC Research, says companies are moving to novel drug delivery systems to extend their patent protection and to differentiate themselves in the market.

"In terms of direction, involved companies tend to cross the spectrum of drug delivery through injectables, inhalation, transdermal, implantation, etc.," he says. "These delivery mechanisms involve primarily enhancing the ability of the drugs they are delivering to tissue to absorb with more bioavailability or to change the nature and manufacture of the formulation to enhance bioavailability."

Some examples of this approach include the use of nanotechnology to deliver drugs to overcome challenges such as bioavailability, instability, solubility, intestinal absorption, targeted delivery or other factors that can inhibit the delivery of drugs.

According to a recent study by Freedonia Group, U.S. demand for drug delivery products will expand 7.2% annually to \$133 bil-



lion in 2015, with the best growth opportunities in specialized pharmaceutical formulations and administration devices that advance the nature of therapy for autoimmune conditions, cancer, heart disease, neurological disorders, and other debilitating health problems.

Demand for oral drug delivery products is expected to grow 4.3% annually to more than \$52 billion in 2015. Monoclonal antibodies are projected to lead gains as advances in biotechnologies contribute new and improved therapies for autoimmune disorders, cancer, and various debilitating diseases.

In fact, many of our industry experts say their companies are pushing the envelope on innovation to develop products with new delivery mechanisms or to reposition products that failed in trials.

Beth Hill, Ph.D., head of drug delivery, packaging, and device development, at Janssen Research & Development, says many companies, including hers, are working to develop products with noninvasive delivery systems.

"For example, if a patient was required to visit an infusion center to have the drug administered, we are trying to simplify the delivery of the drug so it can be done via a clinic visit," she says. "And if a drug required a clinic

visit we are trying to improve the delivery so that a patient can self-administer at home."

An example from Janssen's product lineup is Remicade, which is an anti-TNF-alpha biologic approved to stop further joint damage and improve physical function in patients with moderate to severely active rheumatoid arthritis (RA). It also has applications in gastroenterology and dermatology.

At Janssen R&D, the team is continuing to focus on improving patient outcomes by offering different products and different delivery mechanisms, since not all patients respond the same to treatment.

"Remicade was first approved as an IV infusion product," Dr. Hill says. "Since then, we've launched Simponi, a next-generation RA product, which is self-administered subcutaneously."

Dr. Touch says there is a big emphasis now on incorporating usability studies as part of the general drug-device approval process.

"The FDA and some of the European agencies are asking for studies to demonstrate that a drug delivery device is user-friendly and that the instructions for use are understandable," he says. "There is a field devoted to developing protocols for usability, human factors assessment, and en-



"Drug delivery can be used as a way to generate entirely new drugs."

DR. OLIVER FETZER / Cerulean Pharma

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“We look at other industries, such as material science and electronics, to determine if there are additional and novel ways to deliver drugs.”

DR. LEE SHORTER / GlaxoSmithKline



“The inclusion of a technology with a drug often results in a combination product designation, which means there are two different sets of regulatory considerations that need to be blended.”

DR. BETH HILL / Janssen Research & Development

suring that the device is straightforward for the consumer because there is a drive toward self-administration and home use.”

Impact on Drug Development

Mr. Reynolds says there is a need to take into consideration the final delivery system much earlier in the process.

“The FDA is looking at how the method of delivery impacts the effectiveness of a drug,” he says. “For instance, regulators would want to know if the delivery technique — manual versus auto injector, for example — changes the drug’s effectiveness.”

Mr. Reynolds says companies and regulators are looking at the drug’s delivery system as the integration between the delivery device and the drug container and the formulation.

“Understanding how all of these elements fit together early is critical to making sure the drug delivery is effective,” he says.

Dr. Hill points out that the inclusion of technology with drugs often results in a combination product designation, which means there are two different sets of regulatory considerations that need to be blended together into a single product approval.

Device components of combination products are now subject to regulatory review in the context of the pharmaceutical product.

“For example, if there is a functional dosing component to the product, something that might have been called packaging in the past, this now needs aspects of design control applied to it,” Dr. Hill says. “Transdermal patches, for example, may be regulated by the FDA as combination products because they have a requirement to stick properly at the right time and unstick at the right time.”

Dr. Hill says combination products require establishing new capabilities in the pharmaceutical industry related to analytical characterization, clinical characterization and validation, and product design.

“A new regulatory capability has to be in place for combination products, including the documentation system, and this is definitely a change in the industry,” she says.

The regulatory process is evolving to keep up with innovation, so it’s important that companies talk to regulatory agencies during the development process, says Michael Kaufman, Ph.D., VP, Pharmaceutical Sciences, at Millennium: The Takeda Oncology Company.

“It’s a difficult task to explain a complex product to regulators when seeking approval,” he says. “We have dialogues with regulatory agencies during development so that when we actually file for permission to market the product, regulators are not seeing the technology for the first time.”

Mr. Reynolds says there are evolving guid-

ances from the FDA on combination products, but one critical change is the requirement that early-phase clinical studies incorporate the drug delivery system that will be used with the final product.

“It’s no longer enough to test the drug,” he says. “We now have to test the drug with the delivery system that is being used.”

Al Kearney, Ph.D., VP, drug product development, at GlaxoSmithKline, says preclinical data are important, not just for making sure the technology works but to test for processability.

“Testing the technology has to show there is a high probability of success,” he says. “But the trial has to go beyond just showing the product will work well in humans; we have to show that we can robustly and reliably manufacture it as well.”

Dr. Kaufman agrees, saying companies have to consider whether a new delivery technology can be manufactured in large scale.

“We also need to think about the stability and shelf life of the product,” he says. “We know that consumers will not always store products in the same controlled environment as we do in a trial, so we need to make stable and robust products.”

Oliver Fetzter, Ph.D., president and CEO of Cerulean Pharma, says delivery technologies have to address the endpoints that matter to patients, clinicians, regulators, and payers.

Partnering for Drug Delivery

Ms. Blair points out that when looking for partners, pharmaceutical companies should look for companies that can deliver on their commitments and ideally exceed expectations.

“Many companies face manufacturing challenges,” she says. “This is why it’s important for companies to seek partners that can help fill the gaps and adapt their practices to serve the needs of each individual drug client. Additionally, partners should be committed to maintaining high standards for safety and compliance while still maintaining flexibility and focus on creative problem-solving to meet industry demands.”

Dr. Kaufman says Millennium looks for delivery partners that have technologies that are a fit with the company’s vision.

“We don’t want technology for technology’s sake,” he says. “We look for technologies that synergize with our perceived medical needs in the marketplace. We look for common understanding, common goals, and a general mutual respect for the different cultures of the organizations involved in the partnership.”

Lee Shorter, Ph.D., director, disruptive technology seeker, at GlaxoSmithKline, says any new technology has to be a strategic fit for the company.



“ Sometimes technology can be very enticing, particularly for scientists who want to push the envelope of innovation, but never lose sight of the end goal: giving patients significant, measurable benefits.”

DR. MICHAEL KAUFMAN / Millennium



“ Companies have to take into consideration the final delivery system much earlier in the development process.”

GRAHAM REYNOLDS / West Pharmaceutical



“ We will look at partnering with other companies that may have advantageous types of delivery approaches.”

DR. AL KEARNEY / GlaxoSmithKline

Dr. Shorter believes there has to be some appropriation of risk sharing, because projecting the success of such projects is uncertain.

“We like to get the scientists from both companies to come together to discuss the technology, ask questions, and outline development protocols; this gives us a better understanding of what a partner can bring to the table and provides greater understanding about a drug,” he says.

Dr. Shorter's group at GlaxoSmithKline looks to apply technologies outside the pharmaceutical industry to drug development.

“We look at industries, such as material science and electronics, to determine if there are novel ways of delivering drugs that might provide us with more control and bring a level of

personalized medicine to the compound and its delivery,” he says. “I look at different technologies to see if there is an application back to the pharma industry. I look for an element of creativity and for partners that are willing to expand their business in a new field.”

Mr. Reynolds says entering into partnerships and collaborations early on in the process with delivery and packaging systems companies can be beneficial in terms of avoiding potential issues.

“Optimizing the delivery system at an early stage is critical,” he says. “Early engagement with partners that can help with the process is proving to be more beneficial than trying to do everything ourselves.”

Dr. Touch also points out that early collaboration with CROs can help sponsors address issues related to the design of the product, CMC issues, and the safety and

performance profiles to ensure that the design is fixed before the clinical trial as well as help sponsors design a protocol to demonstrate outcomes based on the drug and device considerations.

“This interactive process reassures both teams that the business and clinical trial end goal, including anticipation of reimbursement strategies, is well-defined and therefore assures that the trials are likely to be successful,” he says. **PV**



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New Drug Delivery Technologies

Pharmaceutical companies — including Cerulean, Janssen Biotech, GlaxoSmithKline, and Millennium, to name a few — are pushing the envelope on innovation to develop products with newer delivery mechanisms or to reposition products that failed in trials or were too toxic for patients.

Cerulean Pharma

Cerulean Pharma's lead program is **CRLX101**, which is in Phase II trials for the treatment of non-small cell lung cancer. The company is also studying the product for ovarian and other types of cancers.



Dr. Oliver Fetzer

Developing CRLX101 as a nanopharma- ceutical, the company deployed a nanoparticle technology to deliver and incorporated a potent anticancer compound, camptothecin, for delivery directly into tumor tissue.

"Two drugs that have been approved — irinotecan and topotecan — are analogs of camptothecin, so we know the compound class has strong anticancer activity," says Oliver Fetzer, Ph.D., president and CEO of Cerulean Pharma. "This compound was too toxic to ever be developed, but the nanoparticle that contains camptothecin is configured as the nanopharma- ceutical CRLX101 and has proven to be incredibly well-tolerated while maintaining its potency. Some patients have been on the drug well over a year with their diseases kept at bay and without any significant adverse events."

Dr. Fetzer says the anticancer agent is delivered directly to the tumor and is released over time, leaving the rest of the body un- harmed.

"We've formed successfully designed nanopharma- ceuticals that have a covalent bond with the drugs they are carrying, creating a true chemical bond that ties the drug into the nanoparticles," he says. "Cracking open the nanoparticle alone is not enough to release the drug. We also have to crack that bond between the drug and the nanoparticle.

We can then use that bond, what we call the linker, in a way that affects the speed and the duration with which the drug is delivered to the cancer cells.

"In our Phase II clinical trials, our primary endpoint is overall patient survival," Dr. Fetzer continues. "Our researchers are measuring how long CRLX101 can keep tumors in check and help keep patients alive and healthy."

GlaxoSmithKline

GlaxoSmithKline is incorporating several unique drug delivery technologies as part of its development platform.

The first delivery system is called liquid dispensing technology, or **LDT**. LDT is a manufacturing process that the company uses for low-dose or potentially highly potent compounds.

"We use a placebo carrier tablet to which we add a liquid or suspension containing the drug in a polymer; the drug is added in very small volumes and very accurately," explains Al Kearney, Ph.D., VP, drug product development, GlaxoSmithKline.

The other technology is DiffCORE, a commercialized modified release technology, which can be used with single compounds or combination products.

"The DiffCORE mechanism allows for a range of different release profiles as well as dosing ranges, from low doses to higher doses," Dr. Kearney says. "By using this technology, we have multiple ways to control drug release."

The tablets typically have an insoluble or



Dr. Al Kearney

enteric coating. Aperatures are drilled into the coating. Then the core tablet can have different types of formulations added to it. This provides another opportunity to modify the release of the drug and achieve a variety of different release profiles.

According to GSK officials, the technology is also able to handle both aqueous and nonaqueous solubility.

Janssen

Several years ago, Janssen Research & Development began investing internally and externally in cell therapy as a platform.

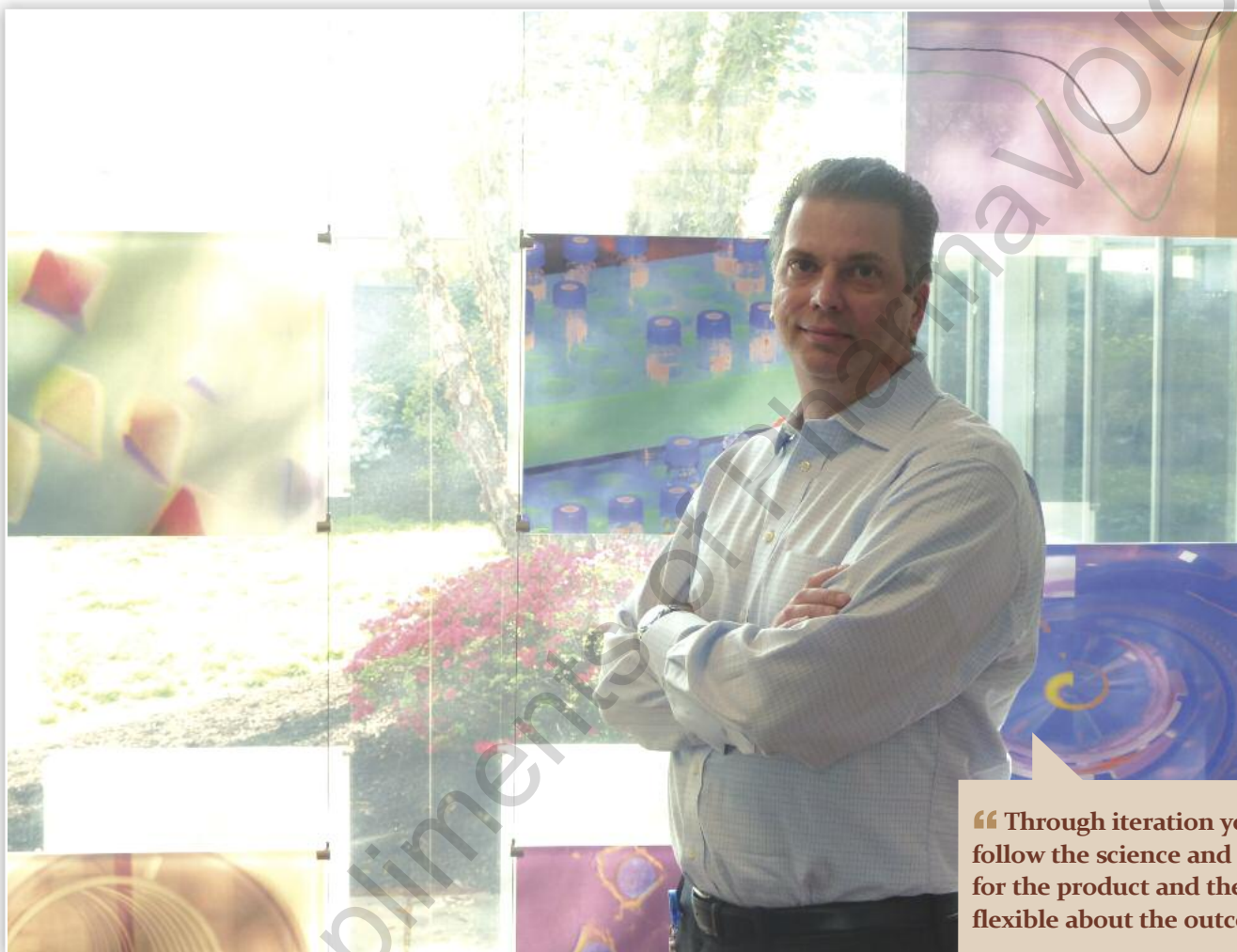
One of the company's most advanced products is a **CELL-BASED THERAPY** for the treatment of age-related macular degeneration.

"In this particular case, the product needs to be delivered in the subretinal space," says Robert Willenbacher, M.D., head of cell therapy, Biotechnology Center of Excellence, Janssen R&D. "With our first entry into clinical development we worked with retinal surgeons to develop a delivery approach that was in line with current surgical thought. We gained some experience and realized that we could improve the procedure in terms of being safer for the patient, less invasive, and potentially far less time-consuming for the surgeon if we changed our approach."

He says this change led the company to partner with iScience Interventional, which supplies Janssen R&D with micro-catheter delivery systems for use in the clinical evaluation of cell therapies used in the treatment of retinal degeneration.

Millennium

Millennium: The Takeda Oncology Company is working with a drug delivery technology called antibody drug conjugates, or **ADC**.



“Through iteration you just have to follow the science and do what’s best for the product and the patient and be flexible about the outcome.”

DR. ROBERT WILLENBUCHER
Janssen Research & Development



Dr. Michael Kaufman

One of the company’s most recent therapies to use this technology is Adcetris, which was approved by the FDA in August 2011 for the treatment of relapsed Hodgkin lymphoma (HL) and systemic anaplastic large cell lymphoma (sALCL).

Seattle Genetics and Millennium jointly developed the product.

The drug delivery technology works by targeting cancer cells by using potent molecules that are attached to a monoclonal antibody.

The ADC then employs a linker system that is designed to be stable in the bloodstream and releases the drug to CD30-expressing tumor cells.

“By combining a very potent drug that has cancer-killing potential with an antibody that directs the drug right to where it has to go, we’ve achieved the goal of tumor-specific drug delivery,” says Michael Kaufman, Ph.D., VP, pharmaceutical sciences, Millennium.

Seattle Genetics and Millennium have formed a collaboration with Ventana Medical Systems to develop, manufacture, and commercialize a molecular companion diagnostic test for Adcetris to look at CD30 expression levels in patients.

“We want to make sure the patients who get this therapy are the ones who are likely to benefit from it,” Dr. Kaufman says. “This combines a lot of the best features of targeted drug delivery and personalized medicine.” **PV**