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Industry update

The present industry update covers the period 1–31 December 2014, with information sourced from company press releases, regulatory and patent agencies as well as the scientific literature. December is traditionally the month of last year-closure announcements or starting looking back into the recent past. The financing community for biotech seems on strong recovery as indicated by reports, but also in view of many deals discussed in these proceedings. The teaming up of a company owning a (novel) active ingredient and another one having a drug-delivery device addressing certain limitations proves to be a recipe for success (Asante, Unilife, Catalent and Endo Pharmaceuticals). Easier use of established treatments such as for diabetes (Asante, Medtronic) as well as expanding limited therapeutic windows such as in stroke (NuvOx Pharma, gelatine-based particles) is becoming as common strategies as the increasing use of nanotechnology (ProNAi, 3D vaccines) and highly integrated devices (mPhase Technologies, Microchip Biotech, Dexcom).

Business development

Financing

Biotech initial public offerings

Biotechnology companies in 2014 have had the best year on the initial public offering (IPO) market since the dot-com boom and hitting their highest point to date of the millennium with more IPOs from biotech and biopharmaceutical companies in 2014 than in the previous 3 years combined in the USA totaling in US\$1.29 billion total capital raised with global investments in the space reaching \$15.3 billion in the first 11 months of the year [1].

Cytosorbents

Starting on 24 December, CytoSorbents, Monmouth Junction, NJ, USA, will begin trading on the Nasdaq Capital Market. The company made a commercialization and distribution agreement with Fresenius Medical Care for 28 countries with its CytoSorb® extracorporeal cytokine adsorber to reduce inflammation in critically ill patients. The technology is based on biocompatible, highly porous polymer beads that can actively

remove toxic substances from blood and other bodily fluids by pore capture and surface adsorption. CytoSorbents further has a number of novel products under development based upon this unique blood purification technology, and is planning a pivotal cardiac surgery trial in the USA to gain also more visibility with investors [2,3].

Asante

Asante, Sunnyvale, CA, USA, filed in December for \$45 million an IPO to progress with its Snap Insulin Pump System market introduction a field dominated mainly by large medical device manufacturers, with Medtronic having the majority share and Johnson & Johnson and Roche amongst others being relevant players as well. The pump system has a modular design with prefilled insulin cartridges and disposable pump bodies to improve conventional pumps requiring the user to fill the pump reservoir with insulin multiple times a week. With the system being cleared by the US FDA in January 2013 for use by adults with Eli Lilly's Humalog® insulin cartridges accounting for about half

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of the prefilled insulin cartridge market, the company hopes that its insulin pump provides to patients greater ease of use [4].

Dexcom

In the same therapeutic area Dexcom, CA, USA, received FDA approval for a new artificial pancreas algorithm to improve the accuracy and performance of its Dexcom G4 Platinum product for blood glucose monitoring its continuous glucose monitoring device. It had also recently a mobile communications device for diabetes monitoring approved. Dexcom Share, which extends the Dexcom G4 Platinum continuous glucose monitoring, wirelessly transmits patients' glucose levels through a smartphone to allow patients to track information [5].

US\$20M NIH grant for intravaginal ring to prevent HIV

The NIH, MA, USA, awarded \$20 million to a collaboration consortium led by the Oak Crest Institute of Science to develop a novel intravaginal ring designed to prevent the spread of sexually transmitted HIV in women. While intravaginal rings show promise as a drug-delivery system to prevent HIV infection, most current prototypes cannot deliver the necessary combination of effective HIV medicines. The platform under development has shown to independently and simultaneously deliver up to five different drugs with controlled doses enabling to find the best combination of drugs for HIV prevention. University of Texas Medical Branch will lead efforts to determine drug safety and efficacy of the antiretroviral-releasing intravaginal ring by conducting preclinical and clinical studies. These devices are relatively cost-effective compared with other treatments, and they are capable of both rapid and sustained drug delivery for at least a month without refrigeration [6].

Provodine® to treat Ebola

Microdermis Corporation, NJ, USA, announced on 3 December that its new antiseptic product, Provodine®, which incorporates a novel drug-dermal delivery system, will be deployed by the US Army in the fight against Ebola virus in West Africa. Preliminary testing by the US Army Medical Research Institute of Infectious Diseases has demonstrated that Provodine® provides superior antiseptic protection within 30 s of exposure with a >99% kill rate against Ebola virus particles making it potentially a final barrier to viral exposure for healthcare workers and emergency responders. This is also extremely important in view that to date a total of 335 relief workers have died while fighting to prevent the transmission of Ebola virus infections in West Africa [7].

Oramed

Oramed Pharmaceuticals, Inc., Jerusalem, Israel, a developer of oral drug-delivery systems, announced on 10 December that it has received \$5 million in connection with the definitive agreement with Guangxi Wuzhou Pharmaceutical Co., Ltd, a subsidiary of Guangxi Wuzhou Zhongheng Group Company Ltd, an investment holding company publicly traded on the Shanghai Stock Exchange. Oramed intends to use these net proceeds for planned US focused clinical development programs for its oral insulin for Type 1 and Type 2 diabetes indications, for preclinical and clinical studies of its oral GLP-1 analog project, and for general corporate purposes [8].

Licensing & collaboration agreements

NuvOx Pharma

NuvOx Pharma (AZ, USA) exclusively licensed on 3 December the US Patent Application 20140004099 entitled 'Dodecafluoropentane emulsion as a stroke and ischemia therapy' from the University of Arkansas for Medical Sciences. The inventors Drs Culp and Skinner, pioneers in the treatment of stroke, discovered that low doses of dodecafluoropentane emulsion (DDFPe) reduced brain damage from stroke by over 80%. The work received an award from the Journal of Vascular Interventional Radiology. Currently, tPA is the only FDA approved drug for treating stroke and only about 6% of patients are treated with tPA because of the narrow time window of 3 h in which the drug can be administered to patients and DDFPe may extend the useful time window for efficacy of tPA to at least 9 h. The company plans to conduct clinical testing of DDFPe in stroke and the indication is available for licensing [9].

Development & manufacturing agreements

Unilife

Unilife Corporation, York, PA, USA, a developer and supplier of injectable drug-delivery systems, announced on 2 December the signing of a worldwide 10-year Commercial Supply Agreement with a global pharmaceutical company, its name to remain confidential, for the use of the Depot-ject™ delivery system with an approved ocular injection therapy. Commercial availability of Depot-ject with this therapy is expected to be available after a 12–24-month process of customization and regulatory approval for the drug-device combination. Compared with conventional practices, Depot-ject is designed to allow to deliver the therapy into the eye through an injection helping to protect a drug depot. Unilife has granted exclusive access to Depot-ject for use with the target drug in the relevant therapeutic area [10].

Catalent

Catalent Pharma Solutions, Somerset, NJ, USA, announced on 2 December to collaborate with Valeion Therapeutics, LLC, focused on the development of biotherapeutics for orphan genetic diseases. The collaboration will focus on two lead product candidates: for the delivery of muscle–protein fusions, and treatment of multiple indications, in the fields of muscular dystrophies, glycogen storage diseases, myopathies and enzyme-deficiency disorders. Catalent will provide the biotechnology, process development and cGMP manufacturing utilizing a novel antibody-based targeting system, with enhanced intracellular delivery of functional proteins, oligonucleotides and small molecules. Catalent's \$26m Madison biomanufacturing facility quadrupled the company's biologics manufacturing capacity [11].

Regulatory news & approvals

Product approval

Teva

Teva Pharmaceutical Industries Ltd, Jerusalem, Israel, announced on 19 December that the FDA approved QNASL® (beclomethasone dipropionate) for the treatment of nasal symptoms associated with allergic rhinitis in children 4–11 years of age. It delivers effective symptom relief at one-fourth of the dosage approved to treat adults and is the first and only waterless hydrofluoroalkane nasal allergy treatment to be approved for use in patients as young as four years of age. The drug is expected to become available by prescription in February 2015 [12].

Endo Pharmaceuticals

Endo Pharmaceuticals Inc., NC, USA, a subsidiary of Endo International plc, and BioDelivery Sciences International, Inc., NC, USA, announced on 23 December that they have submitted a new drug application for Buprenorphine HCl Buccal Film to the FDA under development for the management of severe pain. The drug uses its patented BioErodible MucoAdhesive® drug-delivery technology to deliver buprenorphine across the buccal mucosa. Buprenorphine HCl Buccal Film is being developed and will be commercialized through a worldwide license and development agreement between Endo Pharmaceuticals and BioDelivery Sciences International, Inc. Two pivotal double-blind randomized, placebo-controlled, enriched-enrollment Phase III studies demonstrated safety and efficacy in patients with chronic lower back pain [13,14].

Arrowhead

Arrowhead Research Corporation, CA, USA, added on 22 December another entrant into clinical trials to

commercialize the first RNAi-based compound. It had submitted its investigational new drug application for the candidate ARC-520 to treat of chronic hepatitis B. Two Phase IIb human clinical trials will primarily test the extent of B surface antigen decline compared with placebo after ARC-520 injection in combination with the standard drugs entecavir or tenofovir. It uses Arrowhead's dynamic polyconjugates delivery system, whereby small interfering RNA is carried by nanoparticles that are designed to have properties similar to viruses. One trial will test patients who are negative for hepatitis B e-antigen, and the other those who are positive for hepatitis B e-antigen. The company claims this polymer-based delivery method is superior to lipid-based systems [15].

Medtronic

Medtronic, MN, USA, said in a 19 December release that it completed global evaluations of its new insulin delivery system on the way to an artificial pancreas. This system is easier to use and includes a new predictive low glucose management algorithm that automatically stops the delivery of insulin when a sensor detects a glucose level that is approaching a predetermined low level and resumes when glucose levels have recovered, the company said in a press release. Manufacturing of the system is underway, and it will be introduced in select countries early 2015. A pivotal trial is currently being conducted in eight US trial centers to evaluate predictive low glucose management technology. [16].

Insys Therapeutics

Insys Therapeutics, Inc., AZ, USA, announced on 9 December that the FDA has granted orphan drug designation to its liposome entrapped paclitaxel easy to use candidate for the treatment of gastric cancer. Liposome entrapped paclitaxel easy to use is an improved formulation of paclitaxel, a widely used chemotherapeutic agent, by entrapping the paclitaxel with liposomes, potentially reducing toxicity, while maintaining or enhancing efficacy of the cancer-fighting paclitaxel [17].

Clinical trials

Cerulean

Cerulean Pharma, MA, USA, announced on 23 December that the first patient has received its Phase I/IIa cancer candidate, CRLX301, delivered using its RNA-based dynamic tumor targeting platform. Docetaxel for the treatment of breast cancer, non-small-cell lung cancer and prostate cancer, as well as Sun Pharma's generic cancer medication Docefrez preclinical data show that its nanoparticle–drug conjugate version of docetaxel appears safer and more

efficacious than those older medications and could have new therapeutic benefits in the treatment of multidrug-resistant tumor models [18].

ProNAi

ProNAi Therapeutics, MI, USA, reported on 9 December positive results from its so-called DNAi-based candidate PNT2258 for nonHodgkin lymphoma. Using Marina Biotech's, MA, USA, Smarticles® delivery technology, the results from the Phase II trial show meaningful therapeutic outcomes and a durable clinical response, according to the company. It is the first DNAi-based therapeutic being tested while RNAi is more commonly used to shut down genes [19].

Patents

mPhase Technologies

mPhase Technologies Inc., NJ, USA, provided in December an update on its patent application for a drug-delivery system that is based on mPhase Technologies' award winning advanced battery technology as recognized by Frost and Sullivan's 2013 North American Advanced Battery Technology Innovation Award. This research led to the expansion of mPhase's intellectual property which utilizes mPhase's smart surface technology. In February of 2013 mPhase filed a US Letter Patent Application for a novel drug-delivery system based on its Smart Surface technology enabling the automatic dispensing of a preset dosage of a drug agent or medication. The drug-delivery system includes a housing of one or more reservoirs; each having a medical agent hermetically sealed therein. A membrane extends across each of the one or more reservoirs which is adapted to allow the medical agents to pass there through in response to external stimuli, such as physical puncturing, melting the membranes through use of heating elements or electrowetting in response to a voltage pulse. A wicking material extends across the membranes through which the medical agents are dispensed to a patient. The overall dispensing device can be reduced in size, allowing the drug-delivery device to be located and attached to broader areas of the patient's body for expanded medical applications and treatment [20].

Publications

Hydrolyzable polymer for drug delivery

Researchers at the University of Illinois at Urbana-Champaign, IL, USA, published on 3 December, the development of a hydrolyzable polymer that can be used as a drug-delivery material. The polyurea bonding material, which has been used in paint and adhesives in the past, could be tailored to degrade over a specific period of time, making it usable in

drug-delivery contexts. The highly inert urea bond makes the inexpensive polymer extremely stable, a property that is suitable for some long-lasting applications. The inventors Dr Cheng and colleagues have developed a class of hindered urea bond-containing polymeric materials, poly(hindered urea)s, cost-effective polymers that can be designed to degrade over a specified time period, making them potentially useful in biomedical and other applications [21].

Injectable 3D vaccines

Researchers at the Wyss Institute for Biologically Inspired Engineering at Harvard University and Harvard's School of Engineering and Applied Sciences, MA, USA, published in 8 December a nonsurgical injection of programmable biomaterial that spontaneously assembles *in vivo* into a 3D structure and could fight and help prevent cancer as well as infectious diseases such as HIV. These 3D structures use minimally invasive delivery to enrich and activate a host's immune cells to target cancer or otherwise harmful cells *in vivo*. Tiny biodegradable rod-like structures made from silica, known as mesoporous silica rods, can be loaded with biological and chemical drug components and then delivered by transdermal injection. The rods then spontaneously assemble at the vaccination site to form a 3D scaffold. Surface properties and pore size of the mesoporous silica rods can be tuned, and therefore controlling the introduction and release of various proteins and drugs [22,23].

Microchips Biotech

Microchips Biotech, Lexington, MA, USA, said on 17 December it plans new studies having completed development and clinical demonstration of the drug-delivering implant. The company claims that its device is a fingernail-sized implant placed under the skin can deliver drugs for up to 16 years without replacement. The osteoporosis version of the chip underwent a 2012 first-in-human study in women with the disease, showing increased bone mass comparable to patients with daily injections. The chip comes with reservoirs to hold drugs safely in the body until their seals melt away at predictable intervals to release the drug at the desired dose making it potentially programmable to release in response to certain stimuli (such as low blood sugar), on a timed schedule or on demand from a wireless port [24].

Gelatin-based nanoparticles

South Korean researchers at the University of Illinois Urbana-Champaign, IL, USA, have developed a delivery technique that uses bits of gelatin to encapsulate drugs and carry them to the brain without

surgery. The method shows promise for stroke patients, extending the window during which treatment can be effective. The scientists coated the gelatin nanoparticles with the drug osteopontin, which reduces inflammation and prevents brain cell death after a stroke according to the announcement. To get past the blood–brain barrier, the particles are designed for nasal delivery. As published on 24 December the importance of this delivery method is that it allows for a longer amount of time to treat stroke patients. Gelatin itself is biocompatible and biodegradable, characterized as generally safe by the FDA and is

especially suited to targeting the brain, as the organ houses many enzymes for which it is a substrate [25].

Financial & competing interests disclosure

O Steinbach is an employee of Royal Philips Electronics North America Corporation. The author has no other relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript apart from those disclosed.

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