

## GOOD DRUG THERAPY:

## It's Not Just the Molecule — It's the *DELIVERY*

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**F**OR THE BIOPHARMACEUTICAL INDUSTRY, 2003 was a record-breaking year. The Food and Drug Administration (FDA; Rockville MD; [www.fda.gov](http://www.fda.gov)) granted 25 approvals for new biotechnology drugs and biologics, up 25% from 2002, and companies' earnings exceeded even their own expectations, driving the Nasdaq biotechnology index up 46%. Best of all, the industry raised \$16.4 billion in new financing, an increase of 56% over 2002 figures.

But it doesn't stop there. More than 370 biotechnology drug molecules and vaccines are currently in clinical trials, according to the Biotechnology Industry Organization (Washington, DC; [www.bio.org](http://www.bio.org)). And, with the FDA's 2003 initiative to reduce the review time for new drugs and biologics by 10.5%, these new treatments will be available even sooner than anticipated.

Faced with unprecedented competition, drug companies are evaluating modes of delivery for their prized therapeutics at every step of the design cycle. "Not only can the right drug-delivery platform transport drug molecules more effectively, it can also improve patient compliance and extend the products' lifecycles as patents expire," says Business Communications Co. (BCC; Norwalk, CT; [www.bccresearch.com](http://www.bccresearch.com)) market analyst Shalini Shahani. "Many highly profitable blockbuster drugs will reach patent expiry by 2004–2006, losing about \$37 billion in market value to generic competition," she adds.

Truth be told, the mode of delivery can be the difference between a drug's success and failure — not just for scientific reasons, but because a customer's choice of drug is strongly swayed by the way the medicine is administered. It's no wonder that over 300 companies in the U.S. are feverishly working on developing drug-delivery platforms, the definition of which has expanded to include new, targeted therapies, as well as drug-containing implants, patches, particles and gels. Of the latter category, implantable drug-delivery devices (IDDDs), not including coated stents, are uniquely positioned to

meet a number of drug-delivery challenges — such as targeting the drug to particular cells or tissues, getting hydrophobic drugs absorbed into the bloodstream, and mimicking a therapeutic molecule's natural release profile in the body — either alone or when combined with other technologies.

With sales of \$1.4 billion in 2003, IDDDs currently have the smallest share of the U.S. drug-delivery market, which topped an estimated \$43.7 billion in sales last year, according to BCC.\* This is likely due to a fewer commercial products relative to other categories. However, for the next 4 years, the IDDD market is expected to grow 12.4%/yr, exceeding the overall drug-delivery market growth rate (11.3%/yr). Drivers for this growth include the need for palliative alternatives to needle injections and for controlled-release systems that administer the drug in steady or pulsatile fashion for extended periods.

One drawback of controlled-release systems, generally speaking, is their inability to respond to the needs of a given individual for a particular drug therapy. However, the players in the IDDD market are finding ways to overcome this limitation.

### Implantable pumps

Currently, only two IDDDs are commercially available in select markets. The first is an implantable osmotic pump invented by Alza Corp. (Mountain View, CA; [www.alza.com](http://www.alza.com)) and now developed and marketed by Durect Corp. (Cupertino, CA; [www.durect.com](http://www.durect.com)). Called Duros, it is shaped like a small rod (44 mm × 3.8 mm) and holds 150  $\mu$ L of drug formulation, which is delivered at rates as low as 0.25  $\mu$ L/d  $\pm$  10% for at least 1 mo and up to 1 yr.

When the device is implanted, water from the body is slowly drawn through a semipermeable membrane into the pump by salt residing in the engine compartment. As this water fills the chamber, it displaces a piston, causing the correct amount of drug to be dispensed. The drug release rate can be tailored by varying the composition of the osmotic agent and the surface area and thickness of the semipermeable membrane.

In 2002, the FDA approved the first product to incorporate Duros technology — Bayer Corp.'s (Leverkusen, Germany; [www.bayer.com](http://www.bayer.com)) Viadur (leuprolide acetate) implant for the once-yearly treatment of advanced prostate cancer. More recently, Durect has integrated Duros with an implantable catheter to direct drug flow to the target tissue or a synthetic medical structure (e.g., a graft). The product is being tested with pain medication, but will work with proteins and peptides, says the firm. In addition, BioMedicines, Inc. (Emeryville, CA; [www.biomedicines.com](http://www.biomedicines.com)) has adopted Duros for its Omega Duros implant, which is being clinically tested in the U.S. and Europe for the administration of a genetically engineered form of omega interferon, a treatment for hepatitis C. The drug, which targets only the liver tissues, reduces side effects. Meanwhile, Durect has expressed interest in using Duros to enhance the pharmaceutical portfolio of Johnson & Johnson Co. (New Brunswick, NJ; [www.jnj.com](http://www.jnj.com)), which merged with Alza in 2001.

The other device on the market, an implantable insulin pump called MiniMed 2007 (Figure 1) is manufactured by Medtronic MiniMed, Inc. (Northridge, CA; [www.minimed.com](http://www.minimed.com)). It is used with an external programming device and is also a component of MiniMed's prospective artificial pancreas, a fully implantable insulin-delivery system that incorporates a sensor that continuously monitors blood-sugar levels and transmits glucose levels to the pump for automatic, accurate insulin dosing.



Figure 1. The MiniMed 2007 implantable pump measures 3 in. wide, holds a 3-mo supply of insulin and has a battery life of more than 6 yr.

\*The U.S. drug-delivery market includes sustained-release (e.g., oral, injectable and topical), transdermal, transmucosal, implantable and targeted systems. Source: BCC, Inc.

MiniMed 2007 holds a 3-mo supply of highly concentrated insulin, U-400, which is manufactured by Aventis Pharma AG (Frankfurt, Germany; [www.aventis.com](http://www.aventis.com)), and delivers background insulin to patients around the clock, like a healthy pancreas, says Deanne McLaughlin, the company's communications manager. Users can demand extra insulin at the touch of a few buttons using a handheld Personal Pump Communicator (PPC), which utilizes RF telemetry to communicate with the pump.

Presently, MiniMed 2007 can be purchased only in France, the one country that has approved use of U-400. FDA clearance is expected within the next few years. The artificial pancreas is in clinical trials in the U.S. and France and should be available in 4–5 years.

Meanwhile, Debiotech S.A. (Lausanne, Switzerland; [www.debiotech.com](http://www.debiotech.com)) is taking a micro-electro-mechanical systems (MEMS) approach to miniaturize its MIP implantable micropump for the delivery of insulin. The pumping chip comprises two silicon plates (16 mm × 12 mm × 1.86 mm) with micromachined structures, and a piezoelectric ceramic disc. The volume of the pump chamber changes with the displacement of a membrane that is actuated by the piezoelectric disc, generating flowrates from 10–100 mL/min that are linear with actuation frequency and virtually insensitive to inlet and outlet pressure and actuation voltage.

Debiotech plans to make the final product the size of a thick credit card. "One major hurdle will be formulating a concen-

trated insulin solution or powder, which must move through plastic infusion lines without clogging and then be reliably absorbed," says company president Frederic Neftel. Shahani points out that the cost of production for an implantable pump may be reduced with the MEMS approach, but development costs will soak up these savings. Thus, pumping costs are not expected to come down that much with this approach for some time, if it proves successful.

### Microfabricated devices

Microfabricated chips have an advantage as far as compliance is concerned, since once the chip is implanted, the patient need take no further action, says John Santini, president of MicroCHIPS, Inc. (Bedford, MA; [www.mchips.com](http://www.mchips.com)). The company's first-generation chip measures 15 mm × 15 mm × 1 mm and contains up to 100 350-nL reservoirs that are filled with one or more drugs and capped by a 0.38- $\mu$ m thick membrane made of gold, titanium, and/or platinum (Figure 2). It is designed to deliver a specific amount of drug on demand, and is targeting applications such as the treatment of congestive heart failure and osteoporosis.

The device also has a battery and a microprocessor, into which a patient's drug regimen is programmed before implantation in the abdominal area. After implantation, the dosing schedule can be modified by wireless transmission of a new program to the device. When the device receives a signal from the microprocessor, the battery

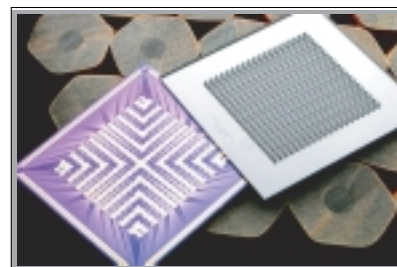


Figure 2. Shown are the back (left) and front (right) of a 400-reservoir microchip device developed by MicroCHIPS, Inc. The back shows the reservoirs where drugs or biosensors can be stored. The front shows the metal traces used to direct electrical current to each of the reservoirs.

sends a 10–50- $\mu$ s pulse of current to a specific reservoir cap, causing the cap to "pop" like a fuse. The reservoir releases drugs into the body, or allows body fluids to enter it and contact an enclosed biosensor, if one is present.

MicroCHIPS plans to have implantable chips for drug delivery and sensing ready for human trials in about 2–3 years. "We have already shown that the technology works in animals," says Santini. The drug payload for MicroCHIPS' first-generation implant is in the range of a few mg/yr range. The next-generation implant is intended to accommodate payloads of 100s of mg/yr. The firm also intends to integrate an implantable glucose sensor in the microchip reservoir, so that the system can be used with an implantable pump for long-term insulin delivery.

At Massachusetts Institute of Technology (Cambridge; [www.mit.edu](http://www.mit.edu)), professor of chemical and biomedical engineering Robert Langer is testing a

### Nanofabricated membranes' passive, precise delivery

IMEDD, Inc. (Columbus, OH; [www.imedd.com](http://www.imedd.com)) has perfected its top-down microfabrication methods to create NanoPore membranes — silicon films covered with arrays of parallel, rectangular channels ranging from 4–50 nm in dia. As a point of reference, a small organic drug is typically 3–5 nm. These membranes are fitted around the NanoGATE implant — a 400- $\mu$ L cylindrical reservoir measuring 1–2 cm long and 3–5 mm in dia., capped at both ends with polymer plugs — to control the diffusion of drugs (solid or liquid) from the NanoGATE capsule. When inserted under the skin, the implant provides a uniform, continuous release of a drug for 3–6 mo. "Any high-molecular compound given by intravenous injection is game, as long as the dose requirement is less than 500  $\mu$ g/d," says Tony Boiarski, director of R&D at IMEDD.

IMEDD is testing NanoGATE *in vivo* for the delivery of alpha interferon (19,000 Daltons) and hopes to begin preclinical trials within the next 6 mo. The firm has also applied for a patent on a lyophilization technique that stabilizes interferon — and possibly other biopharmaceutical proteins — for at least 6 mo at 37°C. Boiarski says that the cost of a 6-mo treatment for hepatitis C using NanoGATE

would be \$10,000 (the implant costs less than \$100 and alpha interferon costs about \$1,000/mg). In contrast, conventional outpatient treatment, which requires intravenous injections 1–3 times/wk, costs \$14,000–\$20,000 for the same indication.

Terry Conlisk, an engineer at Ohio State Univ. (Columbus; [www.osu.edu](http://www.osu.edu)) has developed a computer model to help medical devices like the NanoGATE pump fluids through nanoscale channels, on demand, using electrical charges. Conlisk is presenting his work at BCC's Nanotech and Biotech Convergence 2004 (March 28–30; Cambridge, MA; [www.bccresearch.com](http://www.bccresearch.com)).

Debiotech S.A. (Lausanne, Switzerland; [www.debiotech.com](http://www.debiotech.com)) is also conducting *in*

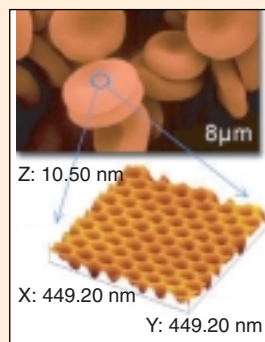


Figure 3. The diameter of a pore in the DebioSTAR membrane is three orders of magnitude smaller than the diameter of a human red blood cell. Pore density can be up to 1 billion pores/cm<sup>2</sup>.



biodegradable microchip (Figure 5) that releases drugs in a pulsatile fashion over several months. Like other IDDDs that deliver drugs passively (see Sidebar), this one does not require a stimulus to trigger the drug release.

The chips are made of poly(L-lactic acid) and have 36 reservoirs that could

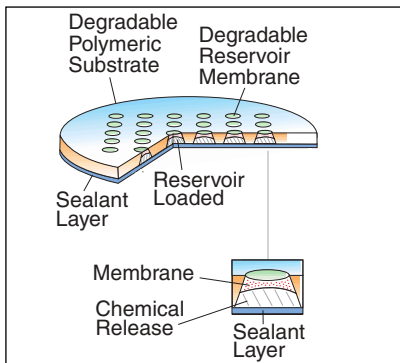


Figure 5. This polymeric microchip fabricated at Massachusetts Institute of Technology contains reservoirs filled with the drug to be released, and a degradable covering that governs the drug's diffusion rate.

each hold 120–130 nL of a different chemical and which are covered by membranes constructed of poly(D,L-lactic-co-glycolic acid).<sup>4</sup> The release characteristics may be tailored for specific applications by varying the attributes of the device (size, polymer), reservoirs (number, volume) and membranes (thickness, molecular mass, material, copolymer ratio),<sup>5</sup> notes Langer. Water uptake and swelling cause the polymer to rupture. Polymers with a higher molecular mass retain their mechanical strength for longer periods, leading to chemical release

at later times. Langer points out that by superposing the release profiles from individual reservoirs, one can potentially release different chemicals in pulsatile and continuous modes.

An alternative to the use of single-use reservoirs is a microchip using valves called “artificial muscles.” The artificial muscle refers to an actuator comprised of a hydrogel and an electrically conducting redox polymer. The polymer is sensitive to pH (an obstacle for monomer-based “muscles,” which do not function at a physiological pH) and applied and chemical potentials, while the hydrogel exhibits swelling and shrinking upon changes in pH, solvent, temperature or ambient light conditions. “By electropolymerizing these hydrogel-polymers onto electrodes, drug reservoirs can be opened or closed via the concentration of the polymer in response to electrochemical actuation,” explains Sylvia Daunert, co-founder of ChipRx, Inc. (Lexington, KY; [www.chiprx.com](http://www.chiprx.com)) and professor of chemistry at the Univ. of Kentucky (Lexington; [www.uky.edu](http://www.uky.edu)).

ChipRx is conducting tests on an IDDD platform demonstrating this concept. The device consists of a thin, torpedo-shaped silicon microchip about the size of a matchstick and covered with thousands of ring-shaped actuators (Figure 6). A biosensor comprising genetically engineered proteins generates a signal when these proteins bind to a target analyte. The magnitude of this signal is processed by control electronics and triggers, if needed, the opening of the rings to release an ap-

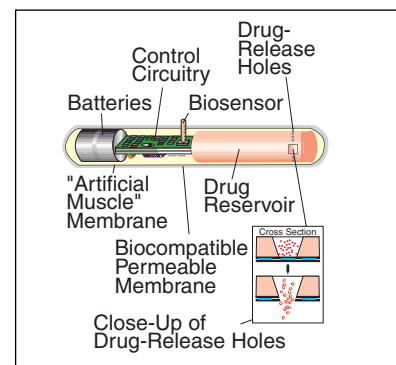


Figure 6. ChipRx, Inc. is working on a fully integrated, self-regulated therapeutic system.

propriate dose of drug from one or more microfabricated chambers. Each chamber can be individually addressed and controlled. The incorporation of telemetry into the device enables data to be wirelessly transmitted to personal data assistants for round-the-clock physician intervention or monitoring of the device's performance.

Such a device would be close to what may be considered by the biopharmaceutical industry as the Holy Grail of drug delivery — a system that combines multiplex sensing and controlled delivery (discrete or continuous) in a closed-loop arrangement, enabling individualized therapy in clinical areas where it is desperately needed. This system would also have to be inexpensive, biocompatible, long-lasting, easy to implant and remove, and comfortable for the patient — a tall order, but not one that is unattainable when approached in an interdisciplinary fashion and with the necessary venture capital.

*vivo* studies for an implantable capsule called DebioSTAR (Figure 3) that uses a nanoporous silicon membrane to deliver peptides, hormones and similar molecules to the body for about 6 mo. Each membrane is tailored to achieve a specific release profile for a particular drug, which can be in the solid or liquid form, using: (1) software that calculates the membrane's thickness (50–200  $\mu\text{m}$ ), pore diameter (1–250 nm) and pore depth (< 50 nm to > 150  $\mu\text{m}$ ); and (2) a novel manufacturing process, says Frederic Neftel, the company's president. “Due to its simplicity and need for very small surface areas, the product costs little to manufacture,” he adds.

Striving to bring the artificial pancreas to fruition, Tejal Desai, formerly of the Univ. of Illinois (Chicago) and now associate professor of Biomedical Engineering at Boston Univ. (MA; [www.bu.edu](http://www.bu.edu)), is working on an implantable micromachined capsule that houses a polymer well containing islet cells derived from pancreatic tissue. A nanoporous silicon membrane fabricated with photolithographic techniques is bound to the well. “The membrane's 24.5-nm-dia. pores are large enough to allow the diffusion of glucose into the cap-

sule, so that the islet cells can use it to produce insulin, which then diffuses out, but small enough to block the entrance of antibodies and other immune-system components,” says Desai. “This permits the use of islet cells from any source without fearing rejection from the patient,” she adds. The capsules are implanted subcutaneously, not more than a few hundred microns from a blood vessel. Desai has tested it on small animals, and is starting *in vitro* trials with larger models (*e.g.*, pigs).

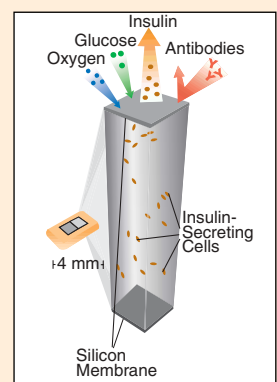


Figure 4. This biocapsule contains insulin-secreting cells. A nanoporous silicon membrane allows the diffusion of nutrients and insulin, but not antibodies.

Image credit: Kirk Woellert and the National Science Foundation.