



APV FOCUS GROUP DRUG DELIVERY

COMBINING SCIENCE & TECHNOLOGY TO CREATE ADVANCED DRUG DELIVERY SYSTEMS

INTERNATIONAL ASSOCIATION FOR PHARMACEUTICAL TECHNOLOGY

NEWSLETTER

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DRUG DELIVERY EVENTS

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3rd APV winter conference 2018 | KN 6718

+ Individualized Medicines for oral use – visions and challenges

January 25-26, 2018 | Innsbruck, Austria

[Details](#)

Intensive patent workshop | KN 3188

+ How to draft, analyse and circumvent a formulation patent

February 26-27, 2018 | Berlin, Germany

[Details](#)

9th Global DDF Summit - Drug Delivery & Formulation

March 12-14, 2018 | Berlin, Germany

[Details](#)

11th World Meeting on Pharmaceuticals, Biopharmaceutics and Pharmaceutical Technology

+ March 19-22, 2018 | Granada, Spain

[Details](#)

Controlled Release Society Annual Meeting & Exposition, 2018

July 22-24, 2018 | New York, USA

[Details](#)

[Suggest a meeting to be announced!](#)

APV CONFERENCE REPORT

Provided by Prof. Dr. Sven Stegemann

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MEDICINES FOR OLDER ADULTS: GETTING PREPARED FOR THE SCIENTIFIC AND REGULATORY EVOLUTION

November 7th & 8th, 2017 in Graz (Austria)

Increasing life expectancy is a fundamental achievement of modern societies, supported by effective drug therapy to treat and manage acute and chronic diseases. Due to the increasing prevalence of chronic diseases, older patients are the major user group of pharmaceutical drug products. They often suffer from multiple diseases, develop disabilities and have to manage complex medication schedules. There is increasing evidence that the pharmaceutical development and drug product design process has to be adapted to the specific needs of the older patient population.

Older patients, often only defined by their chronological age, are a heterogeneous population with many different individual trajectories. Within this population, patients with multimorbidity or at very high age (≥ 80 years) require special attention and have needs beyond the standard care. From a geriatrician's standpoint, prescribing is a fine balance between the risk and the relative benefit, which needs to be seen in the context of the co-morbidities, other medicines and the patient response to a treatment as well as the patients' personal health goals. In hospital settings, the existing drug products have to be modified or compounded in order to achieve the right dose or to enable drug administration (e.g. through feeding tubes). Similar issues are frequently reported from primary care as medication handling issues and unintended errors lead to poor therapeutic outcomes. To overcome these issues, patient centric drug product design is

often being claimed, however, clinical or scientific evidence of this remains very limited. Recent investigations into the management of different packaging designs by older patients provided some good insight into design elements improving usability and user satisfaction.

Implementing patient centric drug product design into an industrial development process has to be seen from an organizational and legislative perspective, since drug development as such is a lengthy and complex process. Moreover, the final drug product has to fulfill many different requirements to assure efficacy, patient safety and accessibility. To achieve the objectives, predictive tools are required to allow the evaluation of different formulations based on relevant in vitro models like dissolution test media that are biorelevant for a specific patient population. With the required development of age-appropriate formulations for pediatric use, experience exists with collaborative efforts to gain the scientific and patient based evidence to improve products for a special patient population. Taking into account that older patients are the major user group of pharmaceutical products, the pharmaceutical industry should be encouraged to evaluate the implementation of patient centric product design based on incremental product enhancement within the development timelines.

Moving to patient centric drug products might also include the use of advanced manufacturing technologies which enable small volume or even personalized manufacturing. Especially the emerging digital health technologies will create new ways of treating and monitoring patients as well as a move from reactive to proactive healthcare delivery. Using product-user interface analysis in the development of computerized medical recording software have been applied successfully to improve the value and performance for healthcare professionals. The same applies for the communication to laypeople like patients to provide important information in a clear and simple way. Human Factor Design has been established for the development of device based drug products following a logic process involving the targeted patient.

To assure the best risk to benefit profile of a drug product, the *"Reflection Paper on pharmaceutical development of medicines for use in the older population"* has been published as a draft for public consultation. The reflections review the scientific information and summarize the identified major aspects that should be considered during development to address the needs of older patients.

This APV conference brought together a broad group of stakeholders and experts from the medical, pharmaceutical, Human Factor Design and technology fields concluding that patient centric drug product design must continue to be supported by scientific and professional collaboration in order to improve medicines for older patients. Based on the feedback, APV will take the leadership in continuing the interdisciplinary collaboration and exchange to build the required scientific evidence to support patient centric drug product design from the concept through to the market.

DRUG DELIVERY PRODUCTS

Provided by Dr. Louise Rosenmayr-Templeton

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LYRICA® CR

In October 2017 the FDA approved Pfizer's Lyrica CR® tablets [1] [2] for the treatment of neuropathic pain associated with diabetic peripheral neuropathy and postherpetic neuralgia in adults. The product is an extended release formulation of pregabalin which was originally licensed in 2004 in Europe and the US as an immediate release capsule dosage form. However, unlike the capsule formulation, Lyrica® CR is not licensed for use in fibromyalgia (a poorly understood chronic condition characterized by wide-spread muscle and soft tissue pain) or as an adjunct therapy for partial seizures.

Pregabalin is related to the anti-epileptic, gabapentin, and like it, is thought to be effective in neuropathic pain through a reduction in calcium-dependent neurotransmitter release in the central nervous system as a result of its binding to the alpha-2-delta protein sub-unit of voltage-gated calcium channels, although the exact mechanism of action is not fully understood.

Lyrica® CR is available in three strengths: 82.5, 165, or 330 mg and is administered once daily after an evening meal (in comparison to the fed state the bioavailability of pregabalin is reduced by around 30% if taken on an empty stomach). The starting dose for both indications is 165 mg rising to a maximum of 330 mg within one week. In the case of postherpetic neuralgia the dose can be increased to 660 mg per day if insufficient pain relief is achieved after two to four weeks and the patients are able to tolerate the medication. Due to withdrawal symptoms, treatment with Pregabalin should be not stopped abruptly.

The inactive ingredients in the sustained release formulation are Kollidon SR (polyvinyl acetate, povidone, sodium lauryl sulphate, and silica), crospovidone, polyethylene oxide, carbomer, magnesium stearate, polyvinyl alcohol, titanium dioxide, talc, polyethylene glycol, and colorants.

Approval was based on the results of a randomized placebo-controlled clinical trial in 801 patients suffering from postherpetic neuralgia. The study design consisted of six weeks of dose optimization conducted under single blind conditions followed by a 13-week double-blind phase in those who had responded to treatment in the first phase. The study results showed that treatment with Lyrica CR was associated with at least a 50% improvement in pain severity in 73.6% of patients compared with 54.6% in the placebo group.

The results in postherpetic neuralgia are accepted as evidence of efficacy in diabetic peripheral neuropathy as both are peripheral neuropathic pain conditions.

The convenience of the once-a-day formulation may help Pfizer stave off generic competition when the US patent for pregabalin expires in December 2018. It is reported that at least 6 companies already have tentative approvals for a generic version of the immediate release Lyrica® capsule which is dosed two to three times daily [3]. The product had US sales of over \$3.1 billion in 2016 with sales still growing significantly (up 26% compared with 2015). Pfizer will launch Lyrica® CR on the US market in December 2017.

TRELEGY® ELLIPTA®

The Committee for Medicinal Products for Human Use of the European Medicines Agency issued a positive opinion on GlaxoSmithKline's Trelegy® Ellipta® product in September 2017 [4] [5]. Trelegy® Ellipta® is a product developed through GSK's partnership with Innoviva Inc. (formerly Theravance Inc.). This product is a fixed combination of fluticasone furoate, umeclidinium and vilanterol presented as a dry powder for inhalation in the Ellipta® device. The inhaler contains two strips of blisters, one containing micronized fluticasone furoate 100 mcg/blister mixed with lactose, and the other containing umeclidinium and vilanterol 62.5 mcg and 25 mcg per blister in a blend containing lactose and magnesium stearate. The umeclidinium and vilanterol are present in the form of the bromide and trifenate salts respectively. The powder within both blisters is dispersed after activation of the inhaler by inhalation to deliver 92, 55, and 22 mcg of fluticasone furoate, umeclidinium, and vilanterol respectively when tested under standardized in vitro conditions.

The combination of fluticasone furoate (a corticosteroid), umeclidinium (a long-acting muscarinic antagonist) and vilanterol (a long-acting beta2-adrenergic agonist) is for the maintenance treatment of chronic obstructive pulmonary disease (COPD) in adults whose symptoms are not sufficiently controlled by a combination of a corticosteroid and long acting beta2-adrenergic agonist. It enables the once daily administration of the three actives in one inhaler and as such is the first triple therapy product of its kind.

Approval was based on Phase III clinical data which showed that Trelegy® Ellipta® improved lung function (as defined by a change from baseline trough Forced Expiratory Volume 1 plus a reduction in the St. George's Respiratory Questionnaire total score at Week 24 of the study) compared with budesonide/formoterol 400 mcg /12 mcg administered twice-daily in patients with moderate to severe COPD not adequately controlled by a dual combination of corticosteroid and long acting beta agonist. The application was also supported by previous clinical experience of the individual components alone or in combination. The product was approved by the FDA in the same month.

References and Further Information

- [1] Entry for Lyrica CR on Drugs@FDA
- [2] U.S. FDA Approves LYRICA® CR (pregabalin) Extended-Release Tablets CV. http://www.pfizer.com/news/press-release/press-release-detail/u_s_fda_approves_lyrica_cr_pregabalin_extended_release_tablets_cv
- [3] [Sagonowsky E](http://www.fiercepharma.com/regulatory/pfizer-wins-lyrica-extended-release-approval-could-it-be-prepping-patient-switch-push) With a year left before generics hit, Pfizer nabs FDA approval for new-and-improved Lyrica. <http://www.fiercepharma.com/regulatory/pfizer-wins-lyrica-extended-release-approval-could-it-be-prepping-patient-switch-push>.
- [4] Committee for Medicinal Products for Human Use (CHMP) Summary of opinion1 (initial authorisation) http://www.ema.europa.eu/ema/index.jsp?curl=pages/medicines/human/medicines/004363/smops/Positive/human_smop_001196.jsp&mid=WC0b01ac058001d127.
- [5] Trelegy Ellipta once-daily single inhaler triple therapy receives positive opinion from the CHMP in Europe for appropriate patients with COPD. <https://www.gsk.com/en-gb/media/press-releases/trelegy-ellipta-once-daily-single-inhaler-triple-therapy-receives-positive-opinion-from-the-chmp-in-europe-for-appropriate-patients-with-copd/>

DRUG DELIVERY PEOPLE

Provided by Dr. Lea Ann Dailey

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DR. RUTH SCHMID-BAUMBERGER is a chemist by training with a diploma and PhD in the Natural Sciences from the Eidgenössische Technische Hochschule in Zürich. Following a short postdoc position at the Institute of Organic Chemistry at the Norwegian Institute of Technology, she joined SINTEF (*Stiftelsen for industriell og teknisk forskning*), one of the largest independent research organisations in Scandinavia, headquartered in Trondheim, Norway, as a research scientist in 1981 and currently holds the position of Vice President in Marketing at SINTEF.

During her career, Dr Schmid-Baumberger has become one of the leading experts in micro- and nanotechnology for healthcare and cosmetic applications. Her research interests are centred on the applications of nano- and microparticles from a wide variety of materials, including biodegradable polymers and hybrid materials, across a wide range of products. They also include the surface modification of polymers and polymer particles to introduce tailor-made properties. Dr Schmid-Baumberger's research extends from basic science covering material science, physics, ultrasound technology and analytical chemistry to applications ranging from cancer research, immunology and imaging technology. Lately, her



work has been focused on the encapsulation of drugs and contrast agents into synthetic nanoparticles for therapy and imaging and the preparation of nanoparticle-stabilized gas bubbles for ultrasound-mediated treatments of solid cancers and brain diseases.

In addition to her scientific and academic roles, she is a past president of the Controlled Release Society and is a current member of the European Technology Platform in Nanomedicine (ETPN) and the EARTO working group "Emerging Technologies for Healthcare".

DRUG DELIVERY GROUPS

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DRUG DELIVERY ACADEMIC RESEARCH GROUPS: PAEDIATRIC DRUG FORMULATIONS

Compiled by Jörg Breitzkreutz, Düsseldorf, Germany

This article provides an overview of academic groups based at European Universities working on paediatric drug formulations. Information has been collected in August 2017 from literature / internet research and from registrations at the annual meetings of the European Paediatric Formulation Initiative (EuPFI) which are co-organised by APV.

This is another publication in the occasional series reviewing the work of research groups exploring different aspects of drug delivery research. It is not intended to provide an exhaustive list of all people involved in this research area, but to give our readers just a flavor. As it is a living document, our readers are most welcome to suggest other research teams they are aware of for inclusion in our next edition (joerg.breitzkreutz@hhu.de).

Bulgaria

Sofia

Institution	Medical University
Group	Faculty of Pharmacy
Key contact	Prof. Dr. Milen Dimitrov
Website	www.pharmfac.net/index_en.html
E-Mail	mdimitrov@pharmfac.net
Research areas	<ul style="list-style-type: none"> - Development and industrial production of paediatric formulations - Coated drug dosage forms - Extemporaneous formulations (EDQM PaedF group)

Denmark

Copenhagen

Institution	University of Copenhagen
Group	Department of Pharmacy, Pharmaceutical Design and Drug Delivery
Key contact	Prof. Dr. Anette Müllertz
Website	pharmacy.ku.dk/employees/?pure=en/persons/321788
E-Mail	anette.mullertz@sund.ku.dk
Research areas	<ul style="list-style-type: none"> - Innovative pharmaceutical formulations, including lipid drug delivery systems - Development of media, simulating the gastrointestinal (GI) fluids. - Development of digestion models for paediatrics and elucidating the mechanisms of solubilization and generated colloid phases in the GI tract

Germany

Düsseldorf

Institution	Heinrich-Heine-University
Group	Institute of Pharmaceutics and Biopharmaceutics
Key contact	Prof. Dr. Jörg Breitzkreutz
Website	www.pharmazie.hhu.de/institute/ptb.html
E-Mail	joerg.breitzkreutz@hhu.de
Research areas	<ul style="list-style-type: none"> - Development and industrial production of paediatric formulations - Mini-tablets, orodispersible mini-tablets, orodispersible films, mucoadhesive buccal films - Individualized Medicines; Extemporaneous formulations (EDQM PaedF group) - Drug printing (2D- and 3D-printed medicines, Bio-printing) - Taste masking technologies and taste assessment by electronic tongues - Acceptability testing in children (cooperation with University Children's Hospital, Dr. V. Klingmann)

Greifswald

Institution	Ernst-Moritz-Arndt-University
Group	Biopharmaceutics and Pharmaceutical Technology
Key contact	Prof. Dr. Sandra Klein
Website	pharmazie.uni-greifswald.de/institut/abteilungen/biopharmazie-und-pharm-technologie/
E-Mail	sandra.klein@uni-greifswald.de
Research areas	<ul style="list-style-type: none">- Biopharmaceutical models- Biorelevant tests for paediatrics- Paediatric biopharmaceutical classification system- Individualized Medicines- 3D Printing (in cooperation with Dr. Seidlitz)

Finland

Helsinki

Institution	University of Helsinki
Group	Faculty of Pharmacy, Division of Pharmaceutical Chemistry and Technology, Pharmaceutical Design and Discovery group
Key contact	Prof. Dr. Anne Juppo
Website	tuhat.helsinki.fi/portal/en/person/juppo
E-Mail	anne.juppo@helsinki.fi
Research areas	<ul style="list-style-type: none">- Development and industrial production of paediatric formulations- Taste masking strategies- Coating of pellets and mini-tablets- Atomic layer deposition for ultrathin coatings- Compounded medicines for children- Inhalative formulations

Turku

Institution	Åbo Akademi University
Group	Pharmaceutical Sciences, Department of Biosciences
Key contact	Dr. Maren Preis
Website	www.abo.fi/fakultet/farmaciforskning
E-Mail	maren.preis@abo.fi
Research areas	<ul style="list-style-type: none">- Drug printing (2D- and 3D-printed medicines, Bio-printing)- Development of film formulations (ODF, MBF)- Multiple-unit dosage forms- Analytical testing of film preparations

Norway

Oslo

Institution	University of Oslo
Group	Department of Pharmacy
Key contact	Prof. Dr. Ingunn Tho
Website	www.mn.uio.no/farmasi/english/people/aca/ingt/
E-Mail	ingunn.tho@farmasi.uio.no
Research areas	<ul style="list-style-type: none">- Development of age-appropriate formulations- Mini-tablets, Pellets- Compatibility of parenteral formulations

Poland

Gdansk

Institution	Medical University Gdansk
Group	Faculty of Pharmacy with Subfaculty of Laboratory Medicine
Key contact	Prof. Dr. Małgorzata Sznitowska
Website	mug.edu.pl/1427.html
E-Mail	msznito@gumed.edu.pl
Research areas	<ul style="list-style-type: none">- Development of paediatric formulations- Mini-tablets: development and testing- Pellets, coated dosage forms- Taste masking- Dermal preparations, Percutaneous absorption

Kraków

Institution	Jagiellonian University
Group	Faculty of Pharmacy, Pharmaceutical Technology and Biopharmaceutics
Key contact	Prof. Dr. Renata Jachowicz
Website	www.en.uj.edu.pl/en_GB/research/research-highlights/pharm
E-Mail	mfjachow@cyf-kr.edu.pl
Research areas	<ul style="list-style-type: none"> - Development of paediatric formulations - Mini-tablets - Pellet formulations - Multiple-unit dosage forms - Analytical testing of paediatric formulations

Portugal**Lisbon**

Institution	University of Lisbon
Group	Faculty of Pharmacy
Key contact	Prof. Dr. Antonio Almeida
Website	www.ff.ul.pt/fgtf/inicio/recursos-humanos/docentes-e-investigadores/antonio-jose-leitao-neves-almeida/
E-Mail	aalmeida@ff.ulisboa.pt
Research areas	<ul style="list-style-type: none"> - Sugar free drug formulations - Intraoral drug formulations: pastilles, oral solutions - Topical drug delivery

Lisbon

Institution	University of Lisbon
Group	Faculty of Pharmacy
Key contact	Prof. Dr. Joao Pinto
Website	www.ff.ul.pt/fgtf/inicio/recursos-humanos/docentes-e-investigadores/joao-fernandes-abreu-pinto/
E-Mail	jfpinto@ff.ulisboa.pt
Research areas	<ul style="list-style-type: none"> - Development of solid drug dosage forms for paediatrics - Taste masking technologies - Stability testing of paediatric medicines - Process analytical technologies

Romania**Cluj-Napoca**

Institution	University of Medicine and Pharmacy "Iuliu Hatieganu"
Group	Faculty of Pharmacy, Department of Pharmaceutical Technology and Biopharmaceutics
Key contact	Prof. Dr. Ioan Tomuta
Website	www.umfluj.ro/informatii-farma-ro/discipline-farma-ro/itemlist/category/71-contact-farma-d4-tfb
E-Mail	tomutaioan@umfluj.ro
Research areas	<ul style="list-style-type: none"> - Mini-tablets: development and testing - Pellets, coated dosage forms - Taste masking - Dermal preparations, Liposomes

Spain**San Cristóbal**

Institution	Universidad de La Laguna
Group	Ingeniería Química y Tecnología Farmacéutica
Key contact	Prof. Dr. Ana Maria Santovena Estevez
Website	www.ull.es/view/centros/farmacia/Inicio/es
E-Mail	ansanto@ull.es
Research areas	<ul style="list-style-type: none"> - Development of liquid formulations for paediatrics - Stability testing

The Netherlands

Groningen

Institution	University of Groningen
Group	Faculty of Science and Engineering
Key contact	Prof. Dr. Henderik W. (Eric) Frijlink, Dr. Caroline Visser
Website	www.rug.nl/staff/h.w.frijlink/
E-Mail	h.w.frijlink@rug.nl
Research areas	<ul style="list-style-type: none">- Solid dosage forms for drugs: tablets, pellets- Biopharmaceutical characterization of drugs- Pulmonary drug administration, dry powder inhalers- Nanoparticles- Formulations, stabilisation of biopharmaceutical drugs (proteins, vaccines)- Orodispersible films (in cooperation with H. Woerdenbag)

Rotterdam

Institution	Erasmus MC
Group	University Medical Center
Key contact	Dr. Lidwien Hanff
Website	www.eur.nl/english/
E-Mail	l.hanff@erasmusmc.nl
Research areas	<ul style="list-style-type: none">- Development of liquid formulations for paediatrics- Extemporaneous formulations (EDQM PaedF group)- Taste masking- Solubilisers

United Kingdom

Bath

Institution	University of Bath
Group	Department of Pharmacy and Pharmacology
Key contact	Dr. Begoña Delgado-Charro, Dr. Nikoletta Fotaki
Website	www.bath.ac.uk/pharmacy/contacts/academics/begona_delgado-charro/
E-Mail	B.Delgado-Charro@bath.ac.uk
Research areas	<ul style="list-style-type: none">- Transdermal drug delivery- Iontophoresis- Nail drug delivery- Dissolution technologies- Non-invasive drug monitoring and pharmacokinetics

Birmingham

Institution	University of Birmingham
Group	School of Pharmacy
Key contact	Dr. Hannah Batchelor
Website	www.birmingham.ac.uk/staff/profiles/clinical-sciences/Batchelor-Hannah.aspx
E-Mail	h.k.batchelor@bham.ac.uk
Research areas	<ul style="list-style-type: none">- Administration of paediatric medicines and the assessment of acceptability- Manipulation of existing medicines for use in children- Food interactions- Paediatric biopharmaceutics classification system- Biorelevant dissolution testing- In silico modelling to predict the performance of medicines in paediatric medicines

Hatfield

Institution	University of Hertfordshire
Group	Department of Pharmacy, Pharmacology and Postgraduate Medicine
Key contact	Dr. Fang Liu
Website	researchprofiles.herts.ac.uk/portal/en/persons/fang-liu(ee2a276b-c65c-4c46-9f8f-cfba3e4f5780).html
E-Mail	f.liu3@herts.ac.uk
Research areas	<ul style="list-style-type: none">- Dermal preparations- Acceptability of medicines in paediatric and geriatric populations

Liverpool

Institution	University of Liverpool
Group	Institute of Translational Medicine
Key contact	Dr. Mark Turner
Website	www.liverpool.ac.uk/translational-medicine/staff/mark-turner/
E-Mail	Mark.Turner@liverpool.ac.uk
Research areas	<ul style="list-style-type: none">- Safety of excipients- Regulatory requirements of paediatric medicines- Clinical studies in neonates (cooperation with Alder Hey Children's Hospital)

London

Institution	University College London
Group	School of Pharmacy, Center for Paediatric Pharmacy Research
Key contact	Dr. Catherine Tuleu
Website	www.ucl.ac.uk/pharmacy/people/academic-research-staff-profiles/catherine-tuleu
E-Mail	c.tuleu@ucl.ac.uk
Research areas	<ul style="list-style-type: none">- Development of paediatric formulations- Drug manipulations and extemporaneous dispensing- Taste assessment (in vitro, in vivo)- Safety and toxicity of excipients for paediatrics (STEP database)- Acceptability of dosage forms (cooperation with Great Ormond Street Hospital)

FEATURED ARTICLE

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SMART DEVICES & DRUG DELIVERY – A HEADS-UP ON LATEST DEVELOPMENTS

By Louise Rosenmayr-Templeton, Tower Pharma Consulting, Vienna, Austria.

Introduction

In the last few years digitalization has leapt from the office and factory into the way health is managed both in hospital and in the community. Digitalization and, in particular, the arrival of Bluetooth technology and the popularity of the Smartphone opens up a myriad of opportunities to monitor health and its treatment in or “almost in” real time, potentially promoting adherence to therapy and the tailoring of treatment to an individual patient's needs. Its sophistication can vary from mobile applications which measure the number of steps taken to facial recognition systems monitoring the administration of medicines. However, its increasing use raises issues of data ownership and use, protection of patient confidentiality and the susceptibility of devices to security breaches. Its use had also wider implications even for more wealthy societies as this technology is only open to the digital savvy and those with good internet connections. This article will not touch further on these security, societal and ethical issues but focus on technology developments in the field and their potential implications for drug development in the future.

Digital Platforms

mySugr

One of the main ways digital technology is used to manage health in the community is through monitoring, data management and advice platforms. mySugr [1], based in Vienna Austria, is an open digital platform used by 1 million people worldwide which aims to simplify diabetes management for patients. The mySugr bundle contains test strips, an Accu-Chek® Guide meter, the mySugr mobile application and diabetes advice on tap from a certified diabetes educator. The Accu-Chek® Guide meter sends the blood glucose values to the mySugr app which enables the patient to review and analyse the data including estimated A1c levels easily and quickly, leading potentially to better management of the disease. The patient has also the possibility to contact a diabetes educator with questions or for advice or share the data with healthcare professionals and care-givers. The app is a class 1 medical device in the US and EU and the Bolus Calculator module has risk class IIb approval (available only in Europe at present). mySugr was acquired by Roche in June 2017 which plans to integrate it into Roche's new patient-centred digital health services for diabetes [2]. As part of the agreement mySugr will remain a separate legal entity and the platform will remain open to patients. Together with mySugr Roche plans to develop new technologies to further improve diabetes management capitalizing on developments in artificial intelligence and big data management.

Ingestible Markers and Adherence to Oral Therapy

Adherence to therapy is a major issue both in clinical research and for ensuing successful therapeutic outcomes. It is thought that 20% to 30% of clinical trials fail due to poor adherence to the study protocol, and even if poor adherence does not impact on the outcome of the trial itself, it results in increased numbers of patients having to be enrolled to ensure that the study results have the intended statistical power. For example, it has been calculated that if 20% of patients do not comply with their medication regimen, then the cohort size needs to be increased by 60% [3]. Any improvement in adherence rates therefore increases the reliability of the data collected and reduces trial costs and the risk

of trial failure. For approved medicines non-adherence has been estimated to cost the U.S. healthcare system alone \$290 billion annually [4] as a result of additional hospital admissions and other healthcare interventions caused by the prescribed treatment not being taken as intended. With diseases like tuberculosis compliance with the prescribed therapy is essential not only to ensure treatment, but also to prevent the development of resistance and spread of the disease. The causes of non-adherence are multi-factorial and difficult for doctors and other healthcare professionals to discern. Common reasons cited for poor compliance are the chronic nature of many therapies, side-effects experienced, lack of belief in medication effectiveness, denial that therapy is required, cost of therapy (an issue in countries where patients must pay or contribute significantly to the costs of their medication) and dosage form and formulation factors such as ease of swallowing, taste, pain on injection and frequency of dosing. A number of companies have or are developing digital tracking of ingestion together with data collection and feedback to monitor adherence and engage patients actively in their therapy.

Abilify™ MyCite™

In November 2017 the FDA approved Otsuka Pharmaceutical Co.'s (Tokyo, Japan) Abilify™ MyCite™, the first ever oral dosage form with a built-in tracking sensor to monitor ingestion [5,6]. Abilify™ MyCite™, which contains aripiprazole, is licensed for the treatment of schizophrenia, acute treatment of manic and mixed episodes associated with bipolar I disorder and as an add-on treatment for depression in adults. The 1mm embedded sensor (Ingestible Event Marker), manufactured by Proteus Digital Health (CA, USA), contains magnesium and cuprous chloride coatings which when wetted by gastric fluid form a circuit that results in a tiny electric charge. This signal is transmitted to a wearable patch, which in turn relays a digital record to a mobile application and then to the Proteus Cloud so that ingestion can be tracked on a smartphone and also accessed via the Cloud. The patch also records the patient's periods of activity and the patient can add details via the app on periods of rest and mood. An icon shows the user if the patch is fully in contact with the skin and functioning properly. The patch is applied just above the lower edge of the rib cage on the left-hand side of the body. The patient has the option of allowing carers and/or their doctor to access the data via a web-based portal.

In its press release [6] the agency highlighted that there is no proof as yet that prescribing Abilify™ MyCite™ aids adherence to therapy, and warned that it should not be used to track real time digestion or in an emergency situation as detection may be delayed (up to 2 hours) or may not occur at all. However, in the majority of cases detection occurs within 30 min.

This was second time that approval had been sought from the FDA for this product. The first time round the agency issued a complete response letter requesting more information about human factors testing and simplification of some of the smartphone app and online portal content to make it easier for patients, especially those with cognitive impairment, to understand and use [7]. The approval shows the commitment of the FDA to supporting innovation in medicines but some physicians have questioned the combination of this type of monitoring with a medication for schizophrenia, a condition where patients can suffer from delusions of being spied on or being poisoned [8, 9].

The tracking used in Abilify™ MyCite™ is known as Proteus Discover™ and was first approved by the FDA as for the ingestion tracking of medicines in 2012. At that time the sensor was not approved to be embedded in a tablet and pharmacies had to be specially contracted to encapsulate it together with the medicine to be tracked. Use of the sensor outside clinical trials only started in 2016 [10] but it has already been shown to have some success in improving adherence in patients with hypertension and diabetes [11]. It remains to be seen if this will also be the case for Abilify™ MyCite™.

ID™ sensor technology

Etecrx Inc (FL, USA) is another company employing an ingestible sensor to track the administration of medicines. Its ID™ sensor technology [12] is embedded in a standard gelatin or hydroxypropyl methylcellulose capsule and sends a signal when it comes into contact with stomach fluids to a reader which is worn round the patient's neck and therefore can be removed between doses, unlike the Proteus patch. This of course has advantages (no potential skin irritation) but also disadvantages (can be forgotten by the patient). No patch is required as the sensor generates a low-power radio signal that can be detected by a small nearby antenna. The company also plan to fit the reader into wrist-bands and mobile phone cases [9]. The data from the reader is forwarded to a mobile phone or other internet connected device via Bluetooth technology. The output of the reader can accessed via a portal by the patient and/or healthcare professionals, and can be linked with data from other devices and sensors. Context specific messages are sent to the patient or others based on adherence and/or other criteria. The capsule is currently only available for use in IRB approved clinical trials as it has not yet received FDA clearance which the company hopes will happen in 2018. So far it has been tested with opioids, HIV medication and some other drugs.

Use of Artificial Intelligence

Proteus Digital and Etecrx are not the only companies developing interactive technology to track patients' adherence to medication through digitalization. AiCure Inc. (NY, USA) has developed an artificial intelligence platform based on technology which can provide facial recognition, automatic medication identification, real time ingestion confirmation and fraud and duplicate enrolment detection all by downloading an app onto a smartphone [13]. The app prompts the patient to hold the medication in front of the camera for identification purposes and then the patient is filmed administering the medication. The data can be analysed to check for adherence and unusual activity to enable intervention by healthcare staff at an early stage. The platform can be customized based on disease type, patient demographics and

risk factors. The advantages of this system are that it is interactive, there is no modification of the dosage form required and no detector system (patch or portable reader) is required to be placed on or be close to the patient's body. The disadvantage is that patients must film themselves taking the medicine which requires privacy and may not be acceptable to all individuals.

The AiCure's technology is aimed at two different markets: clinical development and the monitoring of adherence to medication in the community. For this type of application the AiCure software provides automatic titration, reminders and scheduling information to the trial participants and enables the study site to log interventions and protocol deviations. With regard to the second market for this technology, the AiCure app has been used e.g. to monitor administration of tuberculosis therapy, a task normally carried out in person by a healthcare professional. In this study a 94% mean adherence rate was achieved with the increased convenience of the patients not having to leave their homes and without the costs associated with in-person monitoring [13].

Interconnected Injection Devices

Biopharmaceutical medicines are expensive to manufacture and often prescribed for serious chronic conditions. Due to the instability of these compounds in intestinal fluids and their inability to be orally absorbed, injection is the only option for administration. This route of administration can be off-putting to patients and the nature of some administration schedules make it difficult for patients to keep track of when they should administer their next dose. In addition, the cost of poor adherence in terms of patient health and the serious side-effects often associated with such products make them ideal candidates for support and coaching through digital services. Bayer, Germany has brought to the market an electronic autoinjector designed for patients to use with its Betaseron™ product.

Betaconnect™ – An electronic autoinjector

The Betaconnect™ autoinjector is an electronic autoinjector for the subcutaneous administration of Betaseron™, Bayer's interferon beta-1b product for the treatment of multiple sclerosis [14]. It was recently showcased in a presentation by Dr. Karym El Sayed at the 2nd European Conference on Pharmaceutics which took place on 3rd and 4th April 2017 in Krakow, Poland [15].

The electronic autoinjector was first approved by the FDA in 2015 [16]. The autoinjector is provided by Bayer at no cost to the patient if they register for it on the dedicated website. The autoinjector has three adjustable injection depth settings (8mm, 10 mm and 12 mm) to enable the doctor to determine the correct depth setting and injection technique and provide training to patients and/or caregivers wishing to administer the medication at home. The needle automatically inserts and retracts at a customizable speed on activation of the device, meaning that patient does not need to see the needle. A visual progress viewer enables confirmation that the injection is complete. The device captures data from each injection with regard to injection date, time, speed and depth. Patients can download a myBeta app to activate the Bluetooth® technology within the autoinjector from the Betaconnect™ website. Once activated the injection history data is automatically transferred to a designated Beta nurse and other members of the patient's healthcare team via secure, cloud-based software called the BETACONNECT™ Navigator. The device also allows patients to set reminders of when their next injection is due. Through use of the app on their smartphone, computer or laptop, patients can receive a schedule of their past and future injections, keep track of their injection site rotation (the injection site for Betaseron™ should be rotated in order to avoid irritation at any one site), be reminded about data recordings and enter how well they are feeling on a particular day.

Monitoring Inhaler Use

There are relatively low rates of adherence to preventative medication among asthmatics and sufferers of Chronic Obstructive Respiratory Disease (COPD) resulting in avoidable acute episodes and associated visits to clinics and hospitalisations. A number of companies are working on technologies to track inhaler usage in an attempt to improve adherence and clinical outcomes to therapy for respiratory disease.

Smartinhaler™

The Smartinhaler™ technology by Adherium Ltd (Auckland, New Zealand) enables the application of digital technology to the use of metered dose inhalers, dry powder inhalers and nebulisers [17]. It consists of sensors that are attached to the patient's prescribed medication, mobile applications for iOS and Android and a cloud-based portal for researchers and clinicians. The company offers custom user interface options for an additional cost. The technology has been granted US FDA 510(K) clearance to market and a CE mark. On use the sensors automatically send usage data to a Smartphone with the Smartinhaler™ app via Bluetooth® or over the Smartinhaler™ Home Hub to the Smartinhaler-live.com cloud-based portal. It is also possible to transfer the data via a personal computer using a Smartkey. The technology also is capable of sending audiovisual alerts to patients to remind them when preventative medication has to be administered.

The use of the monitoring technology has been shown to improve adherence in a number of clinical studies in adults and children. In one study use of the device was shown to improve the adherence rate to preventative medication from 30 percent to 84 percent in asthmatic children [18]. AstraZeneca, Glaxo, Teva, Mylan and Ivax are among those who have partnered with Adherium for use of the technology with their asthma medications e.g. Astra Zeneca's Smartturbo™ Pulmicort™. The company recently celebrated the sale of its 100,000th Smartinhaler™.

Others companies developing digital monitoring systems for inhalers include Propeller Health Inc. (WI, USA) [19] which has a clip-on sensor system and has signed deals with Glaxo Smith Kline (for the Diskus™ and Ellipta™ inhaler), Boehringer Ingelheim (for Respimat™) and most recently Vectura; Gecko Health Innovations [20] (MA, USA) (which is now owned by Teva Pharmaceuticals) and Qualcomm which is collaborating with Novartis. The Novartis/Qualcomm collaboration [21] differs from the others in that the goal is to produce a sensor that is integrated into the next generation of Novartis' Breezhaler™ which is used with its portfolio of COPD products.

Comment

Electronically monitoring adherence to medication dosing regimens and providing digital feedback to patients has become an area of intense activity in the last two or three years, with the global market for medication adherence products predicted to grow from \$1.6 billion in 2016 with a compound annual growth rate of 12.3% until 2023 [22]. From a pharmaceutical perspective development of digital technology for inhalers appears to be the most advanced probably as a result of the positive outcomes observed in clinical studies of adherence to respiratory therapy. Developments in the field of oral products seem to be further behind with the benefits of tracking of adherence to oral administration in out-patient settings not yet proven. Most benefit with digital systems seems occur when medication administration and/or disease management is complicated, of a chronic nature and the consequences of non-adherence are not immediately apparent. For oral products which tend to be relatively simple and cheap to manufacture, the need to prove compatibility between the sensors and the formulation and the additional manufacturing costs will always act as a barrier to the use of such technology. Drivers for its use will be increased patient engagement in their therapy due to the support and information provided, the novelty of being able to track usage and receive reminders and, for healthcare providers and payers, the reduced costs due to improved clinical outcomes. However, based on the positive outcomes seen in monitored asthma and COPD treatment and the continuing unnecessary burden placed on cash-strapped healthcare systems due to poor compliance with therapy, the inclusion of digital technology in dosage forms and devices looks set to become more common. Its role in the monitoring of adherence in clinical trials is also likely to expand due to the need for rapid interventions to reduce study costs, and ensure that the study results are not compromised by poor compliance with the protocol.

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COMBINING SCIENCE AND TECHNOLOGY TO CREATE ADVANCED DRUG DELIVERY SYSTEMS

OUR MISSION STATEMENT:

Modern drug delivery research and development is a truly multidisciplinary approach and must combine all relevant scientific, technical, medical and regulatory aspects required for the design, preparation, testing, manufacturing and registration of drug delivery systems and their components. It is the mission of the APV Drug Delivery Working Group to foster and promote all aspects of research and development required to transform drug molecules into safe, applicable and acceptable drug delivery systems, which provide therapeutic benefit, convenience to the patient and improve patient compliance.

Our mission includes in particular the following tasks:

- Thoroughly understanding the physical-chemical and biopharmaceutical properties of the drug substance to be delivered and the components of the drug delivery system
- Understanding the biological barriers and the interactions of the drug molecule and its delivery system with the biological environment and the biological target including PK/PD and PK/safety relationships
- Research on excipients, materials and technologies required for the design, preparation and manufacturing of drug delivery systems for a selected route of administration
- Development and understanding of methods for in vitro and in vivo evaluation of drug delivery systems and their components
- Knowledge of regulatory requirements for clinical testing, manufacturing and registration of drug delivery systems

All disciplines relevant to the above mentioned areas of drug delivery R&D are invited to contribute to the APV Drug Delivery Group:

Pharmaceutics, Biopharmaceutics, Analytics, Biology, Physical Chemistry, Biochemistry, Physics, Engineering Sciences, Nano Technology, Material Sciences, Polymer Science, Toxicology, Drug Safety, Clinical Research, Drug Regulatory Affairs, etc.

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