APV Focus Group Drug Delivery

Combining Science & Technology to Create Advanced Drug Delivery Systems

INTERNATIONAL ASSOCIATION FOR PHARMACEUTICAL TECHNOLOGY

NEWSLETTER **ISSUE 3/2018 - NOVEMBER**

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+ **4th APV Winter Conference 2018- Individualized Medicines – Visions and challenges for all stakeholders in pharmaceutics | KN 6765** — Details
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+ **Parenteral Formulation Development and Drug Delivery | KN 6763** — Details
  February 26-27, 2019 | Berlin, Germany

3rd EUROPEAN CONFERENCE ON PHARMAEUTICS, Bringing science into pharmaceutical practice — Details
March 25-26, 2019 | Bologna, Italy

+ **Advanced Patent Workshop "Master Class" for Pharmaceutical R&D Professionals - How to effectively manage the IP interface | KN 3201** — Details
  April 04-05, 2019 | Berlin, Germany

46th Annual Meeting & Exposition of the Controlled Release Society — Details
July 21–24, 2019 | Valencia, Spain

Suggest a meeting to be announced!

REFLECTIONS ON OUR PATENT WORKSHOP SERIES

By Karsten Cremer

An intensive patent workshop for R&D professionals - is there a need for this? This is what I asked myself about 10 years ago when my colleagues in the APV Drug Delivery Focus Groups suggested that I develop such a course. Yes and no, I thought. Yes, because I was aware that the interface between pharmaceutical R&D and IP is not working well in many companies (R&D: "We should try to protect this new prototype formulation." versus IP: "So why do you think this is an invention?"). No, because R&D professionals are interested in science, technology and/or project timelines, and not so much in dry patent know-how. So I said that I would really like to develop this workshop, but unfortunately I have no time, sorry. After I had escaped two or three times by saying this, it became too embarrassing and I finally started working on the programme.

The first course was scheduled in 2011, it was fully booked, and it was well received by the participants. Of course I had hoped to be able to repeat the workshop sometime - after all, the preparation of the course material was a huge effort. However, I had not expected the overwhelming response which led us to schedule the workshop every year - occasionally even twice a year. In addition, several pharmaceutical companies asked me to conduct this workshop in-house. As of today, several hundreds of pharmaceutical R&D professionals have participated.

In 2017 my colleague, Kurt Schellhaas, and I introduced our advanced patent workshop. The encouragement came once again from the Drug Delivery Focus Group. It was suggested that some former participants of the "basic" intensive course could be interested in a continuation at an advanced level addressing the needs of professionals in roles in which the collaboration with IP experts is particularly close. This workshop also received very positive feedback. As it targets a real niche market, we currently plan to schedule it only every two or three years.

So what is the difference between the two courses? The "INTENSIVE PATENT WORKSHOP: How to draft, analyse and circumvent a formulation patent" is designed to provide basic patent know-how and the working skills to actually apply it in a pharmaceutical R&D environment. It teaches the legal essentials about patents that every R&D scientist or manager should understand. The first part of the workshop uses numerous practical examples especially from formulation development to explain how to deal with third party patents, i.e. how to identify, read, analyse and circumvent them. In the second part, participants learn about the patentability of inventions, and they also get practical tips on how to evaluate R&D data to define inventions, determine their scope, and contribute to the preparation and prosecution of patent applications. The most recent "intensive" patent workshop took place on 05-06 November 2018 and was again highly appreciated.

The course "Advanced patent workshop "MASTER CLASS" for pharmaceutical R&D professionals: How to effectively manage the IP interface" takes a closer look at what it takes to make a patent strong, so that it survives an opposition and can be successfully enforced against infringers. It also deals with patent portfolio strategies, with monitoring and challenging competitor patents. Another module that participants found very helpful is on how to deal with IP in collaborations, which uses real-world case studies to explain the benefits and pitfalls of common IP ownership and licensing terms. The next "advanced" course is planned for 04-05 April 2019.

I thank my colleagues in our Focus Group for their support and encouragement, and I would also like to thank the participants of the previous patent workshops for their valuable feedback and their suggestions which helped us to further improve these courses.

DRUG DELIVERY PRODUCTS

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Provided by Dr. Louise Rosenmayr-Templeton

ARIKAYCE® (amikacin liposome inhalation suspension)

At the end of September the FDA granted Arikayce® liposomal suspension for oral inhalation from Insmed Inc. (NJ, USA) approval for the treatment of mycobacterium avium complex (MAC) infection in adults with limited or no other treatment options following an accelerated review [1, 2]. The product received approval via the FDA's Limited Population Pathway for Antibacterial and Antifungal Drugs (LPAD) for its use in combination with standard guideline-based anti-bacterial therapy in patients with refractory disease, where refractory disease is defined as not achieving negative sputum cultures despite a minimum of 6 consecutive months of multi-drug therapy. It was based on the ability of Arikayce® in combination with standard therapy to achieve sputum conversion (negative sputum cultures for three consecutive months) by month 6 in an ongoing Phase 3 open-label study to a statistically significant greater extent than standard treatment alone.

Arikayce® contains amikacin 590 mg/8.4 mL (corresponding to amikacin sulfate 623 mg/8.4 mL) and was developed using Insmed's Pulmovance™ liposomal technology. In addition to the active substance, the formulation contains cholesterol, dipalmitoylphosphatidylcholine, sodium chloride, sodium hydroxide (for pH adjustment), and water for injection. It has a pH of 6.1 to 7.1 and the lipid to amikacin weight ratio is in the range of 0.60 to 0.79. It is administered once daily by nebulization using the LamiraTM portable Nebulizer System from PARI Pharma GmbH [3]. Using this nebuliser the mean delivered dose from the mouthpiece is approximately 312 mg of amikacin sulfate (53% of label claim) under standardized testing conditions according to the USP<1601> adult breathing pattern (500 mL tidal volume, 15 breaths per minute, and inhalation: exhalation ratio of 1:1). The mass median aerodynamic diameter (MMAD) of the nebulized aerosol droplets is 4.7 µm (4.1 – 5.3 µm) using the Next Generation Impactor (NGI) methodology. The advantage of the liposomal Amikacin is that it is delivered directly to the site of infection, reducing the potential for systemic toxicity [2].

It is the first inhaled therapy specifically for the treatment of MAC and the first product to be approved via the LPAD initiative. However, continued approval is dependent on verification of clinical benefit with the company currently in discussion with the FDA over clinical trial design of a further clinical study. The company is also conducting research to widen the indications for Arikayce including its development as a treatment for lung disease caused by non-tuberculous mycobacteria non-MAC species, e.g., M Abscessus [4].

ONPATTRO™ (PATISIRAN) LIPID COMPLEX INJECTION [5]

On 10th Aug following a priority review, the FDA granted regulatory approval to Onpattro™ (patisiran) lipid complex injection, a RNA interference (RNAi) product from Alnylam Pharmaceuticals Inc. (MA, USA) for the treatment of polyneuropathy due to hereditary transthyretin-mediated (hATTR) amyloidosis in adults [6]. Similarly on 30 Aug the product received a marketing license in Europe for Stage 1 and 2 neuropathy in hATTR adult patients [7], following a positive

opinion from the EMA's Committee of Human Medicinal Products (CHMP) in July 2018 [8]. The granting of both licenses are a first for a RNAi therapeutic but Onpattro™ is also the only specific medicinal treatment for this rare indication to gain approval in the USA.

hATTR amyloidosis is caused by mutations in the TTR gene which encodes for the TTR protein which functions as a carrier for Vitamin A in the body. These mutations lead to the progressive accumulation of amyloid in the body which subsequently causes damage to peripheral nerves and cardiac tissue. This damage results in intractable peripheral sensory neuropathy, autonomic neuropathy, and/or cardiomyopathy, disability and eventually morbidity. The median survival rates for patients after diagnosis is 4.7 years.

Patisiran is a small double-stranded interfering ribonucleic acid (siRNA). It functions to reduce or switch off synthesis of the TTR protein in the liver by binding to the messenger RNA involved in both wild-type and mutant protein translation causing its degradation. As a result levels of both the native protein and the damaging amyloid are diminished. It is formulated as a lipid complex 10 mg in 5ml (2mg/ml) injection and dosed at 0.3 mg/kg every three weeks by intravenous infusion to patients under 100 kg following pre-treatment with a corticosteroid, paracetamol and anti-histamines (both H1 and H2 receptor blockers). The dose for patients heavier than 100 kg is 30 mg. The main side-effects seen in clinical trials are infusion-related reactions and upper respiratory tract infections. Unsurprisingly given the TTR protein's function, Vitamin A levels in the serum are reduced by therapy with Onpattro™ and supplementation is recommended [9].

Approval was based on the results of the placebo controlled Phase 3 APOLLO study. It involved hATTR amyloidosis patients in 19 countries with a diverse range of TTR gene mutations (39 in total) which were treated with either Onpattro™ or placebo every three weeks for 18 months.

The results showed that patisiran therapy met the primary endpoint for the study which was improvement in the modified Neuropathy Impairment Score +7 (mNIS+7) compared with placebo. This score assesses motor strength, reflexes, sensation, nerve conduction and postural blood pressure. Treatment also showed positive benefits with respect to other measures of polyneuropathy including life quality, mobility and level of activity.

References and Further Information

[1] Insmed Announces FDA Approval of ARIKAYCE® (amikacin liposome inhalation suspension), the First and Only Therapy Specifically Indicated for the Treatment of Mycobacterium Avium Complex (MAC) Lung Disease in Adult Patients with Limited or No Alternative Treatment Options. http://investor.insmed.com/news-releases/news-release-details/insmed-announces-fda-approval-arikaycer-amikacin-liposome.

[2] Entry for ARIKAYCE® on Drugs@FDA https://www.accessdata.fda.gov/scripts/cder/daf/index.cfm?event=overview.process&ApplNo=207356

[3] Pari Pharma website. https://www.pari.com/holding-en/research-and-development/.

[4] Insmed Inc. website. https://www.insmed.com/.

[5] The information on Onpattro™ forms part of an Industry Update for August 2018 by Dr. Louise Rosenmayr-Templeton which has been accepted for publication in the journal Therapeutic Delivery, Vol 9 (10) and is reproduced here with the permission of Therapeutic Delivery.

[6] Alnylam Announces First-Ever FDA Approval of an RNAi Therapeutic, ONPATTRO™ (patisiran) for the Treatment of the Polyneuropathy of Hereditary Transthyretin-Mediated Amyloidosis in Adults. http://investors.alnylam.com/news-releases/news-release-details/alnylam-announces-first-ever-fda-approval-rnai-therapeutic.

[7] Alnylam Receives Approval of ONPATTRO™ (patisiran) in Europe. http://investors.alnylam.com/news-releases/news-release-details/alnylam-receives-approval-onpattrotm-patisiran-europe.

[8] Meeting highlights from the Committee for Medicinal Products for Human Use (CHMP) 23-26 July 2018 http://www.ema.europa.eu/ema/index.jsp?curl=pages/news_and_events/news/2018/07/news_detail_002994.jsp&mid=WC0b01ac058004d5c1.

[9] Entry for on Drugs@FDA for Onpattro™. https://www.accessdata.fda.gov/scripts/cder/daf/index.cfm?event=overview.process&ApplNo=210922

DRUG DELIVERY PEOPLE

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Provided by Dr. Lea Ann Dailey

For this issue of the Newsletter, we would like to introduce **GERT STORM** as our featured Drug Delivery Scientist. Prof. Storm is a biologist by training with an undergraduate degree in Biology followed by a PhD in Pharmaceutics both from Utrecht University in The Netherlands. Following his graduate studies, he spent some time in the United States as a visiting scientist at Liposome Technology, Inc. at Menlo Park, California and as visiting assistant professor at the University of California San Francisco, School of Pharmacy. Following a brief position at Pharma Bio-Research Consultancy B.V. in Zuidlaren (The Netherlands), he returned to academia in 1991 after accepting a post as Professor of Targeted Drug Delivery at Utrecht University. From 2012 on, he is also professor (Targeted Therapeutics) at the University of Twente. He also holds a number of honorary posts, such as Honorary Professor in Biomacromolecular Drug Delivery at the University of Copenhagen and Professor at the National University Hospital, Singapore.

Prof. Storm has been a pivotal figure in the fields of biopharmaceutics and advanced drug delivery/drug targeting. With over 600 original articles, reviews and book chapters to his name, he has been listed yearly in the 2014-2018 period, as one of "The World's Most Influential Scientific Minds" based on the Thomson Reuters Highly Cited Researchers list (2002-2017) which was recently taken over by Clarivate Analytics. He has held key roles in the European Foundation for Clinical Nanomedicine (ESNAM/CLINAM), the Controlled Release Society, the International Liposome Society, the Phospholipid Research Center, the Galenos Network, the Dutch Society for Gene Therapy, the European Workshop on Particulate Systems, and The Netherlands Platform for Targeted Nanomedicine (NPTN).

His research is focussed on the clinical translation of targeted nanomedicines, with a special interest in cancer therapeutics and imaging-guided drug delivery. With the creation of Enceladus Pharmaceuticals BV in 2005, he was involved in the clinical development of liposomal corticosteroids for chronic inflammatory diseases. His team has also developed temperature responsive drug delivery vehicles for image-guided targeted doxorubicin delivery with hyperthermia in breast cancer patients (HIFU-CHEM project).

DRUG DELIVERY GROUPS

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Provided by Dr. Dieter Becker

ACADEMIC GROUPS WITH FORMULATION CAPABILITIES FOR POORLY WATER-SOLUBLE DRUGS

This newsletter section is intended to give a brief overview of academic groups working on formulation of poorly water-soluble drugs. It is the seventh of an occasional series giving brief details of European research teams exploring different aspects of drug delivery research. It is not intended to be a comprehensive list of those involved in the area. 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.

The groups working on hot melt extrusion for poorly water-soluble drugs are published in the Newsletter 2013/01. The contact person given is the head of the department.

Belgium

Research Focus	Mesoporous solid dispersions
Institution	University of Leuven
Address	Drug Delivery and Disposition, O&N II Herestraat 49 - box 921, 3000 Leuven, Belgium
Contact	Patrick Augustijns
eMail	patrick.augustijns@kuleuven.be
Web site	https://gbiomed.kuleuven.be/english/research/50000715/50000716/

Denmark

Research Focus	Amorphous solid Dispersions and stabilization, Nano particulate systems
Institution	University of Copenhagen
Address	Department of Pharmacy, Solid State Pharmaceutics, Universitetsparken 2, DK-2100 Copenhagen, Denmark, Phone: +45 35 33 60 32
Contact	Thomas Rades
eMail	thomas.rades@sund.ku.dk
Web site	https://farmaci.ku.dk/

Research Focus	Lipid based systems
Institution	University of Copenhagen
Address	Faculty of Health and Medical Sciences, Department of Pharmacy, Physiological Pharmaceutics, Universitetsparken 2, 2100, Copenhagen, Denmark
Contact	Anette Müllertz
eMail	anette.mullertz@sund.ku.dk
Web site	https://farmaci.ku.dk/

Research Focus	(Phospho)lipid based systems
Institution	University of Southern Denmark; Odense
Address	Campusvej 56, DK-5230 Odense M
Contact	Annette Bauer Brandl / Martin Brandl
eMail	annette.bauer@sdu.dk mmb@sdu.dk
Web site	http://findresearcher.sdu.dk/portal/en/persons/annette-bauerbrandl(dde1ac7d-e5e6-4af8-a0fc-343981b93794).html http://findresearcher.sdu.dk/portal/en/persons/martin-brandl(99207cc9-7617-4a96-8cfe-51e6c9f7f277).html

Germany

Research Focus	Hot-melt extrusion
Institution	Heinrich-Heine University
Address	Düsseldorf, Germany
Contact	Jörg Breitkreutz
eMail	joerg.breitkreutz@uni-duesseldorf.de
Web site	http://www.pharmazie.hhu.de/en.html

Research Focus	Nano-milling
Institution	Freie Universität, Berlin
Address	Department of Pharmaceutical Technology, Biotechnology and Quality Management, Germany
Contact	Rainer Müller
eMail	rainer.mueller@fu-berlin.de
Web site	https://www.bcp.fu-berlin.de/pharmazie/faecher/pharmazeutische_technologie/index.html

Research Focus	Semi Solid / parenteral Lipid based systems
Institution	TU Braunschweig
Address	Technische Universität Braunschweig, Institut für Pharmazeutische Technologie, Mendelssohnstr. 1, 38106 Braunschweig
Contact	Heike Bunjes
eMail	heike.bunjes@tu-braunschweig.de
Web site	https://www.tu-braunschweig.de/pharmtech/institut/arbeitsgruppen/bunjes

Great Britain

Research Focus	Amorphous Pharmaceuticals including manufacturing processes
Institution	University of East Anglia
Address	School of Pharmacy, Norwich Research Park, Norwich, R4 7TJ, United Kingdom
Contact	Mark Searcey
eMail	m.searcey@uea.ac.uk
Web site	https://www.uea.ac.uk/pharmacy

Finland

Research Focus	Amorphous Solid Dispersions
Institution	University of Eastern Finland
Address	School of Pharmacy, P.O.Box 1627, 70211 Kuopio, Finland
Contact	Jarkko Ketolainen
eMail	jarkko.ketolainen@uef.fi
Web site	http://www.uef.fi/en/web/farmasia/home

Research Focus	Stabilized Amorphous Solid Dispersions with Small Molecule Excipients
Institution	University of Helsinki
Address	Faculty of Pharmacy, Viikinkaari 5 E (PL 56), 00014 Helsinki, Finland, phone +358 (0) 2941 911 (Switchboard)
Contact	Jouni Hirvonen
eMail	jouni.hirvonen@helsinki.fi
Web site	https://www.helsinki.fi/en/faculty-of-pharmacy

France

Research Focus	Polymer Gels, Hydrogels, and Scaffolds
Institution	Universite Paris Sud
Address	5 rue Jean-Baptiste CLEMENT,92296 CHÂTENAY-MALABRY, FRANCE, Tel: +33 (0)1 46 83 55 81
Contact	Gilles PONCHEL
eMail	gilles.ponchel@u-psud.fr
Web site	http://www.pharmacie.u-psud.fr/fr/la_faculte/presentation-de-la-faculte.html

Switzerland

Research Focus	Solid dispersion, Lipid based systems,
Institution	FHNW University of Applied Science and Art Northwestern Switzerland
Address	School of Life Sciences, Institute for Pharma Technology, Hofackerstrasse 30, CH-4132 Muttenz, Switzerland
Contact	Georgios Imanidis / Martin Küntz
eMail	georgios.imanidis@fhnw.ch martin.kuentz@fhnw.ch>
Web site	https://www.fhnw.ch/en/research-and-services/lifesciences/pharma-technology

DRUG DELIVERY COMPANIES

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Provided by Dr. Dieter Becker

PHARMACIRCLE (ENCINITAS, USA)

Fact sheet:

Founded:	2003
Location:	199 La Costa Ave, Encinitas, CA 92024, USA
Ownership:	Privately owned
Employees:	>5
Key technology:	The PharmaCircle database enables searches that are otherwise are not possible because the information is extracted and **recompiled** from public data sources and English translation is provided where necessary. Recompilation to a standard data structure is the key technology because similar data (e.g. FDA & EMA) from different sources have a different structure that makes it nearly impossible to search across that data without recompilation. In addition to searches the usable analyze and compare tool is available to get better insights in the facts of interest.
Products:	Web based database with a huge coverage of all information important for pharmaceutical, biotechnology, veterinarian and medical device industry. Information is provided for R&D, regulatory and business departments. Restricted access to licensees with high annual fees. Key content of the PharmaCircle database and capabilities include (bold key for product development; in parenthesis the number of information entries 2016 [not complete]): • Company Capabilities Profiles • **Pipeline & Products Intelligence** (120,000) • **Physical chemical and pharmacokinetic data** (35,000 molecules) • **Formulation and component details, including excipient amounts** (13,500 excipients) • **Drug Delivery Technology and Device Analysis** (5,500 technologies) • Patent Exclusivity Tracking (2,000 US paragraph IV filings) • API Source and Manufacturers Finder • Business Prospecting Tools • Trial Landscape Insights (189,000 clinical trials) • **Key Product Sales & Forecasts** (14,200 product sales reports) • Strategic Deals Analysis • Venture Capital Investment Tracking (5,200 VC transactions) • R&D Cost/Spend Data for individual product/pipeline programs • **Regulatory Approvals Documents Archive back to the 1990s** (63,900 FDA approval documents) • **Drug Label Database & Label Comparison Tools** (87,000 FDA labels) • Weekly Formulation & Drug Delivery Newsletter
Development status:	Database on market since 2003.
Partnerships:	Most of the top 20 Pharma companies and numerous commercial and emerging stage biopharmaceutical companies /suppliers have licensed access to the PharmaCircle database.
Website:	http://www.pharmacircle.com Company presentation 2016
Contact:	PharmaCircle, LLC Sales and Marketing 199 La Costa Ave Encinitas, CA 92024, USA Phone: +1 800-439-5130 Email: info@pharmacircle.com

TOXICOLOGY IN NANOMEDICINE: CURRENT STATUS AND FUTURE PROSPECTS

By Dagmar Fischer
Pharmaceutical Technology and Biopharmacy, Friedrich-Schiller-University Jena, Lessingstraße 8, 07743 Jena

1. The status quo of the use of nanomaterials in drug products

The implementation of nanotechnology in medicine is celebrated as one of the key technologies of the 21st century leading to success stories mainly in the treatment, but also in the diagnosis and prevention of diseases. Nanomaterials may function as active pharmaceutical ingredients per se (e.g. nanocrystals), innovative excipients, drug carriers (e.g. liposomes) or as complexes and conjugates (e.g. drug-poly(ethylene glycol)). They were often referred as "non-biological complex drugs" (NBCD) due to their mostly synthetic origin and their self-assembly during preparation [1]. For drug delivery the use of nanomaterials has been employed to increase drug solubility and stability, improve biocompatibility, accomplish the crossing of body barriers, prolong circulation times and to reduce accumulation in non-target tissues by active or passive targeting [2]. The world of nanomaterials in medicine is highly diverse consisting of hard (iron oxide, zinc oxide, gold, silver, etc.) and soft (liposomes, dendrimers, micelles, etc.) matter materials with different surface structures and charges, shapes and ligands which hampers the establishment of prediction models for structure-activity and structure-toxicity relationships making risk assessments and classification approaches difficult.

Formulation	Distribution	Examples	Pharmaceutical Application
Liposome 	35%	AmBisome®	Intravenous application of liposomal encapsulated amphotericin B (antimycotic)
		Caelyx®	PEGylated liposomal doxorubicin hydrochloride (cytostatic)
Nanocrystal 	29%	Emend®	Aprepitant nanocrystals (antimycotic)
		Rapamune®	Sirolimus/Rapamycin nanocrystals (immunosuppressant)
Emulsion 	9%	Disoprivan®	Oil-in-water emulsion with propofol (narcotic)
		Intralipid®	Intravenous fat emulsion (parenteral nutrition)
Iron-polymer complex 	8%	Ferrlecit®	Sodium ferric gluconate iron complex for intravenous iron substitution (antianemic)
		Injectafer®	Ferric carboxymaltose complex for intravenous iron substitution (antianemic)
Micelle 	3%	Fungizone®	Lyophilized surfactant-containing amphotericin B powder (antimycotic)
		Taxotere®	Surfactant docetaxel injection concentrate (cytostatic)
Others: Drug-protein complex, Drug-polymer complex, Dendrimer, Polymeric nanoparticles, Nanobubbles, Silica nanoparticles, Drug-lipid complex, Drug-metal complex, Protein nanoparticles, Solid lipid nanoparticles, Nanotubes, Metal-protein complex, Metal-nonmetal complex, Metal-polymer complex			

Table 1: Types of nanomaterials used in drug products from 2010 to 2015 and distribution of all submissions (%) modified according to D'Mello S R et al. Nat Nanotechnol, (2017) 12(6):523-29.

In the years 2010-2015 in USA (CDER, FDA) liposomes dominated the nano-related submissions followed by nanocrystals, emulsions, iron-polymer-complexes and micelles (Table 1). Submissions were mainly focused on cancer treatment (40%) and 63% were intended for intravenous administration followed by oral and ophthalmic use [3]. Nanoparticle containing drug products must meet the same standards for quality, efficacy and safety as those without nanomaterials, but special size-related aspects are taken into consideration on a case-by-case approach. In the review process authorities follow the existing regulatory pathways suggesting that the current regulatory framework is capable of managing potential nano-risks [3]. The presence of nanomaterials seems not to complicate or delay the regulatory review.

2. Adequate characterization is the key: The life-cycle concept

To define a control strategy in nanomaterial development and to perform material and process risk management, critical quality attributes have to be identified and linked to preclinical and clinical safety and efficacy. Particularly, for a valid toxicological evaluation of nanomaterials an extensive understanding of their physicochemical properties is required and several initiatives have proposed collections of parameters relevant for physicochemical or toxicological testing (SCENIHR, EMA/CHMP, NANoREG). However, a look in the scientific literature shows that in many cases only the standard characterization of nanomaterials "as synthesized", i.e. as provided by the supplier in dispersion or as dry powder, was performed. Changes in the nanomaterials depending on their fate in the body were often not or insufficiently taken into consideration.

The life cycle of nanomaterials can be categorized into four stages (Figure 1). Beside the stage 1 "as synthesized" testing, changes in the nanomaterials "in relevant biological test media" (e.g. buffers, cell culture media) or in artificial body fluids (e.g. artificial endosomal/lysosomal fluid, artificial mucus) should be evaluated in stage 2. Agglomeration, changes in size, stability, or surface charge are critical quality attributes that are known to influence the distribution in the body, uptake into cells, or elimination. As an example, cationic nanoparticles often tend to agglomerate in salt containing test media, and therefore act like larger entities with lower cell uptake rates or barrier crossing [4].

Additionally, in the life cycle of nanomaterials the "biomolecule corona" (stage 3) plays an important role. Immediately after contact with body fluids or serum-containing cell culture media several hundreds of plasma proteins adsorb to the nanomaterial surface transforming the "chemical identity" of the nanomaterials into a new "biological identity". For silica nanoparticles the modification of the surface by almost 300 different proteins within several seconds of contact with human plasma depending on the nanoparticle surface characteristics could be determined [5]. The new identity was shown to dominate many properties such as colloidal stability, pharmacokinetics and toxicity. The proteins were suggested to function as opsonins (e.g. fibrinogen, immunoglobulins) and complement proteins that promote phagocytosis and clearance of the vectors, contributing to unwanted biological side-effects. Additionally, they may hinder the ability of nanoparticles to bind to their targets and reduce cell uptake. In contrast, pre-coating of nanoparticles with dysosonins such as albumin was shown to avoid RES uptake, extend circulation times and decrease cyto- and hemotoxicity [5]. Although researchers have gained massive information about the composition of coronas due to the tool of proteomics, they do not fully understand them and successful approaches for the controlled use of this kind of information have not yet been exploited in commercial applications [6, 7]. Furthermore, as the term "biomolecule corona" implies, additionally other components like lipids can be found adsorbed to the nanoparticle surface after contact with human plasma or lung mucus which were up to now not systematically recognized [8].

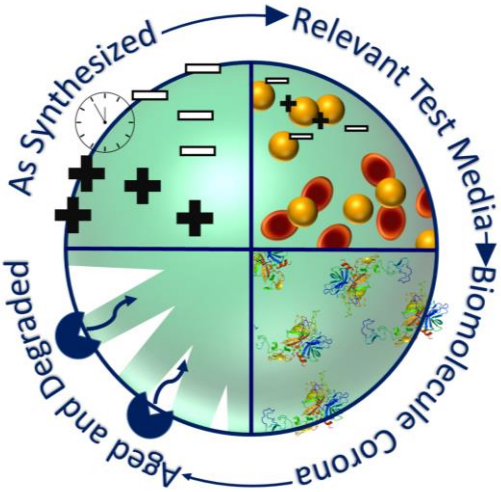

Figure 1: The life-cycle concept in the development and toxicology testing of nanomedicines.

Especially for nanomaterials with longer residence time in the body or slow degradation behavior, stage 4 the "aging and degradation" behavior has to be taken into consideration causing changes in the appearance of the particles, formation of degradation products or the release of substances. For example, iron oxide nanoparticles with various polymeric coatings demonstrated degradation behavior in different artificial body fluids which was found to be dependent not only on the type of the body fluid, but also on the type of coating material as a result of the biodegradability, water permeability, surface charge and acid/base character of the coatings (https://www.nanopartikel.info/projekte/laufende-projekte/nanobel). Since especially in early preclinical development long-term degradation animal experiments (e.g. several months for iron oxide nanomaterials) for large numbers of nanomaterials or high-throughput applications are laborious, expensive and ethically critical, attempts are currently being made to establish simulation models and accelerated stress tests in artificial media, blood, sputum, urine, liver extracts, etc. for this purpose.

The number of robust data sets allowing conclusions to be drawn decreases from stage 1 to 4 in the literature. In stage 4 systematic reports are rare for most nanomaterials. To be able to interpret and predict the toxicological behavior, the inherent impact of nanoparticle properties and the effects of changes under experimental conditions should be used as a basis to generate recommendations for a suitable and robust toxicology testing strategy. A survey among regulatory authorities indicated the assessment of stability, dispersibility, agglomeration and endotoxin testing as highly relevant before entering clinical trials, whereas the testing of the solubilized fraction seems to be relevant at late stage development [9].

3. Shortcomings and future trends in nanotoxicology testings

In vitro nanotoxicology testing, particularly in combination with advanced methodologies like omics or imaging techniques, has the potential to gain a comprehensive insight into cell-based effects. Although in the past few years an exponential increase in publications on nanotoxicology testing has been observed, many of these papers suffer from shortcomings in experimental design and the conclusions drawn. A literature survey of about 10.000 references in the field of nanotoxicity testing between 2000 and 2014 revealed in many studies there was insufficient material characterization, non-adequate or lack of controls and reference materials and study designs that did not met adequate scientific quality requirements. The need to test the empty carrier in addition to the drug containing formulation for the assessment of inherent toxicity was viewed differently by different authorities [9]. Furthermore, the diversity of the methods did not allow a direct comparison of different studies [10]. "No-effect" studies often are not accepted by journals and therefore cannot be taken into account for the safety evaluation of nanomaterials.

In vitro cyto- and hemotoxicity tests are usually based on guidelines for biomaterial testings (DIN ISO 10993, ASTM F756, etc.) with special recognition of the requirements for nanomaterials. Interference of nanomaterials with in vitro cytotoxicity test settings due to interactions with analytes or with the optical absorption and fluorescence read outs were widely reported leading to false interpretations [11]. Whereas acute toxicity testing over up to 72 h are typically performed, currently several groups are trying to set up repeated dose models in cell cultures. Regarding dosimetry, overdose situations using nanoparticle concentrations that are not relevant neither therapeutically nor for safety evaluations, resulted in "spectacular", but therapeutically non-relevant reports. In some cases, in vitro cell monolayers were unspecifically suffocated due to the large amounts of particles [12] used, as were rats during pulmonary applications [13]. Additionally, the number of nanoparticles really getting in contact with cells is often not known due to a lack of

adequate analytical techniques. This strengthens the need for the development of methods that are able to detect single nanoparticles in complex and small samples especially in biological settings. Furthermore, a careful selection of the test species is necessary with human cells preferred in in vitro systems.

The current trend in in vitro nanotoxicology testing is shifting from the traditionally used two-dimensional cell cultures to 3D-systems like spheroids, multilayer co-cultures and microfluidic systems. National and international agencies have supported an increasing number of research projects during the past few years [14]. Although the 2D-methods are simple, fast, cost-saving, highly reproducible and transferrable to high-throughput applications, the transfer of data to the in vivo situation is limited since they suffer from limited complexity compared to body tissues, other cell morphologies, a lack of extracellular matrix and particularly, missing dynamic conditions due to the blood flow as transport medium for the nanomaterials. For iron oxide nanoparticles less toxic effects could be observed in 3D-cell cultures compared to 2D monolayers [15]. This is especially true for the cell or tissue specific targeting of nanoparticles with e.g. antibodies, peptides, etc. Up to now none of the targeted nanoparticles have reached late stage clinical trials or even to the market. After surveying the literature over 10 years only 0.7% (median) of the administered nanoparticle dose was found to be delivered to solid tumors [16]. With respect to in vitro cell culture experiments, it has been suggested that this can be related to the extracellular environment, protein corona and/or the fluidic dynamic conditions, all hampering the interaction of the nanomaterials with their target cells.

Since under static cell culture conditions the sedimentation of nanoparticles might determine the contact with the cells, microfluidic in vitro systems can be used which inhibit sedimentation, support disaggregation of agglomerates due to shear stress and supply cells with nutrients and remove metabolic or toxic products. As a major disadvantage of this technique, the contact of nanoparticles with cells is dependent on the velocity of the flow. Tests in hen's egg have been investigated for their application in nanotoxicology, in order to include all the effects discussed previously, like interactions with blood proteins and cells and dynamic flow under relevant physiological conditions in in vivo experiments without the need for ethical permission in an all-in-one system. Whereas the classical in ovo HET-CAM (hen's egg test on the chorioallantoic membrane, ICCVAM 2010) supplies researchers with toxicological information like thrombotic events, hemorrhage, and vascular lysis, ex ovo shell-less hen's egg systems additionally allow the quantification of lethality after local and systemic administration of nano-sized test materials, the visualization of the nanoparticle distribution and flow behavior by video microscopy as well as the application of imaging technologies such as confocal laser scanning microscopy, Raman spectroscopy, MALDI-TOF and MR imaging. Serial tests with large sample numbers can be performed in a cost effective and time saving manner with high reproducibility to reject inadequate nano-candidates before transfer to animal experiments which contributes to the 3R-EU policy objectives (replacement, refinement, reduction of animal experiments).

4. Data mining

A plethora of publications in the field of nanotoxicology is available, however often with contradictory results. For the first time the limit of 5000 publications per year for the topics nanotoxicology/nanosafety was passed in Pubmed in 2017. Since the start of the millenium more than 30.000 papers were reported in the field. It is not that we do not have enough knowledge about adverse effects of nanomaterials, but the overall picture is difficult to generate since the systematic evaluation of this knowledge included in these papers is still not realized. In particular for the specific development of nanomedicines there is a need for a form of data mining to generate systematic structure-activity relationships and to derive prediction models and pathways of toxicity. Strong regional differences in the toxicological testing of nanomaterials are obvious and confirm the need for harmonization [10]. Although several databases exist, they are focused only on special aspects or suffer from less than systematic data collection. Furthermore, many of them summarize data without a quality control system. The BMBF funded project DaNa2.0 (www.nanopartikel.info) collects, evaluates and presents up-to-date scientific facts evaluated by an interdisciplinary scientific expert team on an internet platform. As a unique characteristic all data are quality controlled with regard to their scientific value according to a "Literature Criteria Checklist". However, such database concepts require standardized formats and harmonized data collection which is not realized often because academic research does not primarily focus on the production of data for risk assessments.

5. Future challenges and directions

The last two decades have seen the implementation of nanotechnology in medicine as a powerful new opportunity. Nanomedicines are complex structures with production processes that often contain far more steps than the formulation of traditional drug delivery systems. Follow-on products, the so-called "nanosimilars", combination products and the development of personalized medicines will pose additional challenges in production and toxicological requirements and are already on the agenda of international working groups. New challenges identified from current discussions between academia, industry and regulators will have to be realized by optimization of integration between advances in material sciences, analytics and validation of adequate test models in appropriate settings and the adaption of existing regulatory standards to foster the translation toward the clinic with subsequent commercialization.

Acknowledgements

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DRUG DELIVERY LITERATURE

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Provided by Dr. Carsten Timpe

RECENTLY PUBLISHED LITERATURE REVIEWS IN THE FIELD OF DRUG DELIVERY

Structural modifications of DS for solubility enhancement (Amorphous Drug Delivery Systems, Cocrystals, Polymorphism)

Expanding the Application and Formulation Space of Amorphous Solid Dispersions with KinetiSol®: a Review, Ellenberger DJ, Miller DA, Williams RO 3rd. AAPS PharmSciTech. 2018 Jul;19(5):1933-1956.

The review gives an overview about the KinetiSol, which utilizes high shear to produce amorphous solid dispersions.

Peptide, Protein-based Drug Delivery

Protein Polymer-Based Nanoparticles: Fabrication and Medical Applications, DeFrates K, Markiewicz T, Gallo P, Rack A, Weyhmiller A, Jarmusik B, Hu X., Int J Mol Sci. 2018 Jun 9;19(6): 1717

Protein nanoparticles are used in a variety of settings and are replacing many materials that are not biocompatible and have a negative impact on the environment. The review gives an overview of the literature pertaining to protein-based nanoparticles with a focus on their application in drug delivery and biomedical fields. Additional detail on governing nanoparticle parameters, specific protein nanoparticle applications, and fabrication methods are also provided.

Dermal and Transdermal Drug Delivery

3D printing applications for transdermal drug delivery, Economidou SN, Lamprou DA, Douroumis D. 3D printing applications for transdermal drug delivery. Int J Pharm. 2018 Jun 15;544(2):415-424.

The applicability of several printing technologies has been researched for the direct or indirect printing of microneedle arrays or for the modification of their surface through drug-containing coatings. The findings of the respective studies are presented, the range of printable materials that are currently used or potentially can be employed for 3D printing of transdermal drug delivery (TDD) systems are also reviewed and moreover, the expected impact and challenges of the adoption of 3D printing as a manufacturing technique for transdermal drug delivery systems, are assessed.

Gene Drug Delivery, Gene Therapy, siRNAs

Non-Primate Lentiviral Vectors and Their Applications in Gene Therapy for Ocular Disorders, Cavalieri V, Baiamonte E, Lo Iacono M. Non-Primate Lentiviral Vectors and Their Applications in Gene Therapy for Ocular Disorders. Viruses. 2018 Jun 9;10(6): 316

In this review, an overview of non-primate lentiviruses is given, highlighting their common and distinctive molecular characteristics together with key concepts in the molecular biology of lentiviruses. Bioengineering strategies are examined, with a focus on their potential clinical applications in ophthalmological research.

Nanosystem-based Drug Delivery

Medical and dental applications of nanomedicines. Kavoosi F, Modaresi F, Sanaei M, Rezaei Z., APMIS. 2018 Oct;126(10):795-803.

This current review summarizes recent applications of nanomedicine in the fields of medicine and dentisty.

Recent advances in "smart" delivery systems for extended drug release in cancer therapy, Kalaydina RV, Bajwa K, Qorri B, Decarlo A, Szewczuk MR., Int J Nanomedicine. 2018 Aug 20;13:4727-4745.

The article provides an overview of smart and extended-release drug-delivery systems for the delivery of cancer therapies, as well as introducing innovative advancements in nanoparticle design incorporating these principles. With the growing need for increasingly personalized medicine in cancer treatment, smart extended-release nanoparticles have the potential to enhance chemotherapy delivery, patient adherence, and treatment outcomes in cancer patients.

Perspectives of Dendrimer-based Nanoparticles in Cancer Therapy, Castro RI, Forero-Doria O, Guzmán L., An Acad Bras Cienc. 2018 Aug;90(2 suppl1):2331-2346.

This article reviews work carried out on the development of dendrimers in combination with drugs, as a potential adjunctive agent in anticancer therapy.

Oral Drug Delivery

Challenges in the local delivery of peptides and proteins for oral mucositis management, Campos JC, Cunha JD, Ferreira DC, Reis S, Costa PJ. , Eur J Pharm Biopharm. 2018 Jul;128:131-146.

This review raises awareness of the issues and strategies in the local delivery of macromolecules for the management of oral mucositis.

Role of self-emulsifying drug delivery systems in optimizing the oral delivery of hydrophilic macromolecules and reducing interindividual variability, AboulFotouh K, Allam AA, El-Badry M, El-Sayed AM. Colloids Surf B Biointerfaces. 2018 Jul 1;167:82-92.

*This review summarizes the recent progress in the use of SEDDS (*Self-emulsifying drug delivery systems) *for protecting protein therapeutics and/or pDNA (plasmid DNA) against enzymatic degradation and increasing the oral bioavailability of various drug substances regardless of the dietary condition.*

Pulmonary drug delivery

Design of Spray-dried Porous Particles for Sugar-based Dry Powder Inhaler Formulation, Kadota K. , Yakugaku Zasshi. 2018;138(9):1163-1167.

For efficient and deeper drug delivery into the lungs via dry powder inhalers (DPIs), the authors designed porous spray-dried particles (SDPs) containing anti-tuberculosis drugs and sugar-based excipients. The SDPs were prepared by spray-drying ethanol solutions.

Alternative application routes (e.g. intrathecal, brain delivery etc.)

Recent advances in carrier mediated nose-to-brain delivery of pharmaceutics, Bourganis V, Kammona O, Alexopoulos A, Kiparissides C., Eur J Pharm Biopharm. 2018 Jul;128:337-362.

The present review article attempts to highlight the different experimental and computational approaches pursued so far to attain and enhance the direct delivery of therapeutic agents to the brain and shed some light on the underlying mechanisms involved in the pathogenesis and treatment of neurological disorders.

Development of controlled drug delivery systems for bone fracture-targeted therapeutic delivery: A review, Wang Y, Newman MR, Benoit DSW., Eur J Pharm Biopharm. 2018 Jun;127:223-236.

This review concerns current therapies employed to stimulate fracture healing pre-clinically and clinically, including a focus on drug delivery systems for growth factors, parathyroid hormone (PTH), small molecules, and RNAi therapeutics, as well as recent advances and the future promise of fracture-targeted drug delivery.

Novel materials, excipients etc. for drug delivery

Sulfonated and sulfated chitosan derivatives for biomedical applications: A review, Dimassi S, Tabary N, Chai F, Blanchemain N, Martel B.. Carbohydr Polym. 2018 (202):382-396.

This paper provides an overview of the strategies used to chemically modify chitosan by introduction of sulfonate groups on the chitosan backbone, focusing on the various sulfonating or sulfating agents used and substitution regiose-lectivity, and highlights their applications in the biomedical field.

Drug delivery for neglected diseases

Innovation in neglected tropical disease (NTD) drug discovery and development, Weng HB, Chen HX, Wang MW. Infect Dis Poverty. 2018 Jun 18;7(1):67.

This paper reviews the recent advances and some of the challenges in the fight against NTDs.

ABOUT THE FOCUS GROUP

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The APV Drug Delivery Focus Group (APV DD) is a section of the APV (Arbeitsgemeinschaft für Pharmazeutische Verfahrenstechnik e.V. / International Association for Pharmaceutical Technology), a major European society for those sharing a professional interest in pharmaceutical sciences. The Focus Group was established in 2003 in response to the increasing importance of drug delivery within modern pharmaceutics.

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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:

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