According to Dr. Naismith, drug delivery technology is expanding its role beyond being a tool for dermal penetration, taste masking, or changing the duration of action of a drug.

"Drug delivery is now meeting very significant new challenges as to how to present and increase the bioavailability of new therapies such as RNAi, antibodies, proteins, antisense products, and so on," he says.

THINK BIG

With many pharmaceutical products losing or about to lose their patent protection, companies are seeking ways to improve the marketability of their products.

In its report — Innovation in Drug Delivery: The Future of Nanotechnology and Non-Invasive Protein Delivery — Business Insights researchers say pharma companies are using innovative drug delivery technologies to expand product life cycles and maximize drug sales.

But Bill Lambert, Ph.D., senior VP, pharmaceutical development, at Pacira Pharmaceuticals Inc., says in general drug delivery technologies tend to be more of an afterthought.

"Many therapies come to market without a drug delivery technology associated with them, even though there are some very obvious advantages to having this connection," he says. "I wonder how many really good drugs haven't been developed simply because an appropriate drug delivery technology was not applied to them."

The opportunity is there to take a more proactive approach, and that is starting to happen at some companies, Dr. Lambert notes.

A move to considering a drug delivery vehicle earlier on in the drug discovery process has been propelled in part by the success of nanotechnology in facilitating the delivery of cancer drugs using NanoCrystal and Abraxane methods, Dr. Naismith says.

There are several companies that are integrating novel drug delivery technologies early on. Among these is Calando Pharmaceuticals, with its targeted siRNA anticancer therapeutic product (CALAA-01). Calando combines proprietary technologies in targeted polymeric delivery systems and siRNA design to create therapeutics.

Another example is Azaya Therapeutics Inc., which is using a nanotechnology-based platform called Protein Stabilized Nanoparticle (PSN) technology to deliver its lead candidate ATI-1123, which is the PSN formulation of Aventis' Taxotere (docetaxel). Docetaxel is a poorly water-soluble semisynthetic taxane analogue commonly used in the treatment of non-small cell lung, prostate, and breast cancers. It is often formulated with a toxic carrier Tween 80 to manage its poor solubility, but this contributes to numerous adverse events such as nausea, fatigue, and anemia. The PNS technology seeks to avoid these formulation issues.

> Pharma companies are using innovative drug delivery technologies to expand product life cycles and maximize drug sales.
>
> — Business Insights

A third example of a company that is marrying drug delivery advances with drug development early on is BioAlliance Pharma SA with its Doxorubicin Transdrug, which is being investigated to treat primary liver cancer. Transdrug is based on nanotechnology developed by BioAlliance, coupled with doxorubicin, an anticancer agent.

More broadly, however, if drug delivery companies are going to move to beyond being service companies to big pharma they need to expand their technologies and business models to develop specific targets and solutions to bioavailability, stability, specificity, and unwanted immune-response problems, Dr. Naismith says.

"Likewise, big pharma companies, as they adapt to the significance of these new therapies, need to expand their in-house drug delivery resources to begin addressing these problems," he says. "New approaches that target genes and gene products eliminate much of the development time, including assay development, screening, medicinal chemistry, lead identification, and lead optimization."

One barrier to wider use of advanced drug delivery technologies, however, is gaining regulatory approval, says Karen L. Moynihan, Ph.D., associate professor at the Keck Graduate Institute.

"Approval of NDA and BLA dossiers for drug delivery products can be delayed, even

DR. KAREN MOYNIHAN, KECK GRADUATE INSTITUTE

Early-stage feasibility studies between drug delivery and specialty companies with pharmaceutical companies will enable new technologies to be paired with drugs that can address unmet medical needs.

GRAHAM REYNOLDS
WEST PHARMACEUTICAL SERVICES

In general, researchers have begun to understand that their role extends into some of the post development areas, such as marketing and the ultimate patient experience with the drug.

when the active ingredient already has been marketed in a traditional formulation, because of issues such as unanticipated side effects, altered safety profiles, and manufacturing reproducibility, as well as characterization concerns arising in the clinical and postmarketing stage of development," Dr. Moynihan says.

ALTERNATIVE DELIVERY

As new classes of therapeutics emerge, such as those that use RNA interference to treat disease, there will be a need for innovative technologies to deliver those therapeutic advances, says Steven C. Quay, M.D., Ph.D., chairman, president, and CEO of Nastech Pharmaceutical Company Inc.

"Delivery is the key to making this new approach a reality," he says.

The Business Insights report notes that noninvasive protein delivery is a major focus of biopharma, with oral drug delivery being viewed as the goal for protein delivery.

Protein drugs have had to be delivered intravenously because the protein is degraded by digestive enzymes before it can be absorbed. The report adds that innovation in drug coatings has provided protein pipeline products with the potential for the first oral protein drug to reach the market within the next 10 years.

Progress also has been made in technologies to deliver proteins and peptides via the intranasal route and by inhalation to the deep lung.

"For nasal delivery, the inclusion of bioadhesive excipients during formulation has lengthened the residence time that a drug can be retained within the nasal cavity," Dr. Moynihan says.

In the area of transdermal delivery of protein drugs, difficulties arose from the molecules not being able to penetrate the skin. But technology advances are enabling proteins to be delivered via microneedles, iontophoresis, or electroporation, the report says.

"Development of new delivery technologies for macromolecules, such as peptides and proteins, is making significant progress in creating better medicines for patients and physicians," Dr. Quay says. "With the approval of more biologics, breakthroughs will emerge as new technologies are developed that reduce, such as through sustained drug release, or eliminate the need for injections by delivery through alternative routes, including nasal, pulmonary, and oral."

In the endocrinology sphere, such as diabetes, obesity, and osteoporosis, noninvasive dosage forms of therapeutic proteins are in clinical development, Dr. Quay says.

Nastech, for example, is developing nasal spray versions of parathyroid hormone for the treatment of osteoporosis; exenatide (Byetta), an adjunct therapy to improve glycemic control in patients with Type 2 diabetes; and insulin, all of which are approved as daily injections.

"We also are developing nasal sprays of other protein drugs not yet approved, such as peptide YY3-36 (PYY3-36) to treat obesity, and carbetocin, a peptide analogue of oxytocin, to treat the symptoms of autism," Dr. Quay says.

In 2006, Nektar and Pfizer received U.S. marketing approval for Exubera, an inhaled form of insulin for the treatment of Type 1 and Type 2 diabetes. In October 2007, Pfizer announced it was discontinuing marketing of the product and returning the rights to Nektar. What the broader repercussions of that decision will be remain uncertain, experts say.

Drug solubility poses significant challenges in delivery. One in 10 marketed drugs has solubility problems, more than one-third

DRIVERS OF INNOVATION IN DRUG DELIVERY

UNMET NEED	INNOVATION
Poor patient compliance	Needle-free injections Noninvasive protein delivery
Poor solubility	Nanobiotechnology Technology to increase solubility
Frequent dosing schedules	Controlled-release injectables Drug-eluting implants

Source: Business Insights Ltd., London. For more information, visit globalbusinessinsights.com.

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DR. ROBERT NAISMITH
LIFE SCIENCE ANALYTICS

Most of the next-generation drug delivery technologies need to be cost-effective and this could be done with a certain degree of innovation.

TROY HARMON
EURAND

A continued collaboration between commercialization experts and their development colleagues is instrumental in efficiently developing new technologies for market success.

of pipeline products are poorly soluble, and almost two-thirds of drugs in early preclinical development have low solubility, the Business Insights report notes.

Nanotechnology offers one solution. Examples of nanoparticles that increase drug solubility are liposomes, mixed micells, and inulin glasses, the report says. Benefits of liposomes include solubilizing lipophilic drugs, enhancing the immune response to antigens in vaccines, and enhancing dermal skin penetration. Liposomes have the largest commercial potential for drug delivery because they offer the most flexibility in physico-chemical characteristics compared with mixed micells and inulin glasses, the report says.

Despite significant advances, tried-and-true drug delivery technologies — inhalation, depot injections, transdermal, and oral routes of administration — continue to lead the way, says Troy Harmon, VP of business development at Eurand.

"The approach is not changing, but the technologies, especially in oral drug delivery, are showing continuous improvement and as such are extending drug delivery to more and more molecules," Mr. Harmon says. "Examples of this are bioavailability enhancement technologies, gastroretention, controlled-release formulations for poorly soluble drugs, controlled-release orally disintegrating tablets, and so on."

The body's biological barriers can hamper how drugs are delivered and distributed and thus can impact their effectiveness, experts say.

"Tailoring drug chemistry to overcome these barriers would lead to immeasurable improvement in drug effectiveness in the treatment of many medical conditions," Dr. Tomlinson says. "The future of drug delivery lies in tailoring drug properties to administration approaches that use microelectronics and probably nanofabrications."

PATIENT FOCUS

A long-standing issue for the healthcare industry is patient compliance. The reasons for poor patient adherence are many-fold, but among them are how easy the product is to use, complexity in terms of dosing regimens, and difficult delivery mechanisms.

"Ease of use, convenience in use, and drug effectiveness serve to promote product compliance," Dr. Tomlinson says. "Drug reformulations that enable a safer and more effective delivery increase compliance and enhance patient quality of life. For example, a transdermal insulin skin patch, such as the one in development at Altea Therapeutics, could replace painful needle injections and provide a safer and more effective delivery."

An example of a technology designed to improve patient uptake is Grunenthal GmbH's broad-spectrum antibiotic, Clarosip, which uses an innovative delivery mechanism designed to ensure children take and complete the course of clarithromycin.

"The technology consists of a straw that contains and releases an antibiotic formulated to have a neutral taste so a child will not notice its presence in a drink," Dr. Naismith says.

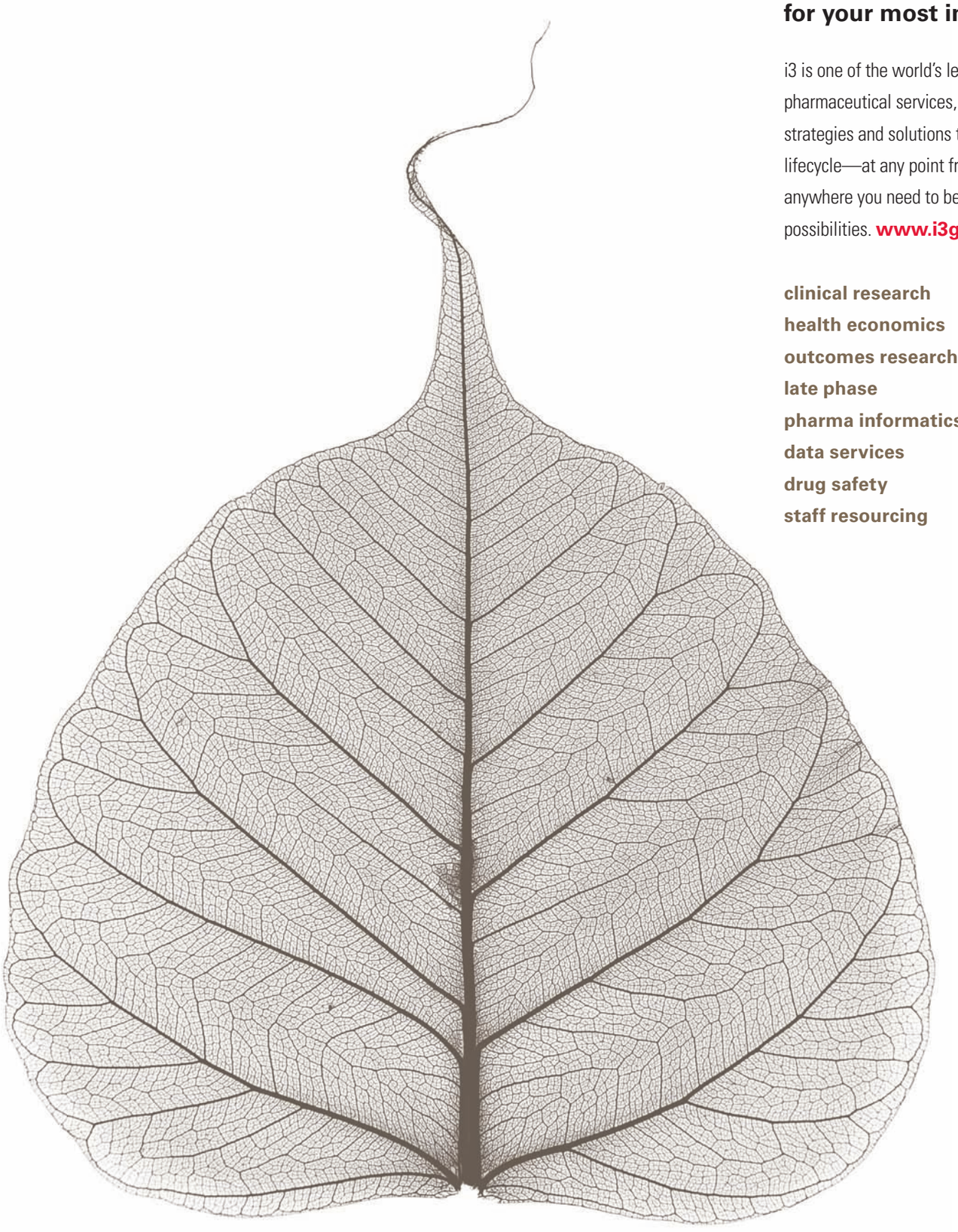
In an effort to assist patients who experience difficulty in swallowing capsules and tablets, Eurand's ODT technology, AdvaTab, is designed so that the drug disintegrates rapidly in the mouth. AdvaTab also can be combined with Eurand's particle technologies: Microcaps, a taste-masking technology; and Diffucaps, the company's controlled-release technology.

Understanding the patient's comfort with a product is important, and Dr. Moynihan suggests including patient focus groups early in product development and getting input from patients and healthcare providers on a product's expected performance profile.

KEY TRENDS IN DRUG DELIVERY

- **Big pharma companies** are acquiring drug delivery companies to develop in-house products with innovative drug delivery.
- **Noninvasive protein** delivery and the move toward targeted therapies are areas of focus. The next range of noninvasive protein products is forecast to be transdermal patches, with transmucosal and oral delivery to follow.
- **Nanomaterials** have a future potential for rapid topical delivery of active compounds because of their small size, allowing nanoparticles to enter human tissues and cells quickly. The future of nanotechnology lies in the generation of new carrier molecules and materials (nanoparticles, nanoshells, and self-assembles structures) for generating advanced delivery of drugs to their therapeutics targets.
- **There are high expectations for RNAi** in targeted drug delivery, particularly in cancer, rheumatoid arthritis, brain diseases, and viral infections.
- **The future of stem cells** lies in its integration with nanotechnology to revolutionize current neurological and blood and immune disorders.
- **Delivery of drugs by the transmucosal route** is evolving into a fusion of transdermal and oral drug delivery.

Source: Business Insights Ltd., London. For more information, visit globalbusinessinsights.com.



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DR. BILL LAMBERT
PACIRA PHARMACEUTICALS

Probably one of the biggest breakthroughs will be with regard to injectables, for example using antibodies to target specific cells and bringing a payload to a specific area.

DR. STEVEN QUAY
NASTECH PHARMACEUTICAL

Looking further into the future, we recognize the need to develop technologies for a potential new class of therapeutics that use RNA interference as a way to treat disease.

"Avoiding needle use, providing a significant reduction in dosing frequency, and developing conveniently sized, patient-friendly devices are of paramount importance for any drug delivery based product," she says. "When considering treatments for chronic medical conditions, it is essential to understand what reimbursement levels can be expected, as this aspect may also affect adoption of a novel product by patients."

Even the development of smaller needles has helped to make injectables more palatable for patients.

"Over the past 15 years to 20 years, there's been a dramatic decrease in the diameter of needles, and the pain factor is getting to the point where it's almost a non-issue," Dr. Lambert says. "Companies are taking those small needles and putting them into pens, which disguises the injection, and this has increased the patient acceptance of injections."

Graham Reynolds, VP of safety and administration systems at West Pharmaceutical Services, says for many newer drugs administration by injection or infusion provides the most effective route into the patient and, in some cases, the fastest route to market.

"Biopharmaceutical research and development has significantly increased the number of injectable drugs coming to market," Mr. Reynolds says. "Those biotech-derived medicines are aimed at a range of therapeutic areas and, because of the chemical structure of the drugs, will need to be administered by injection. When this is combined with the move toward at-home administration, safety, ease of use, and accuracy of dosage become very important factors for drug manufacturers."

THERAPEUTIC FOCUS

Emerging drug delivery technologies have the potential to improve treatment in a variety of diseases and therapeutic areas, including cancer, diabetes, CNS disorders, and infectious diseases, according to Business Insights.

"Technologies such as microfluidics for targeted drug delivery nanoparticles have created a considerable impact on the therapeutic approaches to these diseases," Dr. Naismith explains.

Researchers in South Africa have developed a nano drug delivery system with the potential to treat tuberculosis. Existing TB treatments have a number of shortfalls, including patient noncompliance because of the extended treatment time. By developing polymeric nanoparticles loaded with anti-TB drugs for sustained release, dosage and dosage frequency are reduced.

Dr. Lambert says cancer research will be a major benefactor of advanced technologies because of the importance of selectively targeting cancerous cells and avoiding healthy tissue.

"Another area where drug delivery technologies can be used successfully is for peptide administration," he says. "An example of this would be leuprolide for cancer treatment. Drug delivery technologies have taken once-a-day peptides and turned them in to treatments that can be administered once a month, such as Atrix's Eligard, or every three or four months, such as Lupron Depot for the palliative treatment of advanced prostate cancer."

> Key drivers for drug delivery innovation are poor solubility, poor efficacy, and frequent dosing regimens of current drugs.
>
> — Business Insights

The area of CNS also can benefit from novel drug delivery technologies that are designed to overcome the limitation of drug permeation of the blood-brain barrier, Dr. Naismith says.

"Pulmonary drug delivery technologies have overcome this limitation by using peptidergic drugs not only for lung diseases

DR. ERIC TOMLINSON
ALTEA THERAPEUTICS

The future of drug delivery lies in tailoring drug properties to administration approaches that use microelectronics and probably nanofabrications.

but also for fast and effective delivery of drugs into the systemic circulation for treating pain and certain endocrinology and genetic disorders," Dr. Naismith adds. "Similarly, transdermal delivery technologies have been effective in these therapeutic areas."

The inescapable question of safety also arises. Controlled-release technologies have the potential to limit side effects and thus improve safety profiles and alleviate regulatory concerns, Dr. Lambert says.

Pacira, for example, has developed a sustained-release injectable drug delivery technology to address limitations associated with traditional methods of injectable drug administration.

The technology, DepoFoam, is a multivesicular liposome that has a honeycomb-like structure, which is different from a traditional liposome that has concentric membranes.

"A traditional liposome generally wouldn't have a good sustained-release factor because when the outer membrane breaks, it releases a very large portion of the trapped material," Dr. Lambert says. "DepoFoam releases one small cell at a time, for a much more prolonged release."

Controlled-release versions of pharmaceutical products using inhalation and oral technologies are being developed by SkyePharma. The company's Geomatrix systems control the amount, timing, and location of the release of drug compounds in the human body.

Dr. Quay points out that there have been issues with the idea of chronic delivery of drugs via the lungs because of the concern over the possible impact on pulmonary function.

Nastech seeks to address these concerns by designing its nasal sprays so the drug droplets that are created and dosed to the nose will not be inhaled into the lungs.

"As another example, there are concerns over low bioavailability and variability for proteins when delivered orally," he says. "In the case of Nastech's nasal formulation technology, we have identified tight junction modulating excipients that provide enhanced bioavailability with low toxicity to address this concern."

One obstacle for companies can be drug compound stability, Mr. Reynolds says.

"Companies tackle this by freeze drying the product, which means it has to be reconstituted at the point of care," he says. "Alternatively, if the drug can be packaged as a liquid, the manufacturer needs to find packaging components that will not interact with the drug. Extractables and leachables associated with drug-to-package interaction can be a major concern."

Developments are being made to overcome this challenge. For example, West Pharmaceuticals has introduced stoppers and syringe components that come with a certificate of analysis to identify the extractables, the specifications, and the quantity of the extractables for each lot of components, Mr. Reynolds says.

Experts say there is no single best approach, but rather the goal should be to match appropriate technologies with the pharmaceutical product and its physicochemical characteristics.

"Drug delivery technologies that lower doses, make feasible products from difficult drugs, improve the taste of dosage forms, make once-daily products from solubility-challenged drugs, and exploit chronotherapeutic opportunities will all help make drugs of the future better for the end-user," Mr. Harmon says. ✦

There are more than 200 specialty drug delivery companies.

— Business Insights

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

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