Industry update: the latest developments in therapeutic delivery

The present industry update covers the period 1–31 March 2015, with information sourced from mainly company press releases, regulatory and patent agencies. In a transaction that has been valued at over US\$70 billion Actavis has announced it completed the acquisition of Allergan. A number of companies including Columbia Labs, Biohaven and Oxis have announced collaborations/licensing deals in the area of drug delivery technologies. March also saw the announcements from a number of companies including Delcath, Novan and Flamel, of positive clinical trial data for products utilizing different therapeutic delivery options.

Keywords: clinical trial • liposomes • nanoparticle • nanotech

Acquisitions & licensing

Actavis completes Allergan acquisition

On 17 March Actavis plc (Dublin, Ireland) announced that it has completed the acquisition of the pharmaceutical company Allergan, Inc. The deal announced consisted of a cash and equity transaction valued at approximately US\$70.5 billion. With a combined annual pro forma revenue of more than US\$23 billion anticipated in 2015, the acquisition will create a top 10 global pharmaceutical company, in terms of sales revenue.

Announcing the completion of the acquisition Brent Saunders, CEO and President of Actavis stated: “Supporting the growth of this innovative industry model is our strategically focused R&D engine, built on novel compounds in specialty and primary care markets where there is significant unmet medical need, and fuelled by approximately US\$1.7 billion in annual investment. With an innovative product development portfolio exceeding 20 near-term projects and a world class generics pipeline, which continues to hold an industry-leading position in First-to-File opportunities in the USA and more than 1000 marketing authorizations globally, we are uniquely positioned within our

industry to ensure our development activities support sustainable long-term organic growth” [1].

Columbia Labs license intravaginal ring delivery technology

The licensing exclusive worldwide rights to a novel intravaginal ring (IVR) technology for the delivery of one or more pharmaceuticals with varying dosages and release rates in a single segmented ring was announced by Columbia Laboratories, Inc. (MA, USA) on 30 March.

This technology was co-developed by Dr Robert Langer from the Massachusetts Institute of Technology (MIT) and Dr William Crowley from Massachusetts General Hospital (MGH) and Harvard Medical School. As part of the licensing deal the co-inventors Drs Langer and Crowley will join Columbia as strategic advisors.

Commenting on the announcement of the agreement Dr Langer said: “This technology affords the opportunity to expand intravaginal delivery of drugs to include larger molecules, such as peptides, alone and in combination.” According to Dr Crowley, “A self-administered vaginal ring provides patients with a simplified drug delivery sys-

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tem and should improve compliance and therefore treatment effectiveness.”

The advantage of the segmented IVR developed by Drs Crowley and Langer is that the polymer composition and its segmentation capability confer the ability to deliver drugs at different dosages and release rates. A proof of concept study using drugs such as progesterone and leuprolide has already been carried out and has demonstrated sustained release for up to 3 weeks.

According to the terms of the licensing deal Columbia has agreed to minimum annual expenditures to develop novel products using the IVR technology, various stages of product development and commercialization will trigger undisclosed milestone payments to MGH and MIT. The agreement also allows for royalty and sublicense revenues to accrue to MGH and MIT from products utilizing the IVR technology [2].

Biohaven to licence Zydis from Catalent for antianxiety product

Portage Biotech, Inc. (Toronto, Canada) announced on 24 March that a company it holds a 54% equity stake in, Biohaven Pharmaceutical Holding Company Limited (Biohaven, CT, USA), has entered into an exclusive world-wide agreement with Catalent Pharma Solutions (NJ, USA) to provide Catalent's Zydis® Orally Disintegrating Tablet technology for Biohaven's lead drug development candidate, BHV-0223. Catalent's Zydis technology is a proprietary, freeze-dried, oral solid dosage form that disperses instantly in the mouth – no water is required. The Zydis technology has already been used in over 20 commercial products in 50 different countries. Biohaven's lead candidate is a reformulated glutamate modulating agent under development for treatment-resistant mood and anxiety disorders [3].

Product license & commercialization agreement for MultiCell Immunotherapeutics & Oxis Biotech

MultiCell Immunotherapeutics, Inc. (MCIT, RI, USA), a majority owned subsidiary of MultiCell Technologies, Inc. (MCET) announced on 12 March that it had signed an agreement with the Florida-based immunotherapeutic company, Oxis Biotech, Inc. (FL, USA). The R&D and product license agreement will see three novel antibody-drug conjugates (ADCs) containing Oxis' lead drug candidates being developed using MCIT's proprietary ADC platform technology. Oxis disclosed that the proposed product candidates are in the areas of the treatment of triple-negative breast cancer, multiple myeloma and associated osteolytic lesions.

Under the terms of the agreement disclosed, Oxis has paid MCIT a license fee of US\$500,000, and will reimburse development costs of up to US\$1.125 million. Payments of US\$12.75 million in clinical development milestones have been agreed and Oxis was granted an option to purchase manufacturing rights to the three ADCs upon payment of an additional US\$10 million. Other terms also include a worldwide exclusive license to sell the three product candidates under development and a proposed royalty of 3% of net yearly sales. As part of the agreement MCIT has retained all rights to its ADC platform for all therapeutic indications, and is free to pursue its own drug development programs and to partner with other interested pharmaceutical and biotechnology companies.

MCIT's ADC platform technology is based on proprietary multivalent, cleavable linkers that allow the release of the conjugated therapeutic actives both intra- or extracellularly upon binding of the antibody to the target cell [4].

Industry updates

Report claims nanotech to be the next big thing in cancer drug delivery

5 March saw the release of a Frost & Sullivan (CA, USA) report entitled: 'A competitive analysis of the global breast cancer therapeutics market'. According to the report research breakthroughs are going to drive delivery of cancer drugs using nanoparticles. The report highlights novel developments such as nanococoons and micro bubble liposome particle delivery as some of the potential game changing technologies in this area. A useful summary of the contents of the report is also available in an 'In-pharmatechnologist' article [5,6].

Increase in demand for high-quality vegetarian capsules

According to a press release on 26 March announcing a US\$25 million investment to its increase production capacity and deliver further quality enhancements for its vegetarian capsules, Capsugel (NJ, USA) there is a significant increase globally in the demand for vegetarian encapsulation options for both the health and nutrition and pharmaceutical segments.

Announcing the investment Guido Driesen, President and Chief Executive Officer, Capsugel stated: "Consumers' appetite for clean-label products is at an all-time high, and continuing to grow. This trend has contributed to a significant increase in demand for high-quality vegetarian capsules."

Capsugel's vegetarian portfolio includes Vcaps®, Vcaps® Plus, DRcaps™ and Plantcaps® capsules. The company is investing in all four of these products but

with a particular emphasis on increasing production of its premium Vcaps Plus vegetarian capsules [7].

Collaborations

Althea to collaborate with two more pharmaceutical companies

Ajinomoto Althea, Inc. (CA, USA) announced on 31 March that it has partnered with two more pharmaceutical companies. These partnerships will allow the undisclosed companies to access Althea's Crystalomics® drug delivery technology. According to company reports 4 out of 10 of the world's top pharmaceutical companies have already signed agreements with Althea since Ajinomoto's acquisition of Althea and the Crystalomics technology. Althea's proprietary Crystalomics formulation technology enables formulations including crystal suspensions of the active pharmaceutical ingredient and it is claimed that products formulated with the Crystalomics technology can be delivered at low viscosity and high concentrations in a small volume. It is claimed that the Crystalomics technology enables manufacture of dosages with an extended release of a week or longer [8].

Regulatory news & approvals

Adamis provides update on epinephrine prefilled syringe new drug application

Adamis Pharmaceuticals (CA, USA) announced on 27 March that it had received a complete response letter (CRL) from the US FDA regarding its new drug application (NDA) Epinephrine Injection USP 1:1000 0.3 mg prefilled single dose syringe (PFS) product, for the emergency treatment of acute anaphylaxis.

The company had submitted a NDA to the FDA pursuant to Section 505(b)(2) of the Food, Drug & Cosmetic Act, as amended, for approval of the Epinephrine PFS product in May 2014.

Providing an update Adamis president and CEO Dr Dennis Carlo said: "We are reviewing the CRL and plan to request a meeting with the FDA to discuss the letter, including clarifying the product delivery volume specifications. Although we expect to have more clarity with respect to timing, we believe we can satisfy all of the requests in the CRL and will work closely with the FDA to address the items raised in the CRL and finalize its review of our NDA. Adamis remains committed to bringing the epinephrine PFS to market."

The company indicated that questions raised by the FDA pertain only to chemistry, manufacturing and controls (CMC) relating to the volume of dose delivered by the syringe, including the ability to deliver volume within the levels contained in the labeling claim and as required by the FDA. According to the company no other safety or efficacy issues were raised,

and the NDA will remain open until the Chemistry, Manufacturing and Controls issues are resolved [9].

Clinical trials

Delcath announces submission of Phase III trial results for publication

Delcath Systems, Inc. (NY, USA) announced on 15 March that the results from its Phase III clinical study, which completed enrollment in 2009, have been submitted for publication. The clinical study utilized Delcath's Hepatic Delivery System for Melphalan Hydrochloride for the treatment of melanoma patients with liver metastases. Delcath's Hepatic Delivery System is designed to administer high-dose chemotherapy to the liver while controlling systemic exposure.

The proposed article submitted for publication is entitled 'A random-assignment study of hepatic arterial infusion of melphalan with venous filtration via peripheral (percutaneous) hepatic perfusion (PHP) (Delcath System) versus best alternative care for ocular and cutaneous melanoma metastatic to the liver' and it details the findings from the company's recently completed Phase III clinical study [10].

Novan Phase II acne study update

On 18 March Novan Therapeutics (NC, USA) announced that the company had achieved target enrollment in its Phase IIb clinical study with SB204 for the treatment of acne vulgaris. The Phase IIb study is a randomized, evaluator-blinded, vehicle-controlled study evaluating 200 subjects with moderate to severe acne vulgaris across 20 sites throughout the USA. The primary objective of the study is to compare efficacy, tolerability and safety of SB204 Gel versus Vehicle Gel applied topically once or twice daily for up to 12 weeks. Primary outcome measures include the change in number of inflammatory and noninflammatory lesions, as well as success on an Investigator Global Assessment. Novan's patented Nitricil™ technology claims to overcome the delivery issues associated with nitric oxide by stably storing the gaseous species as a solid that can be transformed into targeted therapeutics.

Following the successful enrollment of the Phase IIb acne study, Novan proposes to launch the clinical development of SB206, a topical antiviral that could lead to a treatment for human papillomavirus infections. SB206 is expected to enter a Phase II clinical trial in the second quarter of 2015 for the treatment of external genital warts [11].

Flamel Technologies announces positive First-in-Man clinical trials

Flamel Technologies (Lyon, France) announced on 27 March the results of a First-in-Man clinical study

in healthy volunteers using its proprietary LiquiTime® drug delivery platform applied to guaifenesin.

The company conducted a 16-subject four-way crossover pharmacokinetic study in healthy volunteers evaluating three different twice-daily formulations of LiquiTime guaifenesin against immediate release guaifenesin tablets dosed every 4 h. The trial was intended to provide sufficient data for the company to choose the best prototype to move forward into a pivotal study.

The results of this pilot study indicated that none of the prototype formulations satisfied all of the criteria necessary for proving bioequivalence of area under the curve (AUC) to the immediate release guaifenesin tablets under FDA requirements. The company has indicated that the chosen formulation will be optimized and scaled up over the coming months and it plans to perform a pivotal study in 2016.

LiquiTime is a patent-protected technology designed to provide a controlled, extended release of oral liquids principally for paediatric and geriatric patients [12].

Acura Pharmaceuticals provides an update on its Nexafed(R) extended-release clinical study

Acura Pharmaceuticals (IL, USA) announced preliminary topline results from a pilot clinical study which demonstrated bioequivalence of one formulation of NEXAFED (pseudoephedrine HCl) extended-release tablets to Sudafed® 12-h tablets on 23 March. NEXAFED extended-release tablets employ Acura's IMPEDE 2.0 enhanced methamphetamine-resistant technology which uses a unique polymer matrix to disrupt the conversion of pseudoephedrine into methamphetamine.

The study was conducted in 12 fasted, healthy subjects and was designed to measure the systemic absorption of pseudoephedrine, from a single dose each of two experimental NEXAFED extended-release formulations compared with Sudafed 12-h tablets. The results reported indicated that NEXAFED formulation B met FDA's standards for bioequivalence for maximum plasma concentration (C_{max}) and extent of absorption (AUC). NEXAFED formulation A met the bioequivalence criteria for extent of absorption but was low for maximum plasma concentration [13].

Adamis announces positive Phase I results

Adamis Pharmaceuticals Corporation announced positive results of its pharmacokinetic (PK) study for its dry powder inhaler product, APC-5000 on 3 March. The study was a Phase I PK study comparing the bioavailability of Adamis' APC-5000 Dry Powder Inhaler (DPI) to GlaxoSmithKline's Advair® Diskus® DPI.

The APC-5000 DPI utilizes the patented/proprietary Taper DPI inhaler device. In this product it has

been designed to deliver the active without the use of any additional excipients. It was also developed to deliver a higher percentage of fine particles to the airways with better delivery efficiency, and thereby decreasing the drug deposition in the throat and mouth. The study results confirm that systemic exposure to the drugs FP and SX is reduced after treatment with APC-5000, as compared with Advair Diskus, thereby potentially increasing the overall safety of the product [14].

Early-stage development

Genisphere's 3DNA® drug delivery platform reports success in preclinical treatment of posterior capsular opacification

Genisphere LLC (PA, USA) reported on 26 March that it had achieved positive preclinical data for the treatment of posterior capsular opacification (PCO), a clouding of the eye lens which can be a complication of cataract surgery. The company claimed it had succeeded in the immune depletion of Myo/Nogcells which are implicated in PCO. The company has indicated that this immunodepletion strategy could find use in the treatment of other fibrotic diseases. The intellectual property platform upon which the drug delivery platform is based has recently been licensed from LIMR Development Inc. a subsidiary of the Lankenau Institute for Medical Research (PA, USA). Genisphere's 3DNA nanotechnology platform is a 3D structure made entirely out of DNA. The 3D structure is a highly branched and functionalized molecule built from interconnected monomeric subunits of DNA – and can be used for targeted drug delivery [15].

Generex reports on its buccal insulin project

Generex Biotechnology Corporation (MA, USA) provided an update on 15 March (GNBT) on the status of its buccal insulin formulation enhancement project. This project is based on the proprietary Generex Oral-lyn™ buccal insulin spray product.

The company's Chief Operating Officer Dr David Brusegard stated: "We are pleased to report that our preliminary efforts have succeeded in increasing the insulin concentration in the product by approximately 400 percent via *in vitro* testing while preserving the solubility and stability of insulin in the formulation."

Generex also announced that it has entered into a Research Service Agreement with the University of Guelph (Ontario, Canada) whereby the university will conduct a study of the relative bioavailability of the enhanced formulation in dogs in the University's Comparative Clinical Research Facility. Allowing a direct comparison with the canine studies the university undertook of the original formulation of Generex Oral-

lyn for proof of concept, safety and toxicity. It is hoped that the new dog study will allow a rapid assessment of the added value of the improved formulation.

It is anticipated that if the canine study meets expectations the next step will be an update to the Generex Oral-lyn IND on file with the FDA in support of the human studies necessary to validate the enhanced formulation and set the stage for commercialization [16].

Electronic oral drug-delivery capsule aims to transform GI health care

At a presentation at the 6th annual American Gastroenterological Association Tech Summit in San Francisco on 19–20 March, Jeff Shimizu, Chief Technology Officer and Vice President of MediMetrics, claimed that small bowel capsules are a convergent technology in evolution with potential utility in targeted drug therapy, which could revolutionize health care.

“Electronics can do a number of different things that we couldn’t do otherwise,” he said. “You can acquire information, aggregate information from different sources, use that information to change behaviour over time ... adapt based on the data that comes in and, of course, you can network – one device can talk to the next. [There are] a lot of interesting possibilities which expand once you start putting these things into action.”

MediMetrics’ CE-marked electronic oral drug-delivery pill, IntelliCap, is currently being used clinically in the USA and Europe for drug absorption studies. The capsule entails two pieces – an electronic end including a pH sensor, battery, wireless real-time, in-and-out communications and a drug reservoir on the other side. The capsule is then put together, swallowed and passed through the body within 24–48 h providing a tool for studying drug absorption in the gastrointestinal tract [17].

Intellipharma reports positive Phase I clinical trials of its Rexista Oxycodone XR tablets

Intellipharma (Toronto, Canada) provided an update on recent Phase I clinical trials on 30 March. The three Phase I pharmacokinetic clinical trials compared Rexista™ Oxycodone XR to Oxycontin™ under single dose fasting, single dose steady-state fasting and single dose fed conditions in healthy volunteers. In the first study, a single-dose steady-state fasting study, the company reported that Rexista Oxycodone XR met the bioequivalence criteria for all matrices. The second study reported was a single-dose fasting study and it confirmed that Rexista Oxycodone XR met the bioequivalence criteria for all matrices. Topline data reported

for the third study, a single-dose fed study, showed that Rexista Oxycodone XR met the bioequivalence criteria for all matrices.

Rexista Oxycodone XR is a nongeneric extended release formulation and is intended for the management of moderate to severe pain when an around-the-clock analgesic is required. The formulation is intended to present a significant barrier to tampering when subjected to various forms of anticipated physical and chemical manipulation commonly used by abusers. It is also designed to prevent dose dumping when inadvertently co-administered with alcohol. In addition, when crushed or pulverized and hydrated, the proposed extended release formulation is designed to coagulate instantaneously and entrap the drug in a viscous hydrogel, which is intended to prevent syringing, injecting and snorting.

Intellipharma recently submitted an investigational new drug application to the FDA for Rexista Oxycodone XR in anticipation of the commencement of Phase III clinical trials. Planning has begun for the Phase III trials that will examine the efficacy and safety of Rexista Oxycodone XR in individuals with chronic low back pain [18].

Use of nanoparticles to deliver antibiotics

A presentation by Dr Cristiane Carvalho-Wodarz, from the Helmholtz Institute for Pharmaceutical Research, Saarbrücken, Germany to the 13th European Respiratory Society Lung Science Conference in Estoril Portugal on 13–15 March described recent work carried out by her group in the area of developing antibiotic-loaded nanoparticles. The results presented by Dr Carvalho-Wodarz’s group claim that inhalation of these clarithromycin-loaded nanoparticles achieved similar distribution of the active to that found by oral or intravenous delivery. According to Dr Carvalho-Wodarz: “The delivery of nanoparticles in this way enables their deposition in cells cultivated *in vitro* in a similar way to the deposition *in vivo*, which take place in the alveoli.”

Staphylococcus aureus was the model chosen by the researchers for their *in vitro* bronchial cell work, since it is one of the major causes of hospital-acquired infection and also plays a crucial role in the lung infections which are common in the genetic disorder cystic fibrosis.

The work presented that the clarithromycin-loaded nanoparticles, were able to access the bacteria located both in biofilms or inside individual lung cells.

Following on for the work presented Dr Carvalho Wodarz’s group intends to progress into *in vivo* animal models with an eventual aim developing an inhalable drug-loaded nanoparticle product for the treatment of drug resistant lung infections [19].

Patents update

InSite Vision settles patent infringement lawsuit against Mylan

InSite Vision (CA, USA) announced on 17 March that it, along with other plaintiffs, had entered into a settlement agreement to dismiss a patent infringement lawsuit against Mylan Pharmaceutical, Inc. concerning Mylan's abbreviated new drug application seeking marketing approval from the FDA of a 1% azithromycin ophthalmic solution before the expiration of the patents protecting AzaSite®.

Under the terms of InSite Vision's license agreement with Akorn, Inc., the AzaSite royalty payable to InSite Vision will increase from 8 to 9% for annual net AzaSite sales of less than US\$20 million. The AzaSite royalty on annual net sales between US\$20 million and US\$50 million remains at 12.5% and the royalty on annual net sales greater than US\$50 million remains at 15%.

InSite's DuraSite and DuraSite 2 drug delivery systems 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 and the DuraSite platform is employed in AzaSite (azithromycin ophthalmic solution) [20].

Financial & competing interests disclosure

E Harris is a partner in Innovation21 Ltd, providing consultancy, advisory and evaluation services to pharmaceutical/biotechnology companies and government funded agencies. 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.

No writing assistance was utilized in the production of this manuscript.

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