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Industry Update: The latest developments in therapeutic delivery

The present Industry Update covers the period 1–28 February 2014, with information sourced from company press releases, regulatory and patent agencies, as well as the scientific literature. February is traditionally the month of annual reports – looking back and looking forward, hence a number of market reports on past, present and future developments in drug delivery were released. An increased trend in deal making for targeted drug delivery, as in 2013, will continue to drive partnerships in 2014. In 2013, the number of drug delivery deals inked in the healthcare industry stood at close to 400 and added up to US\$2.3 billion. Closer collaboration or acquisition of drug delivery specialists by ‘big pharma’ are observed, such as Lupin and Nanomi, Teva and NuPathe, and Novo Nordisk and Zosano Pharma. Alternatively, one can see exclusive intellectual property or distribution rights deals such as MNG Pharma with Samyang Biopharmaceutical or Songry with a USA-based university. A few regulatory delays due to rejection (IntelGenx and Durect) joined the usually reported approvals, and iontophoresis was favorably re-evaluated in a recent US FDA hearing. A number of publications have proven that the sophistication and miniaturization of drug-delivery devices (inner-ear delivery) and particles (triggered supraparamagnetic and ‘sticky’ particles) is moving further at an ever faster pace.

Business development

Financing

2013 reports

Finding new ways to deliver existing drugs, ways to make a new drug more efficient or ways that make a patient’s life easier, are driving forces in the biotech and pharmaceutical industry, as reported in this journal monthly. Rather than ‘big pharma’ on its own, it is their partnerships with smaller specialty companies that bring new solutions to the market, and 2013 again saw several big deals. Several larger deals of the giants in the pharmaceutical industry who license technology from smaller, specialty start-ups dedicated to a particular space were closed in 2013. These are mainly hinging on milestones down the road as opposed to a huge upfront payment. The promised funds add up to more than US\$2.3 billion, not including the amounts yet to be disclosed [1]. Over the course of February, *Research and Markets* published

several reports, including market forecasts to 2017. In the European market this was worth \$39.9 billion in 2012 alone, segmenting the drug-delivery market into oral, pulmonary, transdermal, injectable, ocular, nasal, topical, implantable and transmucosal drug delivery. Over the years, drug-delivery technologies have grown phenomenally from plain drug reformulation and release technologies, to innovative platforms that hold a huge potential for the effective delivery of biologicals and novel drugs. Patent expiration of certain blockbuster drugs, a growing demand for self-administration and home healthcare devices, rising incidence of chronic diseases such as cardiovascular diseases, diabetes and cancer, and a growing focus on pediatric and geriatric patients, are accelerating the growth of this market. However, drug failures, recalls and technical barriers are estimated to hamper this expansion. Expanding applications of drug delivery into niche therapeutic areas, strategic

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collaborations, and self-administration and home-care drug-delivery devices represent vast opportunities for key players in this market [2].

Lupin Ltd

Lupin Ltd, Mumbai, India, has bought the Dutch delivery technology company Nanomi BV, thereby positioning the Indian generics firm in the injectables space. The deal, the financial terms of which were not disclosed, was announced in a filing on the Bombay Stock Exchange (BSE) on 3 February. Nanomi manufactures uniform custom-made monosphere particles for pharmaceutical and life science specialty products [3].

InSite Vision Inc.

InSite Vision Inc., CA, USA, announced on 4 February that 2013 net sales of Besivance®, for the treatment of bacterial conjunctivitis, triggered an additional \$1 million milestone payment from the Besivance royalty purchasers, SWK Funding LLC (a wholly owned subsidiary of SWK Holdings Corporation, TX, USA), and Bess Royalty, L.P. The \$16 million total cash consideration to InSite Vision included a \$15 million upfront payment in April 2013 and a \$1 million milestone payment, which will be paid in February 2014. The company is developing new ophthalmologic products for unmet eye care needs based on its DuraSite® platform technologies that extend the duration of drug retention on the surface of the eye, thereby reducing the frequency of treatment and improving the efficacy of topical drugs. Currently, InSite Vision is preparing a new drug application (NDA) for commercial approval by the US FDA of BromSite™ for the prevention of pain and inflammation associated with ocular surgery. The company is also advancing two novel ophthalmic therapeutics through Phase III clinical studies: AzaSite Plus™ and DexaSite™ for the treatment of eye infections, and has a pipeline of earlier stage product candidates based on its platform technologies [4].

Teva Pharmaceutical Industries Ltd

Teva Pharmaceutical Industries Ltd, Jerusalem, Israel, announced on 21 February the successful completion of the tender offer by Train Merger Sub, Inc., a wholly owned subsidiary of Teva, for all of the outstanding shares of common stock of NuPathe Inc., PA, USA. Upon completion of the merger, NuPathe will become a wholly owned subsidiary of Teva. NuPathe's first commercial product is ZECURITY® (sumatriptan iontophoretic transdermal system [patch]) for the acute treatment of migraine, and it has a strong pipeline based on biodegradable implant technology that allows the delivery of therapeutic levels of medication over a

period of months with a single dose. Other candidates are NP201, for the continuous symptomatic treatment of Parkinson's disease, which provides up to 2 months of continuous delivery, and NP202 for the treatment of schizophrenia and bipolar disorder, by providing 3 months of continuous delivery of risperidone, an atypical antipsychotic [5].

Novo Nordisk

Zosano Pharma, CA, USA, the developer of a microneedle patch for various applications, signed a deal on 5 February with Novo Nordisk (NC, USA) to deliver semaglutide, an analogue used to treat Type 2 diabetes. As part of the agreement Zosano will collect \$60 million for the first product in the deal and \$55 million for each additional product. The Zosano Pharma patch delivers compounds such as peptides, proteins, small molecules and vaccines into the skin's outer layer using a dry coating on an array of titanium microneedles. Novo will have exclusive worldwide development and commercialization licensing of the product. The patch has passed early- and mid-stage trials in more than 450 patients [6].

Cystinosis Research Foundation

The Cystinosis Research Foundation (CRF [CA, USA]) reported on 19 February that in 2013 it had awarded more than \$2 million to researchers investigating better treatments for cystinosis, a rare metabolic and genetic disease affecting children and young adults. In 2013 the FDA gave final approval to an improved cystinosis treatment originally discovered by CRF-funded researchers. Although stem cell and gene therapy holds promise for a cure, the FDA approval of delayed-release cysteamine was the most significant improvement in the treatment of cystinosis in decades. This new treatment would replace the need for hourly eye drops to treat corneal cystinosis. The CRF has raised more than \$23 million and funded 114 studies and fellowships in 11 countries since 2003. In addition, the Scientific Review Board, a renowned group of cystinosis experts and scientists who evaluate every research application, believe there will be an autologous stem cell trial for patients with cystinosis within 4 years. Cystinosis slowly destroys every organ in the body, including the liver, kidneys, eyes, muscles, thyroid and brain. There is a medicine – cysteamine – that prolongs the children's lives, but there is currently no cure [7,8].

Licensing & collaboration agreements

Sonrgy

On 10 February, San Diego-based drug-delivery company Sonrgy acquired exclusive rights to an

ultrasound-based nanotech delivery platform developed at the University of California, San Diego, CA, USA. The license gives Sonrgy global development and marketing rights to the technology, which uses a focused beam of ultrasound to release drugs at the site of a tumor, which are themselves delivered by nanocarriers. This might address challenges related to stability and controlled release in nanoscale drug delivery [9].

Biodelivery

With funds from a direct offering, BioDelivery Sciences (NC, USA) announced it was looking to raise \$60 million to boost programs in its lineup, including the launch of its opioid dependence film Bunavail™, making use of the company's own Bema® delivery technology, and continue on the approval path for its pain gel for diabetic neuropathy. The company signed the deal (confirmed on 13 February 2014) to ramp up to the launch of its Bunavail opioid dependence oral film in particular, preparing for a 7 June FDA decision. Bunavail, which is a bioerodible film placed on the inner lining of the cheek, quickly delivers a dose of the drug buprenorphine/naloxone, dissolving within 15 to 30 min across the mucous membrane. They are also looking to advance its Phase III topical pain gel to treat symptoms of painful diabetic neuropathy with the new funding [10].

Development & manufacturing agreements

BMG Pharma

BMG Pharma S.r.l. (Milan, Italy) announced on 17 February that it has signed an exclusive distribution agreement with Samyang Biopharmaceutical Corporation, granting them rights to promote, sell and market its novel mucositis management product GelX® in the territory of South Korea. It will receive an undisclosed down payment from Samyang Biopharmaceutical Corporation, who will exclusively market GelX in South Korea. GelX provides fast pain relief and eliminates swallowing issues and discomfort associated with mucositis related to chemotherapy, radiotherapy and other pharmacologic therapies. It has a mechanical action indicated for the management and relief of pain by adhering to the mucosal surface of the mouth, soothing the lesions caused by chemotherapy and/or radiation therapy [11].

Regulatory news & approvals

Product approval

IntelGenx Technologies & Redhill Biopharma

Canadian delivery specialist IntelGenx Technologies and Israeli partner RedHill Biopharma received on 4 February an FDA rejection for their dissolvable migraine film. However, both companies reported that

this not related to study data but third-party manufacturing practices. IntelGenx's VersaFilm™ delivery technology is used with Merck's migraine drug Maxalt® and the thin film is designed to dissolve faster in the mouth than the available disintegrating tablet form. IntelGenx already used VersaFilm to deliver drugs for depression, erectile dysfunction and neuropathic pain. Both companies intend to go for European approval, having already had a meeting with German regulators in October 2013 and they are expecting approval later this year [12].

Durect

On 18 February, Durect, CA, USA, suffered a regulatory setback with the FDA rejection of its Posidur™ treatment for postoperative pain, requesting further safety data for the proposed label. Posidur is a postoperative pain-relief depot that utilizes Durect's patented SABER® technology to deliver bupivacaine to provide up to 3 days of pain relief after surgery. The company is in discussions with potential partners regarding licensing development and commercialization rights [13].

Iontophoresis

Iontophoresis, the use of an electric current to deliver drugs, is to be re-evaluated by the FDA to determine if restrictions for the technique should be lessened with technology advances, as reported from *Medscape Medical News*. The FDA held a hearing on 21 February in which an advisory panel recommended to the regulators to reconsider the current classification of class 2, which is the same category as jet injectors and infusion pumps. However, for the delivery of certain other drugs, the devices are labeled as class 3, the same category as artificial disc replacements and implanted neurostimulators, which must undergo a full drug-like premarket application. The panel recommended to reassign these electrophoresis devices down to class 2 for local drug delivery, treating them like any noninvasive device in view of sufficient safety data presented. The main adverse events of iontophoresis are burns on the skin and studies have shown that skin reactions are mostly mild without the need for treatment [14].

Teva

On 26 February, European regulatory authorities gave Teva (Jerusalem, Israel) a positive opinion for its DuoResp® Spiromax® inhalation powder, designed to treat asthma and chronic obstructive pulmonary disease (COPD). The inhaler is being tested in two late-stage trials that are expected to be completed this year, but are not pivotal for final market approval. The DuoResp Spiromax inhaler, a breath-actuated technology to

deliver a consistent dose of the dry powder, uses the corticosteroid budesonide to treat inflammation associated with the lung conditions, as well as the beta-2 agonist formoterol fumarate dihydrate to relieve constriction of the airways. Teva is competing in the asthma and COPD market with GlaxoSmithKline's and Theravance's EU-approved (November 2013) Relvar® Ellipta®, as well as their Anoro™ Ellipta and Breo™ Ellipta™ products [15].

Clinical trials

Invion

On 19 February, 3M Drug Delivery Systems joined forces with Invion, Brisbane, Australia, to develop inhaled drugs for inflammatory airway diseases. Using 3M's pressurized metered-dose inhalation technology, the two companies jointly will address toxicology and Phase I studies of the delivery of Invion's INV102 nadolol beta blocker, as well as its INV104 zafirlukast leukotriene receptor antagonist, being the first inhaled delivery formulation. Nadolol, approved for high blood pressure, migraine and chest pain, could benefit from the new inhaled version for conditions such as asthma, COPD and cystic fibrosis, according to the company. Invion also has two clinical Phase II trials for smoking cessation ongoing [16].

Patents

Mallinckrodt

Mallinckrodt, Dublin, Ireland, were granted US Patent Number 8,658,631 on February 25, which contains composition claims directed to unique design, formulation, pharmacokinetic and release characteristics of XARTEMIS™ XR. XARTEMIS XR is an investigational extended-release oral formulation of oxycodone and acetaminophen specifically designed with immediate- and extended-release components that has been studied with twice-daily dosing for the management of acute pain in a post-surgical model. The release profile of XARTEMIS XR combines Mallinckrodt-proprietary technology and Depomed's advanced Acuform® drug-delivery technology [17].

Publications

Nasal vaccine delivery

On 12 February, researchers at Duke University reported to have shown in early tests that a nasal vaccine for West Nile virus is effective in mice after two doses as opposed to the traditional three for other vaccines. The nasal administration, presented at the American Society for Microbiology Biodefense and Emerging Diseases Research Meeting in Washington, DC, USA, could offer a quick-hit solution to what has become a global issue in that currently no vaccine for the disease

is available for humans. Duke researchers modified an existing experimental nasal formulation of antigens to cut the number of immunizations needed from three in 3 weeks to two over a period of 2 weeks [18].

Tailored delivery nanoparticles

Research in drug delivery is moving further and further into the nanoscale and new manufacturing techniques are important to bring them closer to the clinic. As communicated on 28 February, scientists at the Japanese Okinawa Institute of Science and Technology have reduced nanoparticles down to their most effective parts to create them in one step, avoiding potentially dangerous chemicals. Using an iron and silver core surrounded by a silicon shell, they have developed nanoparticles that are magnetic, biocompatible and suitable for imaging, as published in the journal *Nanoscale*. The nanoparticles can be tailor-made for different functions around the core, including drug delivery. Given that the particles are superparamagnetic, controlled drug delivery inside the body might be feasible through a magnetic field [19].

Inner-ear delivery

A new miniaturized wearable device is being investigated for its potential in the delivery of drugs to the inner ear that might potentially treat hearing loss in a less invasive way than via constant injection. Researchers at Draper Laboratory in Cambridge, MA, USA, published on 26 February in the Royal Chemical Society's journal *Lab on a Chip* a small intracochlear device designed to treat sensorineural hearing loss by delivering drugs into the fluid of the inner ear, bypassing injections. In collaboration with the Massachusetts Eye and Ear Infirmary, the device is designed to be used with drugs currently in development for hearing loss. The device uses a drug reservoir that pushes drugs out, while it maintains crucial pressurization in the ear drawing other fluids in. The researchers have tested the device both *in vitro* and *in vivo* with successful results, and the next step will involve long-term testing, as well as further miniaturization. The National Institutes of Health funded the project through its own National Institute on Deafness and other Communication Disorders [20].

'Sticky' nanoparticles could help keep arteries open without a stent

Stenting procedures have been effectively used for years, but despite being minimally invasive when it comes to drug-eluting stents, alternative means of delivering drugs such as paclitaxel are under investigation according to a new study published in the journal *Nanomedicine: Nanotechnology, Biology and Medicine*,

on 19 February. Researchers from Clemson University, SC, USA, have developed injectable nanoparticles that could deliver drugs slowly to prevent the closing of arteries over time without a stenting procedure. The 'sticky' particles latch onto damaged tissue by attaching to the rough edges of the artery walls, preventing the growth of scar tissue and allowing the artery to heal. One of the drugs proposed is paclitaxel, used in many stents for the same purpose [21,22].

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