

# Technologies that deliver

Scientists are churning out new ways to deliver therapies faster than regulatory agencies can evaluate them. Paroma Basu takes a peek at the future.

Imagine a diabetic—let's call him Mark—who is preparing for his third insulin shot of the day. Mark picks up his syringe, stares at the needle and suddenly decides he doesn't need a shot after all. He hates injections and—just this once, he tells himself—stashes the syringe away for later.

Nearly 10 million diabetics neglect their insulin treatment, many of them because of just such an aversion to needles. Soon, Mark—and millions of other diabetics like him—might be able to sniff insulin through his nose or spray a clear insulin mist directly into his mouth and lungs.

Nektar Therapeutics, a drug-delivery company based in California, is conducting phase 3 clinical trials for Exubera, its much-anticipated inhaled insulin product. Exubera, expected to hit the market within two years, generates an aerosol cloud from insulin by compressing air and crushing the drug into tiny particles that disperse throughout the lungs.

Driven by the limitations of existing delivery methods and the emergence of new classes of genomic drugs in the pipeline, companies are flocking to the thriving drug delivery industry. "The synthesis of the medicine is only one part of the drug. Without delivery you just won't have a successful treatment," says Robert Langer, a chemical and bioengineering professor at the Massachusetts Institute of Technology and a past chairman of the US Food and Drug Administration (FDA)'s science advisory board.

A dizzying array of new delivery technologies is surfacing every year, as researchers scrutinize every part of the body—including the skin, nose, lungs, intestine and back of the eye—to transport a drug precisely to its target. Therapies can now be administered by patch, implant, controlled-release pills, long-acting injections or programmable microchips.

The stakes are high because a therapeutic agent often thwarts a disease only when it is delivered accurately—otherwise, as in the tragic examples of gene therapy, the cost could be death.

At the same time, the burgeoning number of cutting-edge delivery methods is leading to increasingly bewildering regulatory protocols. Government agencies are struggling to evalu-

ate unprecedented delivery approaches through traditional channels. As a result, many revolutionary technologies are languishing just out of reach, trapped in a regulatory stranglehold.

## Entry-level techniques

Every human orifice is now a potential portal for drugs. Even that old standby, the oral pill, is no longer just a pill. Alza, a leading drug delivery company in California, has come up with OROS, a technology that uses osmosis—the natural movement of water across membranes—to control drug delivery from a pill for up to 24 hours. The European company SkyePharma's GEOMATRIX technology allows one tablet to simultaneously release two different drugs at different rates. The technology layers drug compounds and controls diffusion rates, allowing a pill to dispense single or multiple doses to several sites within the digestive system.

Some companies are looking even further into the future, envisioning a world of 'smart' delivery systems that monitor chemical signals in the body and release the right doses of drugs accordingly.

"Research [in this field] is headed towards highly controlled, on-demand drug release systems that allow physicians to control drug timing and drug release rates," predicts John Santini, the chief executive officer of Massachusetts-based microCHIPS. Santini's company is developing a fingernail-size silicon microchip that is inserted just under the skin

of the abdomen. The chip includes hundreds of tiny wells, each containing drug doses that can be released in any combination on command from preprogrammed microprocessors, remote controls or biosensors.

With its 1.5 million pores, the skin could be another gateway to success. Alza's e-Trans is an electronically driven skin patch, now in phase 3 trials for delivering the analgesic fentanyl to patients in acute pain; Utah-based Zara uses heat to achieve transdermal delivery; and Israeli transPharma Medical's ViaDerm uses radiofrequency waves to poke little microchannels in the skin that allow molecules through.

If the delivery techniques headed to the market seem like the stuff of science fiction, the reasons for their innovation are simple enough. A single successful product—such as inhaled insulin—could potentially generate billions of dollars in profit. Sales of alternative delivery systems reached \$38 billion in 2002. Analysts expect the market to continue growing, predicting that drug delivery will account for 39% of all pharmaceutical sales by 2007, according to a recent market report released by the UK publisher VisionGain.

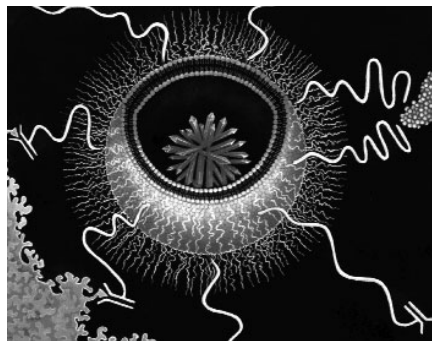
Patents for several blockbuster drugs are scheduled to expire shortly, so new delivery technologies are one way companies can repackage products and avoid competition from generics, says John Waslif, the analyst who compiled VisionGain's report. For instance, when Pfizer's angina drug Procardia approached the end of its patent a few years ago, the company rereleased Procardia, this time in the form of sustained-release tablets. Pfizer renamed the product Procardia XL.

Despite all the technologies in the pipeline, only a handful of alternative methods exist in the market—notably Ortho Evra, a weekly birth-control patch that releases estrogen and progestin through the skin. More recently, the FDA approved Gliadel, a dime-sized, polymer-based wafer that administers chemotherapy directly to brain tumors and dissolves in brain fluids within three weeks.

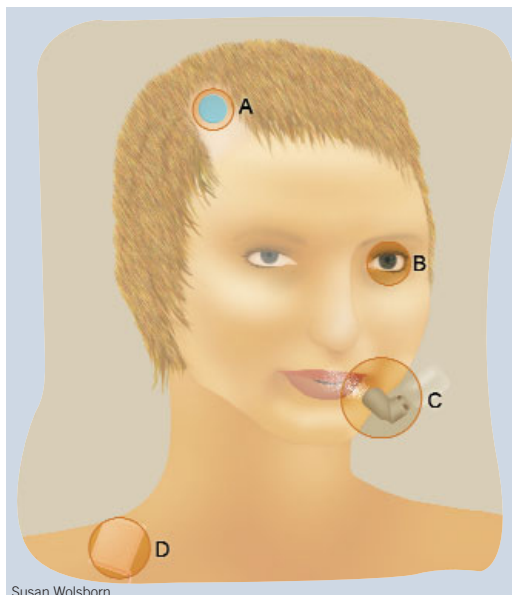
## The rise and fall of gene therapy

An idea for a new technique is just that—an idea. No matter how promising a technology sounds at first, there are still toxicity tests to be conducted, clinical trials to be held and patients to be convinced; any of those steps could transform a 'miracle' into just another has-been. If there's one story that clearly illustrates the disappointing failure of a seductive idea, it's gene therapy.

The technique, which aims to cure disease by replacing faulty genes with functional ones, is perhaps the most celebrated concept in deliver-



**Delivering DNA:** Lipid-bound vesicles can carry genetic material into cells.



Susan Wolsborn

Technology/company	What it does	Targeted disease	Stage
A. Gliadel/Guilford Pharmaceuticals (Maryland, USA)	Dime-sized wafer administers chemotherapy to brain tumor site and dissolves within three weeks	High-grade malignant glioma	Market approval in more than 20 countries
B. Vitrasert/Control Delivery Systems Inc. (Massachusetts, USA)	Implant inserted behind eye continuously releases drugs for up to three years	Uveitis (disease afflicting back of eye)	Phase 2 clinical trials
C. AERx/Aradigm Inc. (California, USA)	Inhaler pushes liquid drugs through tiny nozzles to create a fine mist	Type 1 and 2 diabetes; potential for cancer, hepatitis C and emphysema	Phase 3 clinical trials
D. Transdermal lidocaine system/Vyteris Inc. (New Jersey, USA)	Controllable, painless electric current drives lidocaine through skin	Local dermal anesthesia; potential for migraine and Parkinson disease	Pending approval of New Drug Application

ing therapies—and the least successful. Once hailed as a miracle cure, the field has virtually stalled on the difficulty of ferrying corrective genes into cells without triggering a violent immune reaction.

In 1999, 19-year-old Jesse Gelsinger died during a gene therapy clinical trial at the University of Pennsylvania. Last fall, two children developed leukemia during a gene therapy trial in France for X-linked severe combined immunodeficiency syndrome. More recently, researchers conducting a gene therapy trial for hemophilia and cystic fibrosis found that the viral vector in use also has the potential to switch on cancer genes.

Researchers have traditionally stripped viruses of certain genes to create vectors that evade the immune system. Unfortunately, the approach hasn't been entirely successful. Viral vectors can trigger negative immune responses or deposit genes to the wrong site within chromosomes. "Without safe delivery, gene therapy cannot succeed," says Langer.

Responding to the recent incidents, The US National Institutes of Health's Recombinant DNA Advisory Committee (RAC) in June announced it will reassess its protocol for evaluating new vectors. Rigorous questions about safety, efficacy and specificity need to be revisited, says Theodore Friedmann, director of the human gene therapy program at the University of California at San Diego and chair of the RAC until June. "These are questions we've always asked to one extent or another," Friedmann says. "But now there is a higher level of urgency."

At the same time, "methods of gene delivery are getting better and better," insists the Salk Institute's Inder Verma, a leading gene therapy

expert. Still, many scientists have moved away from viruses entirely, instead working on non-viral vectors.

One nonviral approach is to coat genes with synthetic polymers. Other researchers use liposomes, or methods like electroporation, where DNA is injected into target tissue while an electric field pierces holes into cell membranes. Nanotechnology is also influencing vector research: Japanese and Belgian researchers recently demonstrated the use of a hybrid vector to deposit genes in cancerous liver cells, using nanoscale fat globules coated with a protein isolated from the hepatitis B virus.

#### Bureaucratic breakdown

All the clever ideas for delivering therapies may never evolve into real products unless clear-cut guidelines emerge to smooth their regulatory path. Regulatory agencies are becoming increasingly befuddled over how to evaluate the bulk of new delivery methods. In the US, for instance, the FDA has three separate centers devoted to evaluating drugs, devices and biologics. But many of the new products are not a clean fit in any one center and could potentially be classified as a drug, a device *and* a biologic. Regulatory hurdles may only become more tortuous as the industry grows, with researchers exploring more body parts—such as nerves or children's ears—to deliver drugs. Companies will also move toward delivering entire cells to create new tissue, or toward the much-hyped technique of RNA interference, predicts Langer.

The root of the confusion is a nebulous FDA phrase—"primary mode of action"—that is used to ascertain which center regulates what product, says Jon Kahan, a Washington,

D.C.-based regulatory attorney. Kahan anticipates a unique regulatory dilemma for every new 'combination' product. For instance, problems could arise with a product such as microCHIPS that administers 30 to 50 variations of several different drugs, Kahan points out. "Would we have to go through a combination approval for every drug or variation?" he asks. "It really is a stupid situation."

Problems were evident in the regulatory path of Johnson and Johnson's Cypher Sirolimus-Eluting Coronary Stent, approved earlier this year and expected to be a blockbuster. Cypher is a metal grid that stretches clogged arteries open. To lessen the chance of commonly occurring metal-related infections or scarring, the stent is coated with sirolimus, a slow-release drug. Regulatory officials were stumped by the fact that Cypher is both a drug and device, each part dependent on the other. After negotiating for three years, the FDA agreed, to the surprise and relief of many, to regulate Cypher as a device rather than evaluate it in the long process of drug review.

Last December, the FDA opened the Office of Combination Products to facilitate approvals for products like Cypher. The new office will focus on better communication with companies, as well as on fine-tuning agency rules to enhance cross-consultation between the various center authorities, says Mark Kramer, the new president of the office. "We need to have an armamentarium in place so that we don't waste time deciding how or who will regulate the products," says Kramer. "We also need to know what's coming down the pipes so that we can anticipate all these new technologies."

*Paroma Basu is Nature Medicine's news intern.*