An industry update: the latest developments in therapeutic delivery

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The present industry update covers the period 1–30 June 2017, with information sourced from company press releases, regulatory and patent agencies as well as scientific literature. The combination of drug and devices such as improved, safer injectables (see various market reports, companies Adamis and Baxter), patches (Microdermis) and (nano)carriers are moving increasingly from the R&D stage into clinical trials and toward the market. This addresses increased safety and effectiveness requirements, limiting physico-chemical properties of active ingredients, cost-effectiveness and patient comfort through ease of use. Further attention in the market is on local delivery methods (such as intraocular by Icon Bioscience, Glaukos) and the sheer infinite possibilities of nanotechnology such as LDL nanocarriers, microneedles and hydrogel cubes. Another 21st century key technology area is mobile applications (Vital Art and Science) and connected devices (SmartPill, Pop Test Devices) which are increasingly finding their way into the drug delivery field to enable, for example, closed loop monitoring of drug dosing in trials and of patients with their care providers. Not surprisingly companies are increasingly utilizing convergence to combine their diverse capabilities (Vetter Pharma/Microdermis, TXCell/Lentigen Technology).

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Business development

Market reports

A series of reports have been published in June, forecasting the years to come using baselines of 2014–2016. The global topical drug delivery market can be split into transdermal and topical drug delivery devices or formulations (liquid, semi-solid, solid) [1] and might peak at USD 194.2 billion by 2024. Likewise the needle-free market is expected to grow to USD 10.61 billion by 2021 [2] with major growth drivers being biologics, prevalence of chronic diseases and more needlestick injuries. These framework conditions accelerate the opportunities for safety syringes, prefilled syringes and auto-disabled syringes. Obstacles that face market expansion, however, are the increased risk of bloodborne infections when using injectables and the option of using other drug delivery methods (e.g., oral and transdermal). The same publisher also reported on the global hollow microspheres market through 2021, including its use in drug delivery [3]. The opioid abuse epidemic has become a considerable medical and societal issue. Hence, the need for safer and nonaddicting analgesics to relieve pain has been raised. The nonopioid pain patch market features a moderate degree of competition and is a niche in the general pain relief market with only a few key competitors [4]; it is projected to grow to USD 3391.2 million by 2021.

Financing

NantCell

NantCell, Inc., CA, USA, part of NantWorks companies, announced on 27 June to enter into a merger with Altor BioScience Corporation (Miramar, FL, USA). With an upfront payment reflecting a 20% premium to its 2017 equity financing and a 33% premium for the one in 2016. Further shareholders will have two contingent value rights for additional payments once regulatory and sales milestones are achieved. NantCell works on innovative

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antibodies – regarding T-cell and NK-cell-based therapies based on the proteomic profile of the patient's tumor irrespective of the cancer's pathology. The acquisition is expected to close in the third quarter of 2017 [5].

Lubrizol

Lubrizol LifeSciences (Wickliffe, OH, USA), part of Lubrizol Corporation, reported on 6 June to continue its investments with USD 60 million in particle sciences and additional Current Good Manufacturing Organization manufacturing capacity to expand its polymer, drug formulation and manufacturing (including medical devices) capabilities [6].

Licensing & collaboration agreements

Vetter Pharma

On 1 June, Vetter Pharma, Ravensburg, Germany (a worldwide specialist in aseptic production of prefilled drug delivery systems), and Microdermics (a medical device company), Vancouver, Canada, entered into a strategic cooperation to develop novel hollow, metal microneedles to enable the pain-free, intradermal administration of biologics and vaccines. The demand for alternatives to needle injections is expected to grow by 480 million units by 2030; microneedles are expected to reduce the injectable dose and accelerating drug absorption. Vetter as a contract development and manufacturing organization will focus on the late stage development and upscaling while Microdermics' new solution will be in Phase I trials expected to initiate in 2017 [7].

Vital Art & Science

Vital Art and Science LLC, Dallas, TX, USA announced on 19 June to license the myVisionTrack® (mVT®) service developer for home vision monitoring of patients with maculopathy. It will be deployed in Genentech's clinical trials for new ophthalmic drugs and devices to enhance the patient's experience and communications with healthcare providers and for clinical trial design. Genentech already uses mVT in a Phase II trial (LADDER) to investigate sustained delivery of LUCENTIS® (ranibizumab injection). Patients with wet age related macular degeneration already use Genentech's port delivery system and will perform vision testing with the mVT service at hospital check-in and at home [8].

Development & manufacturing agreements

TxCell

TxCell SA, Valbonne, France, teamed up on 19 June with Lentigen Technology, Inc. (LTI), a wholly-owned subsidiary of Miltenyi Biotec GmbH, Germany, to manufacture the lentiviral vector for its first CAR-Treg program in transplant rejection. Immunotherapies based on regulatory T cells give promise to treat severe inflammatory and autoimmune diseases as well as transplant rejection. LTI will be the contract manufacturer for its HLA-A2 CAR lentiviral vector that is expected to enter clinical studies at the end of 2018 for use in solid organ transplantation (lung and/or kidney), assessing the toxicity profile, evaluating inflammation markers and tolerance induction [9].

NovaMedica

NovaMedica, Moscow, Russia and Pfizer, New York, NY, USA announced on 1 June that they will jointly build a manufacturing plant in the Kaluga region, Russia, in order to supply the Russian market with injectables [10]. They already announced in 2016 a long-term strategic partnership, and Pfizer has already transferred the manufacturing rights of 30 drugs to NovaMedica [11]. The facility will be designed for a capacity of more than 38.5 million units of production (lyophilized and solutions in ampules and bottles) with the option of expansion to prefilled syringes, bottles and disposable packages for infusion as well as isolated blocks for the production of standard and cytotoxic drugs.

Regulatory news & approvals

Product approval

Icon Bioscience

Icon Bioscience, Newark, CA, USA, a privately held biopharmaceutical company and inventor of the Verisome® drug delivery platform for intraocular eye care therapeutics, announced on 26 June to have received notification from the US FDA on acceptance to file the new drug application for DEXYCU®, indicating completion for an agency review with potential approval in early 2018. DEXYCU uses Verisome technology as a biodegradable

extended-release formulation to dispense the dexamethasone into the anterior chamber of the eye with a single injection during cataract surgery. The standard of postsurgery care is the self-administration of eye drops four-times a day over a period of weeks [12].

Adamis

Adamis Pharmaceuticals, San Diego, CA, USA, received FDA approval for a single-dose epinephrine prefilled syringe with the trade name of SymjepiTM on June 15. While it is not a direct interchangeable generic it is offered as a lower-cost alternative to its competitor Mylan's EpiPen[®]. This top-selling product with more than USD 1 billion in sales has long dominated the epinephrine (adrenaline) injection market. It is the drug of choice for immediate administration for acute anaphylactic reactions caused by insect stings/bites, allergic reaction to foods, drugs and other allergens as well as idiopathic or exercise-induced anaphylaxis. Adamis is now evaluating different strategies for product roll out including licensing right partners in the USA [13].

Genentech

Roche group member Genentech, San Francisco, CA, USA announced on 22 June that RITUXAN HYCELATM (rituximab and hyaluronidase human) for the treatment of adults with various blood cancers by subcutaneous injection have been approved by FDA. This new formulation is the combination of intravenous Rituxa[®] monoclonal antibody with hyaluronidase, an enzyme to facilitate under the skin delivery. This approval followed clinical studies showing equivalence in biodistribution and effectiveness of subcutaneous delivery compared to injections. Importantly, there appears to be a 77% preference by patients over intravenous delivery, which also comes along with time effectiveness in treatment. However, it needs one full dose of intravenous Rituxan to be eligible for the new drug [14].

Baxter

Baxter, Deerfield, IL, USA reported on 7 June that FDA approval and the commercial launch of a ready-to-use clindamycin injection in saline being the third premix of its nature since August 2015. Clindamycin is a common antibiotic for serious infectious diseases when penicillin is contraindicated. It will take advantage of Baxter's GALAXY container technology, a non-PVC (polyvinylchloride) and non-DEHP (Bis(2-ethylhexyl) phthalate) system also having the advantage of a longer shelf life when stored at room temperature. Furthermore, the use of premixed standard dosing can help to increase patient safety and comfort avoiding medication errors, premixed medications also offer efficiencies for hospitals by simplifying the preparation process [15].

Recall

Pfizer

On 19 June, Pfizer recalled four injectables from its Rocky Mount (NC, USA) plant after detecting microbial contaminations during an internal manufacturing process inspection. One of the injectables, sodium bicarbonate, is already in short supply on the market. The site has been the subject of previous recalls, complaints and FDA inspections, but passed reinspection in 2014 with no findings [16].

Teleflex

Teleflex Inc., Wayne, PA, USA announced on 22 June a worldwide, voluntarily FDA Class I recall of its Venture[®] catheters. They are applied in interventional guidewire-steered procedures accessing coronary and peripheral vessels, which may include the delivery of saline or diagnostic contrast agents. Coating material inside the device may be at risk to shed off and hence create the risk of embolism, none of which have been reported though [17].

Clinical trials

Emory University School of Medicine

Emory University School of Medicine in Atlanta, GA, USA, published online on 27 June in *The Lancet*, data from the first Phase I human trial showing that dissolvable microneedles are as effective as conventional hypodermic needles and patient-preferred alternatives for administering the influenza vaccine. The patch is composed of micron-scale, vaccine-filled needles embedded in a soft polymer base, and can be stored and distributed without refrigeration. It can also be safely self-administered by patients and can dissolve rapidly as it delivers the vaccine.

The combination of efficacy, safety and ease of use of the patch for immunization may promote its common use, increased rates of influenza vaccination and reduced cost [18].

Glaukos Corporation

Glaukos Corporation, San Clemente, CA, USA, working on the treatment of glaucoma, announced on 21 June that a study of 53 glaucoma subjects showed that the *iStent Inject*[®] *Trabecular Micro-Bypass*, combined with topical travoprost, delivered a 35% reduction in mean intraocular pressure[19]. The study sponsor's primary device, the *iStent Trabecular Micro-Bypass Stent*, was approved by the FDA in 2012. In course of cataract surgery inserted through a small corneal incision made during the *iStent* is designed to reduce intraocular pressure by restoring the natural physiological outflow of aqueous humor through the conventional pathway. Glaukos is also evaluating a Travoprost Intraocular Implant with the *iDose*TM delivery system in a Phase II investigational new drug trial. Implanted during a microinvasive procedure, the *iDose* is designed to continuously elute therapeutic levels of a proprietary formulation of travoprost for extended periods of time. Travoprost is designed to increase outflow primarily through the uveoscleral or unconventional pathway and to a lesser extent through the conventional pathway. When the implant's medication is depleted, the implant can be removed and replaced in a similar microinvasive procedure [20].

Modra Pharmaceuticals

Modra Pharmaceuticals, Amsterdam, The Netherlands, announced on 14 June the initiation of its first Phase II study with its new compound (ModraDoc006/r) in metastatic castration-resistant prostate cancer. This is a novel oral formulation of docetaxel co-administered with boosting agent ritonavir[®] to enhance the chemotherapy's bioavailability. This may offer better drug administration and hence patient compliance [21].

Patents

Smart pill

Pop Test Devices and Palisades Therapeutics have teamed up to address the current opioid epidemic. This invention relates to an ingestible drug delivery device that is configured for wireless communication with other ingestible drug delivery devices. A patent on the smart pill drug delivery device was published on 1 June. Its functionality addresses risks of overdosing of prescription opioids of label use and counterfeiting. The device exchanges the prescribed dosage of the patient and upon deviation notifies the one inside the patient not to release the drug to prevent overdose. They can also be used to communicate information back to the pharmacist and clinician, and may also be used in law enforcement [22,23].

Publications

LDL nanocarriers

On 24 June, Zhu *et al.* published work on how low-density lipoproteins (LDLs) represent a novel class of nanocarriers for the targeted delivery of therapeutics into cells that overexpress the LDL receptor. A reconstituting procedure of the hydrophobic LDL core with a binary fatty acid mixture combined with tumor targeting capability of the apolipoprotein results in drug loaded LDLs that can effectively target cancer cells overexpressing the LDL receptor, while also showing minor adverse impact on normal fibroblasts. This study suggests that the reconstituted LDLs are enabling metabolism-triggered drug release while preventing the payloads from lysosomal degradation [24].

Skin reconstitution

According to an article published on 20 June by researchers of the Université Lyon, France, reconstructing functional skin after a wound remains a challenge due to the complexity of healing. In this regard, biocompatible nanoparticles (NPs) carrying and releasing bioactive drugs in a controlled and sustained manner may significantly improve the efficacy of wound therapies compared with current treatments. Topical administration of drug-loaded NPs allows optimal delivery to the dermis and improves product efficacy. Scaffold-associated NPs reflect also a new concept of 'dressing' that has shown benefits in preclinical models [25].

Bone delivery

Molly Stapelton of the University of Delaware, DE, USA and others wrote an overview article on therapeutic delivery to the bone. Bone-targeting drugs can be designed to either have two general targeting moieties, affinity

to hydroxyapatite or positively-charged Ca^{2+} , to increase efficacy and reduce toxicity either systemically or cell targeted. This literature review surveys the current developments in bone-targeting moieties with its efficacy and limitations and future trends [26].

Hydrogel cubes

Researchers at the University of Alabama at Birmingham, AL, USA and the Texas Tech University Health Sciences Center, Lubbock, TX, USA reported on micro-cubes enclosing a hydrophobic anticancer drug. It has cancer cell delivery properties and hence can resolve solubility challenges of certain drugs. *In vitro* experiments with the anticancer drug BA-TPQ (which is highly potent but with limited solubility, and hence has low bioavailability and toxicity) have demonstrated that drug-loaded hydrogel cubes are more potent against liver cancer cells than normal. Hydrogel cubes loaded with BA-TPQ can be delivered iv., as well as orally as experiments have shown [27].

Other reviews published in June addressed nanoparticulate therapy in cancer [28] and targeting and delivery of therapeutic enzymes [29].

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