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Delivering on convenience

The drive to enhance biologic therapies through more convenient delivery methods is creating dealmaking opportunities for companies with innovative delivery technologies.

Rachel Brazil

Drug delivery technology is an expanding market, predicted by analysts to grow significantly over the coming years. One factor contributing to this expansion is the need for new delivery methods for biologic drugs—not only established classes such as monoclonal antibodies, but also emerging RNA-based therapies and gene therapies. Biologics are expected to account for half of the top best-selling drugs in the near future, but most must be delivered intravenously, which is costly and inconvenient.

The search for alternatives is driving the development of a panoply of new delivery technologies. Furthermore, the pressure of the coming biosimilars wave is likely to provide a push from pharma, who "will seek to differentiate themselves via additional drug delivery offerings and patient-support solutions," said Aidan King, managing partner at Fountain Healthcare Partners. "Companies offering drug delivery platforms for biologics should benefit from this," he added.

For example, the search for new ways of delivering biologics has led to a flurry of deals for Halozyme, whose Enhanze drug delivery platform enables subcutaneous injection of molecules as large as 200 nm, including most monoclonal antibodies, cytokines, recombinant enzymes, proteins and peptides. It does this by degrading the polysaccharide hyaluronan, which forms part of the subcutaneous space beneath the skin. In December 2015, Lilly became the latest company to partner with the clinical-stage biotech. Lilly will pay Halozyme $25 million and milestone payments of up to $160 million for the development of each of up to five collaborative products. Other companies partnering with Halozyme include Roche (for its anticancer monoclonal antibodies Herceptin (trastuzumab) and MabThera (rituximab)), Baxalta (for HyQvia, an immunoglobulin therapy for primary immunodeficiency), AbbVie, Pfizer and Janssen.

Lilly, whose portfolio is dominated by injectable biologics, is one large pharma company that is investing in more than just particular deals. In May 2015, it announced a new drug delivery and device innovation center in Cambridge, Massachusetts. Divakar Ramakrishnan, vice president of delivery and device research and development (R&D) at Lilly, said the company felt that a dedicated center was necessary because of "the amount of innovation we are seeing externally and the need to integrate it with our systems." The center is set to increase Lilly's drug delivery R&D capacity by 50% and be a hub for external partnerships. "We want to be able to make some strategic partnerships to enable some disruptive innovations," said Ramakrishnan.

Skin solutions and beyond

There are many ways drugs can enter the body (**Fig. 1**), but delivery through the skin is an approach with a track record of success and therefore remains a key focus for innovative drug delivery technologies. Subcutaneous injectable delivery devices are being developed to traverse epidermal layers. For example, Unilife is developing prefilled self-administered injectors that are preassembled and simple to use. After an injection, the patient peels off the device and throws it away. In 2014 Unilife inked a 15-year deal with Sanofi, worth at least $50 million, to be its sole provider of wearable injectors. In 2015 the company made deals with AbbVie as well as an agreement with MedImmune to develop customized wearable injectors for monoclonal antibodies in late-stage clinical development.

Non-invasive transdermal delivery systems are also gaining popularity owing to their ease of use. Similar to the familiar nicotine and hormone patches, newly approved transdermal pharmaceutical formulations include Neupro (rotigotine), a dopamine agonist for the treatment of Parkinson's disease, and Zecuity (sumatriptan) in the form of a single-use, battery-powered patch for migraine treatment. Newer patches in development are more powerful and allow for more effective and uniform adsorption.

Companies are continuing to explore other delivery routes for biologics, too, such as the lungs (**Fig. 1**). Pulmonary delivery with inhalers has long been a successful approach for respiratory disorders such as asthma, but it has proved much more challenging as a route for systemic delivery of biologics. Several attempts to introduce inhaled powdered insulin have failed. Exubera was launched by Pfizer and Nektar Therapeutics, but in response to low patient take-up, Pfizer quickly pulled out of the market back in 2007. In 2014, the US Food and Drug Administration approved another inhaled insulin powder, Afrezza, developed by MannKind and Sanofi, but in January this year Sanofi announced it was discontinuing its involvement in marketing the product, again because of low sales.

Efforts for oral delivery of biologics (**Fig. 1**), another highly challenging area, might hold more promise at present. In January 2016, MedImmune entered into a partnership with Rani Therapeutics to evaluate its oral drug delivery approach for metabolic diseases. The startup's 'robotic pill' can deliver biologics orally. As acidity builds in the small intestine, the pill's outer polymer layer dissolves, setting off a chemical reaction producing carbon dioxide, which then gently inflates a balloon-like structure. This pushes needles made of sugar into the intestinal wall to deliver preloaded drugs. The company is also working with Novartis.

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Devices take the lead

The rapid advancement of medical technology—particularly the growth of digital health and associated devices such as mobile apps, wearables and smartphones—is having a significant effect on drug delivery. These devices offer drug delivery developers not only new ways to access areas but also new ways to monitor the uptake of the drug.

Illustrating innovation in drug delivery devices are next-generation inhalers for respiratory diseases such as asthma and chronic obstructive pulmonary disease (COPD). "Linking drug delivery systems to compliance monitoring via healthcare IT is an area that I think will emerge as an attractive investment field," said King. "The advent of smartphones and delivery systems that can provide real-time feedback on compliance and clinical outcomes is quite exciting."

An example is the partnership between Novartis and mobile technology specialist Qualcomm to develop a completely integrated, connected smart inhaler for COPD, anticipated to launch in 2019. The improved device incorporates a small module that reports when the inhaler is used and sends the data to the patient's mobile phone, allowing individuals to monitor their progress and usage. In a similar agreement in 2015, GlaxoSmithKline and Propeller Health entered into a collaboration to develop a custom sensor for the Ellipta dry-powder asthma and COPD inhaler. That sensor collects and records data that are then sent to GlaxoSmithKline for analysis by its researchers. Boehringer Ingelheim, Teva and AstraZeneca are all working on integrating connected inhalers and apps.

Remotely controlled implanted devices are another new delivery method gaining attention, particularly for long-term delivery of hormones. The pioneer in this field is MIT spin-out Microchips Biotech, founded by serial entrepreneurs Robert Langer and Michael Cima. Cima describes the device, which is implanted under the skin, as the first artificial gland: "Where there is a deficiency or dysregulation, we can overcome that because we can replace that organ's function with an electronic device." The microchip device contains hundreds of hermetically sealed drug reservoirs from which microgram drug doses can be released over many years. The implant has been clinically validated in human studies of parathyroid hormone delivery in osteoporosis patients. In 2015, the company partnered with Teva Pharmaceuticals for a limited number of products, receiving $35 million up front with additional milestones.

The device's ability to deliver a more natural hormone profile and to be reprogrammed caught the attention of the Gates Foundation, which provided Microchips with funding to develop a contraceptive device. The company hopes it will reach the market by 2018.

Location-specific delivery

One of the biggest challenges remaining is how to deliver drugs to a specific location. This is crucial for ocular drug delivery. "Systemic administration does not deliver drugs to the intended site with an appropriate concentration," explains Paul Ashton, CEO of the drug delivery company pSivida. "Compared with drug delivery to other parts of the body, ophthalmic drug delivery has met with significant challenges posed by ocular barriers." pSivida's solution is the bioerodible eye implant Durasert—a miniaturized, injectable, sustained-release drug delivery system. Through nanostructuring it can sustain drug release over months or years. In 2011 pSivida received $2.3 million from Pfizer to create an implant for delivering Xalatan (latanoprost), its treatment for glaucoma and ocular hypertension. pSivida is also collaborating with Alimera Sciences for the delivery of the diabetic macular edema therapeutic Iluvien (fluocinolone acetonide).

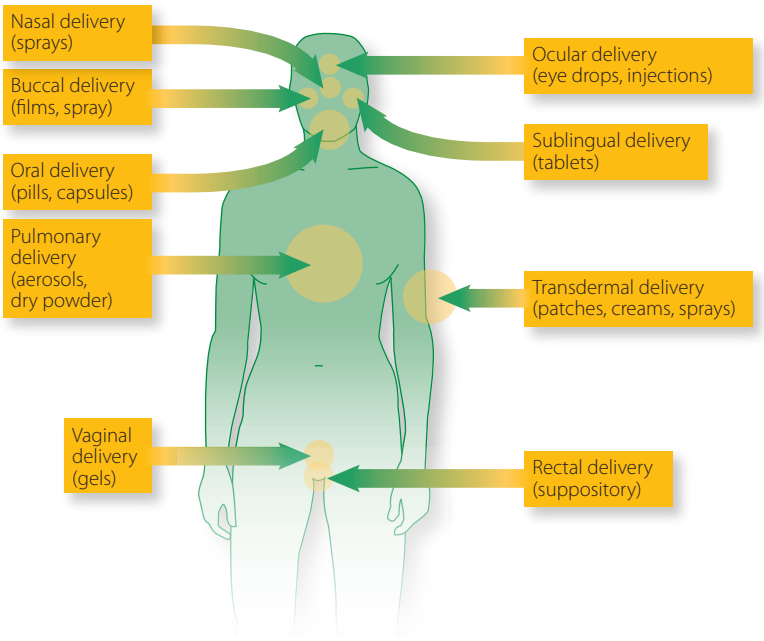

Figure 1: Illustration of the various drug delivery routes into the body. Currently delivery through the skin is a key focus route for innovative technologies such as subcutaneous injectable delivery devices and non-invasive transdermal systems.

More emphasis on localized drug delivery seems likely over the next decade. pSivida is also developing Tethadur, a platform made from fully erodible nanostructured elemental silicon that is designed to provide sustained local delivery of large biological molecules, including peptides, proteins and antibodies. Currently there is no approved technology that can accomplish this. Ashton added, "both our Durasert and Tethadur technologies have applications beyond ophthalmology." The company is working on an implant to provide pain relief for severe knee osteoarthritis.

The brain is another challenging organ for drug delivery in terms of location, but deals are currently being made in this area. "In the last three decades, pharma companies have spent billions of dollars, but have failed to deliver effective new brain drugs," said Jamal Temsamani, director of drug development at the biotech Vect-Horus. "The major roadblock is the blood-brain barrier. It excludes from the brain almost 100% of biopharmaceuticals and more than 98% of all small-molecule drugs." Vect-Horus and others are using 'Trojan horses'—proteins or small peptides capable of ferrying a drug payload, either directly coupled or encapsulated in a nanocarrier. Vect-Horus has already signed three collaboration agreements, including a 2015 deal with Sanofi to develop an antibody therapy for neurodegenerative diseases.

Momentum for the future

Anand Subramony, vice president of biopharmaceutical development at MedImmune, said there has been momentum in drug delivery technology during the past few years but says that growth "depends on how much risk people want to take in terms of investigating new emerging delivery systems." According to King, "the challenge for all sides is to be able to demonstrate that drug delivery systems really improve compliance, optimize the pharmacokinetic and pharmacodynamic profile of a drug and drive improved clinical outcomes. The results to date have been quite positive," he concluded.

Rachel Brazil is a freelance life sciences writer.