APV FOCUS GROUP DRUG DELIVERY

COMBINING SCIENCE & TECHNOLOGY TO CREATE ADVANCED DRUG DELIVERY SYSTEMS

INTERNATIONAL ASSOCIATION FOR PHARMACEUTICAL TECHNOLOGY

NEWSLETTER **ISSUE 2/2019 - JULY**

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

\+ **11th conference of the European Paediatric Formulation Initiative with Preconference workshops**
September 10-12, 2019 | Malmö, Sweden — Details

Skin and Formulation, 5th Symposium & 17th Skin Forum
September 23-24, 2019 | Reims, France — Details

\+ **12th World Meeting on Pharmaceutics, Biopharmaceutics and Pharmaceutical Technology**
March 23-26, 2020 | Vienna, Austria — Details

Suggest a meeting to be announced!

CONFERENCE SUMMARY

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2nd APV Conference on the Patient Centric Medicines Initiative (PaCeMe In)
Tailor Medicines for older patients in pharmaceutical development: From new regulation to a rational science-based process.

"I will remember that there is art to medicine as well as science, and that warmth, sympathy, and understanding may out-weigh the surgeon's knife or the chemist's drug." - Hippocratic Oath

Over many decades, healthcare professionals have focused on disease science to generate a mechanistic understanding of different diseases and to identify targeted interventions to correct the underlying cellular and molecular deviations. The molecular entities developed by the pharmaceutical industry are supported by scientific evidence for efficacy generated in randomized and double-blind clinical trials. It is not surprising that after decades of success by focusing on disease science the pharmaceutical industry and healthcare disciplines have developed a high degree of routine and standard processes in drug product development.

Nevertheless, important changes in demographics, connectivity, urbanization and consumer empowerment continue to alter patients' attitudes and even generate new patient populations, which are increasingly questioning the drug therapy as a pure health repair intervention. That a drug works for a certain percentage of patients with a specific disease will no longer be sufficient for general prescribing in a try-and-error manner. The evolving geno- and phenotyping capabilities will further personalize the therapeutic intervention, which also includes all aspects of the physiological, physical, mental, psychological, social and environmental factors of the patient. With disease science still being a leading principle of drug development, we will also need to develop the science around the "art to medicine" by a systematic integration of the patient perspective into the drug product design and development.

The 2nd APV Conference of the Patient Centric Medicine Initiative (PaCeMe In) brought together again leading experts from medicine, epidemiology, ethics, patient engagement, regulatory authorities, clinical studies and the pharmaceutical industry to discuss how to tailor medicines to patients and specifically to the major user group of drug products, the older and multimorbid patients.

Prescribing drug products and managing chronic disease in older and multimorbid patients goes beyond the traditional single disease concept and requires an integrative approach. The therapy has to consider the entire process of care that include preventive measures as well as terminal care. That such integrated approaches improve the therapeutic outcomes have been demonstrated for older patients with hip fracture by reducing the mortality by 63 % as well as reducing functional limitations, length of hospital stay as well as re-hospitalization.

Significant increase in life expectancy since the mid of the last century raised the number of centenarians from about 72.000 in 1975 worldwide to about half a million today. This sharp increase in the life expectancy and the very old, multimorbid patient population will challenge our reactive healthcare systems. Preventive treatment and focus on health and quality of life will become important areas of the healthcare system creating new opportunities for the pharmaceutical industry. Geroscience evolved as a new discipline from biologists to understand the multifactorial process of aging and senescence on the genomic, cellular and molecular level as well as its relationship to morbidity, disability and frailty. The results are starting to provide validated markers to determine biological age as well as potential new clinical targets to prevent aging. Metformin is one of the first compounds that is being investigated in clinical trials for the general decline of age-related disease and specifically the reduction of cancer, enhanced cognitive functions and decreased mortality. The systematic collection of genomic, phenotypic, biologic and other health related data and its digital analysis provide a new and effective tool to understand and predict individual patient trajectory and will lead to more personalized therapeutic approaches.

Despite the inevitable changes in the demographics dictated by the baby boomers becoming now the "aging boomers", the major cut-off age in clinical trials is still set at 60 years. The pharmaceutical industry might argue that clinical trials in older and multimorbid patients are discouraging the industry as this would further add to the complexity and cost of drug development. While these arguments cannot be ignored, we also have to acknowledge that regulatory authorities are reluctant to approve and physicians are reluctant to prescribe drugs to older and multimorbid patients without sufficient evidence for their efficacy and safety. As a result, the monoclonal antibodies against the Tumor Necrosis Factor (TNF inhibitors) for the treatment of Rheumatoid Arthritis are rarely prescribed to patients older than 60 years due to a lack of clinical guidance to mitigate a potential higher risk of serious infection in older patients. Consequently, patients who could benefit from the drugs do not receive the treatment and the industry does not exploit the full commercial potential of their drug product. In order to support the inclusion of older patients in drug development, recommendations have been developed on how to perform clinical trials in this patient population. These recommendations provide very practical guidance, but also reveal the opportunity for other endpoints relevant to older patients like endpoints on quality of life. Such endpoints have been shown to result in higher reimbursement by the healthcare system.

The importance of the patient perspective throughout the drug development continues to become a substantial part of regulatory guidance. The EMA`s Geriatric Medicines Strategy is moving forward to improve evidence-based medicines and informed prescribing. The Assessment Report requires epidemiology data defining the relevant patient population and the reporting of all clinical data according to four age groups (< 65 years; 65-74 years; 75-84 years; 85 years and older) including information about comorbidities, co-medications and safety signals observed in the trials. Limitations in data will be reported in the Summary of Product Characteristics (SmPC) and patient leaflet. To support the industry with guidance, EMA has provided Reflection Papers on the pharmaceutical development of medicines for older people focusing on the product design and its usability by older patients and on physical frailty focusing on the baseline characterization of the frail. The FDA put its recent focus on understanding the disease and therapeutic burden of specific diseases, which is now being translated into a series of Patient Focused Drug Development Guidelines. These guidelines will provide the road map of how to capture what are important outcomes for the patients and how these aspects can be measured in clinical trials. This FDA initiative is in accordance with the FDA's experience of best leading change through implementing emerging guidelines along with newly starting drug development programs, which will than become a general procedure in drug development.

Patient engagement and involvement has been triggered through direct collaborations with patient advocacy groups and patient organizations especially starting with rare disease. Today, patient engagement is used with a variety of different definitions covering the range from patient co-creation through to sales support. Until there is a clear definition, the term patient engagement in the context of drug product development should mean the direct involvement of patients, their experience with the disease as well as therapy and input to the drug product design as well as expected outcomes. Observational studies on existing drug products have provided some preliminary insights into the acceptability of different drug products. The results confirm the importance of dosage forms and their size (e.g. tablets, capsules) as well as special functional patient characteristics involved in drug administration (e.g. dysphagia).

The importance of working directly with patients and e.g. performing acceptability studies in the targeted patient has been demonstrated in the pediatric patient population. For the past decades it was assumed that liquid solutions would be the most accepted and easiest to administer oral dosage forms for children. When comparative studies were performed in patient populations between 2 days and 6 years, mini-tablets performed superior in nearly all age groups leading to a paradigm shift in oral pediatric dosage forms. Similar results were also obtained with orally disintegration films. Multiparticulate drug delivery systems like pellets and minitablets can additionally provide taste masking, different drug release profiles as well as a high degree of dosing flexibility. As it cannot be assumed that acceptability will be equivalent to the pediatric population, it would be highly desirable to investigate the acceptability of such systems in older patients including the acceptability of the metering or device and packaging component.

Achieving the best overall benefit-to-risk for patients including the patient relevant outcomes involve all stakeholders providing healthcare products or services to the patient. Each stakeholder has disciplinary knowledge and expertise that is essentially contributing to the overall therapeutic outcomes. Multidisciplinary discussions and collaborations have already shown positive effects on identifying medication errors and their underlying root causes. As such they are an essential part of developing the science around the "art to medicine". For example, Patient Reported Outcomes in clinical trials to capture the true feedback from patients are based on a validated set of precise questions, which could also serve physicians in daily practice in better monitoring the real patient outcomes.

The Patient Centric Medicines Initiative (PaCeMe In) has been formed as a platform for multidisciplinary industrial-academic collaboration to develop a meaningful road map and practical guidance to comply with future patient centric product development requirements. The objective of PaCeMe In is to understand and respect each stakeholder requirements and commonly agree on the right balance between the wishful and the feasible to provide best overall benefit-to-risk to patients.

In conclusion, the focus of pharmaceutical sciences on the technical aspects of drug delivery and dosage forms enabled the pharmaceutical industry to provide new drug products to the market over the past decades. This business model has come under considerable pressure in recent years, not least due to increasing visibility of non-adherence, medication errors, poor effectiveness and reluctance of regulatory authorities to approve and of doctors to prescribe medicines to older patients without sufficient clinical and real-world evidence. There is consensus that these trends are caused by a lack of patient involvement and considerations of their needs during drug development leading to products that are not fit-for-purpose for a majority of patients. With regulatory authorities, healthcare professionals and patients increasingly addressing the lack of patient focus in drug development, the pharmaceutical industry is starting to face the commercial implications of limited drug usage as well as missing important new business opportunities by providing patient centered solutions for treatment and prevention to older and multimorbid patients. Patient centric drug development is neither a gimmick nor a disruption, it is a source of opportunities and innovation in a continuously changing world.

DRUG DELIVERY PRODUCTS

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Provided by Dr. Louise Rosenmayr-Templeton

SIXMO IMPLANT

Sixmo for the treatment of opioid dependence received a positive opinion from the EMA's Committee for Medicinal Products for Human Use in April 2019 and received final marketing authorisation in the EU in June [1, 2]. It contains 74.2 mg buprenorphine, the opioid partial agonist/antagonist, as the hydrochloride salt in a non-biodegradable ethylene vinyl acetate copolymer implant [2, 3]. It is specifically indicated as a substitution therapy for clinically stable adults suffering from opioid dependence who require no more than 8 mg sublingual buprenorphine daily. In addition, its administration should be co-current with appropriate medical, psychological and social support.

The Sixmo kit contains four implants, each 26.5 mm long and 2.4 mm in diameter which are individually packed plus an applicator. The dose is four implants to be surgically inserted subcutaneously by an appropriately trained physician in the upper arm for 6 months. At the end of the six-month treatment period the implants are surgically removed and a second cycle of treatment can be initiated by implanting four further implants in the opposite arm. It is anticipated in the majority of cases that following the second cycle of treatment the patient returns to sublingual buprenorphine therapy.

Approval was based on data generated form three pivotal clinical trials, in a total of 626 adult patients. One of these studies involved individuals suffering from opioid use disorder who were considered clinically stable on sublingual buprenorphine. The results showed that 96.4% of patients in the Sixmo group responded to treatment, compared to 87.6% of patients treated with sublingual buprenorphine.

The marketing authorization holder is L. Molteni & C. dei Fratelli Alitti Società di Esercizio S.p.A. As part of the approval, a risk mitigation strategy has been put in place and a post-marketing study will be commissioned to evaluate issues associated with implant breakages and insertion and removal of the implants.

ZOLGENSMA® Suspension for Intravenous Infusion [4]

On 24 May the FDA granted approval for Zolgensma® (onasemnogene abeparvovec-xioi), for the treatment of spinal muscular atrophy (SMA) in children under two years [5, 6] with bi-allelic mutations in the SMN1 gene, including those who are pre-symptomatic at diagnosis. In SMA the survival motor neuron 1 (SMN1) gene, which encodes the survival motor neuron (SMN) protein, is mutated. The lack of functional SMN leads to motor neurons cell death, severe muscle weakness and paralysis. Infantile-onset SMA is the most serious and common sub-set of this rare, genetic condition with annually around 450 to 500 babies being affected by SMA in the US alone. The genetic condition manifests itself in children having difficulties in holding their head up, swallowing and breathing with the infants either dying or requiring permanent ventilation before the age of two. These symptoms can be apparent at birth or develop later when the child is around 6 months old.

Zolgensma® is an adeno-associated (AAV9) virus vector-based gene therapy. Zolgensma® was developed by AveXis, Inc. (IL, USA) which is now part of Novartis (Basel, Switzerland) [7]. It is designed to deliver one copy of the human SMN1 gene into the target motor neuron cells to replace the missing or defective gene. The suspension is dosed intravenously based on weight (1.1×10^{14} vector genomes per kg of body weight) with one infusion over 60 min being sufficient to result in expression of the SMN protein in the pediatric patient's motor neuron cells, thus, improving the infant's muscle strength and chances of survival.

The product is supplied at a nominal concentration of 2.0×10^{13} vg/mL as a kit containing 2 to 9 vials which come in 2 fill volumes: 5.5 mL or 8.3 mL. The sterile suspension formulation also contains 20 mM Tris (pH 8.0), 1 mM magnesium chloride (MgCl2), 200 mM sodium chloride (NaCl) and 0.005% poloxamer 188.

FDA approval for Zolgensma®, which had been previously granted Fast Track, Breakthrough Therapy, and Priority Review designations, was based on the results of one ongoing Phase 3 and one completed Phase 2 clinical study in 36 children suffering from infantile-onset SMA. In the ongoing Phase 3 treatment with Zolgensma® has enabled 19 out of the 21 children enrolled to survive significantly longer than would have been predicted based on the standard prognosis for children with this condition, with 13 of these 19 having reached at least 14 months of age. In addition, the genetic replacement therapy resulted in the pediatric patients having significantly improved motor function [5, 6]. The main side-effects of therapy are elevated aminotransferases and vomiting and, as a result, liver function tests are needed prior to administration and monitoring afterwards. The product carries a boxed warning with respect to the development of acute, serious liver injury.

In addition, to its fast-tracked approval by the FDA, AveXis received a rare pediatric disease priority review voucher from the agency, which it can use to obtain priority review on another compound. Elsewhere, the product is also undergoing accelerated review by the EMA who previously granted it PRIME (PRIority MEdicines) designation, and also has accelerated Sakigake designation in Japan [5].

References and Further Information

[1] New long-lasting implant to treat opioid dependence. https://www.ema.europa.eu/en/news/new-long-lasting-implant-treat-opioid-dependence.

[2] Sixmo. https://www.ema.europa.eu/en/medicines/human/EPAR/sixmo.

[3] Sixmo. Summary of Product Characteristics.

[4] The information on Zolgensma® is based on part of an Industry Update for May 2019 by Dr. Louise Rosenmayr-Templeton which has been accepted for publication in the journal Therapeutic Delivery, Vol 10 (8) and is re-produced here with the permission of Therapeutic Delivery.

[5] FDA approves innovative gene therapy to treat pediatric patients with spinal muscular atrophy, a rare disease and leading genetic cause of infant mortality. https://www.fda.gov/news-events/press-announcements/fda-approves-innovative-gene-therapy-treat-pediatric-patients-spinal-muscular-atrophy-rare-disease.

[6] AveXis receives FDA approval for Zolgensma®, the first and only gene therapy for pediatric patients with spinal muscular atrophy (SMA). http://investors.avexis.com/phoenix.zhtml?c=254285&p=irol-newsArticle&ID=2399684.

[7] AveXis, Inc website. https://www.avexis.com/about.

FEATURED ARTICLE

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Vaccines and Adjuvants with Liposomes

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1 Introduction

The introduction of vaccines into medical practice is one of the most outstanding accomplishments of modern medicine, with a major impact on mortality reduction and population growth. By the use of vaccines up to 3 million deaths are prevented each year; in addition, many children are prevented from lifelong disability [1, 2]. For some diseases, like tuberculosis and whooping cough, the existing vaccines do not provide sufficient immunity. There are also diseases like human immunodeficiency virus (HIV) and malaria for which so far no effective vaccine exists [3-5]. Besides humans also hundreds of millions of animals are protected from life-threatening diseases by the use of vaccines. By vaccination of livestock animals' food safety, especially in developing countries, and the economic efficiency of animal farming can be improved. [4, 6, 7].

As a consequence, the market for vaccines is a relatively attractive and the fastest growing sector within the pharmaceutical market. The market value for human vaccines increased to almost USD 24 billion in 2013. It is estimated to grow further to USD 100 billion in 2025. GlaxoSmithKline plc (GSK), Merck & Co [8], Pfizer Inc., and Sanofi were the market leaders in 2016, and shared 88% of the total vaccine market share globally. The sales of the pneumococcal vaccine of Pfizer and Daewoong, Prevnar 13®, reached USD 6.0 billion in 2016 and was the best-selling vaccine in that year.

In the human vaccines market more than 120 new products are under development [9]. The launch of new vaccines for key indications e.g., malaria, cancer, HIV and tuberculosis, is expected in the coming years and will be a key driving force for the vaccine market.

Vaccines can be administered by various administration routes, such as the subcutaneous, intramuscular, intranasal, topical, nasal, oral routes, etc. First generations of vaccines were made by use of live attenuated organisms or inactivated organisms [4, 10, 11]. In 1925 Ramon demonstrated for the first time that artificial enhancement of diphtheria and tetanus antitoxin levels is possible in horses [12] by addition of substances like agar, metallic salts, lecithin or saponins. In the 1940s the first trials were performed with water-in-oil emulsions as adjuvants developed by J.T. Freund and K. McDermot. These "Freund" adjuvants comprised mineral oil emulsions (Freund's Complete Adjuvant: including inactivated and dried mycobacteria; Incomplete Freund's Adjuvant: is a plain emulsion without mycobacteria). Incomplete Freund's Adjuvants are no longer used in marketed vaccines as they are poorly tolerated due to the non-degradable mineral oil component [10, 13].

Modern antigens mimicking antigens from pathogens are isolated proteins (glycoconjugates), or are made by recombinant DNA technology (recombinant subunit antigens). These highly purified and homogenous antigens often induce only a low immune response and for this reason are not sufficiently immunogenic for an efficacious vaccination. In this case adjuvants are needed to boost the immune response to the highly purified antigens [4, 10, 11]. These adjuvants potentiate cellular or humoral immune response, where the latter is the immune response involving the transformation of B cells into plasma cells that produce and secrete antibodies to a specific vaccine antigen.

Adjuvants are antigen specific and therefore their composition has to be tailored in terms of optimized efficacy, safety and costs [14]. In the literature adjuvants have been classified e.g. according to their mode of action [13], their source (vegetal, bacterial, chemical) [15], into immune stimulant and delivery systems [10], or conventionally into mineral compounds, bacterial products, oil-based emulsions, Immunostimulating Complexes (ISCOMs) and liposomes [14].

Since 1930 aluminum based adjuvants have been used in vaccines and they have been the sole adjuvants approved for use in humans for a long time [10, 13]. There is some preclinical evidence that aluminum and other metals like iron or copper are involved in the pathogenesis of neurodegenerative diseases e.g. Alzheimer's Disease by promoting abnormal aggregation of β-amyloid protein, aggregation of tau protein, by inducing oxidative stress and cellular dysfunction [16-19]. Although the US-FDA considers the use of aluminum containing adjuvants as safe [20], it can be expected that future vaccines will be preferably formulated without thes**e** aluminum containing adjuvants and lipid carriers may be preferred.

2 Phospholipids in vaccine adjuvants for human use

Phospholipids, mainly phosphatidylcholine (often named "lecithin" in American literature) and other phospholipids (also synthetic), relevant for the adjuvant use have been investigated and used in vaccine adjuvants dosage forms for formulation of e.g. emulsions, liposomes or ISCOMs.

2.1 Emulsions

The first oil-in-water emulsion adjuvant (MF59, comprising squalene, polyoxyethylene sorbitanmonooleate and sorbitantrioleate, as emulsifiers) was approved for use in humans (Fluad®: seasonal influenza vaccine) in 1997 [10]. Squalene oil is the preferred oil for use in biodegradable oil-in-water emulsions. The quality (physiochemical parameters such as particle size and stability) of emulsions has a direct impact on the efficacy and safety of emulsion adjuvants [12]. The only oil-in-water emulsion used in the clinic containing a natural phospholipid as an emulsifier is SE (stable emulsion) of the Infectious Disease Research Institute (IDRI, Seattle) [10, 21, 22].

2.2 Liposomes

For the first time the preclinical use of liposomes as adjuvants was described in 1974 [23]. Natural lipids, with exception of phosphatidylserine (PS) and lysophospholipids, do not possess specific immunological effects. The charge of the liposomes used for delivery of antigens or/and immuno-stimulants can influence their adjuvant potency. Liposomes which are positively charged (cationic liposomes) are taken up better by macrophages and dendritic cells than neutral or negatively charged liposomes [24], therefore, giving rise to an enhanced immune response. Lipid particles like liposomes are taken up more efficiently by Antigen Presenting Cells (APC) than soluble molecules resulting in a stronger immune response by particulate antigens independently of the route of administration [25].

Liposomes are able to deliver a wide range of type of antigens (e.g. proteins, peptides, polysaccharides, deoxyribonucleic acid (DNA), ribonucleic acid (RNA) etc. [26]) and to co-deliver a wide range of immuno-stimulants [10]. An update on ongoing pre-clinical research is included in reference 27 [27].

2.2.1 Clinical research with Liposomal Adjuvants

The most prominent and promising clinical research with vaccines, involving the use of phospholipids, is nowadays being performed by GSK with their AS01 adjuvant. This adjuvant comprises a saponin (Quillaja saponaria Molina: fraction 21 = QS-21)), monophosphoryl lipid A (MPL) and liposomes. The adjuvant comprises 1,2-dioleoyl-sn-glycero-3-phosphocholine (DOPC), cholesterol and MPL, QS21 in a 20:5:1:1 (w/w) ratio. When using the AS01 formulation, liposomes consisting of DOPC and cholesterol (chol) are mixed with the immuno-stimulants MPL and QS21. The antigen is presumably not encapsulated in the liposomes, since the vaccine formulation is delivered in the form of a mix of antigen and adjuvant formulations [10] which are combined prior to administration. The following ongoing development activities with GSK adjuvants can be found (Table 1) [28].

Table 1: Clinical vaccine research projects at GSK

Adjuvant system	Composition	Vaccines licensed or in Phase III trials	Vaccines in Phase I or II trials	Development discontinued
AS01	Combination of QS-21, MPL and liposomes	Malaria vaccine (Mosquirix™ also known as RTS,S or RTS,S/AS01)	Malaria next generation COPD exacerbation Haemophilus Influenza and Moraxella catarrhalis Tuberculosis vaccine HIV vaccine	
AS01E	Tetravalent inactivated purified dengue virus TDENV-PIV	Dengue fever	-	
AS02	Combination of QS-21, MPL and oil in water emulsion	-	-	HIV vaccine Tuberculosis vaccine Therapeutic melanoma vaccine Malaria vaccine
AS03	Combination of an oil in water emulsion with alpha-tocopherol as immune enhancing component	Pre-pandemic H5N1 vaccine Pandemic H1N1 influenza vaccines (Arepanrix™, Pandemrix™)	-	
AS04	MPL is adsorbed onto aluminium hydroxide or aluminium phosphate	Human papillomavirus vaccine (Cervarix™) Hepatitis B for pre- and haemodialyis patients (Fendrix™)		Herpes simplex vaccine
AS15	Combination of immunostimulants CpG 7909, QS-21 and MPL with liposomes			MAGE-A3 Cancer, Immunotherapeutics: melanoma and non-small cell lung cancer vaccines

Abbreviations: COPD: Chronic Obstructive Pulmonary Disease; CpC 7909: an immunostimulatory nucleotide

Further liposomal vaccine/adjuvant formulations which have been under development since 2015 by several companies using various technologies are provided in Table 2 (the technologies are listed alphabetically).

Table 2: Liposomal vaccine/adjuvant clinical research projects

Project	Use	Antigen	Status	Phospholipid/ Formulation	Company
Biphasix™	Cancer		Pre-clinical	HSPC, multilayered, lipid-based microvesicles	Helix Biopharma Canada, VIDO-InterVac
DepoVax™/ VacciMax®	Cancer, infectious diseases	- HLA-A2-restricted peptides (DPX-0907) - Survivin (DPX-Survivac) - Animal vaccines	Phase I/II Phase I/II Field trials	Virosomes	Immuno Vaccine Technologies Inc, Canada
Lipovaxin-MM	Immunotherapy for malignant melanoma	VH domain antibody fragment	Phase I	Liposomes, POPC, PE-PEG-2000	LipoTek Pty Ltd, Australia
ONT-10 (BGLP40)	Cancer	Sequence of tumor-associated antigen MUC-1	Phase I	Liposomes	Oncothyreon; USA
RNAdjuvant®	-Rabies -RSV -HIV Influenza		Rabies Phase I	DOTMA, DOTIM, DOPC and DOGs	CureVac AG Germany
RUTI®	Tuberculosis	Detoxified, fragmented Mycobacterium tuberculosis cells	Phase I	Liposomes, SPC	Archivel - Spain
Vaxfectin®	- HSV-2 - Cytomegalo-virus - dengue	- DNA - DNA - Plasmid DNA	Phase I Preclinical Phase I	DPyPE, cationic lipid	Vical Corp USA
Versamune™	- Cancer - influenza - melanoma	- short HPV proteins - Trp2 antigen	Phase I Preclinical Preclinical	Liposomes DOTAP	PDS Biotechnology USA
VLP	- Cytomegalo-virus - influenza		Preclinical	Virus like particles	VBI Vaccines Inc. (Variation Biotechnologie Inc), Canada

Abbreviations: DOG: Deoleoylglycerides; DOTAP: N-[1-(2,3-Dioleoyloxy)propyl]-N,N,N-trimethylammonium methyl-sulfate; DOTIM: 1-[2-(9-(Z)-octadecenoyloxy)ethyl]-2-(8-(Z)-heptadecenyl)-3-(hydroxyethyl)imidazolinium; DOTMA: 1,2-di-O-octadecenyl-3-trimethylammonium propane (chloride salt); DPyPE: (±)-N-(3-aminopropyl)-N,N-dimethyl-2,3-bis(cis-9-tetradeceneyloxy)-1-propanaminium bromide; HSPC: Hydrogenated Soybean Phosphatidylcholine; PE-PEG-2000: 1,2-distearoyl-sn-glycero-3-phosphoethanolamine-N-[methoxy(polyethylene glycol)-2000] (ammonium salt); POPC: 1-Palmitoyl-2-oleoyl-sn-glycero-3-phosphocholine; SPC: Soybean phosphatidylcholine.

2.2.2 Products with Liposomal Adjuvants

Liposomal vaccine formulations which reached the market comprise liposomal/"virosomal" vaccine formulations for vaccination against influenza and hepatitis A (see Table 3).

Table 3: Vaccines with virosomes which reached the market

Trade product	Antigen	Indication	Company	Route of admin.	Formulation	(Phospho)-lipid
HAVpur®	Inactivated hepatitis A virus	Hepatitis A	Chiron Behring	Parenteral	Virosome / Suspension	Phospholipids
Epaxal®/ Hepaxal Berna®	Inactivated hepatitis A virus	Hepatitis A	Crucell (J&J)	Parenteral	Virosome / Suspension	Egg PC
Inflexal®/ Infectovac®Flu	inactivated infuenza virus	Influenza	Crucell (J&J)	Parenteral	Virosome / Suspension	Egg PC
Invivac®	sub-unit of influenza virus	Influenza	Solvay Pharma	Parenteral	Virosome / Suspension	Egg PC

Virosomes are reconstituted virus envelopes that act as antigen carrier and adjuvant (due to their particulate form). They do not contain the genetic information of the original virus, so no infection can occur. The virus antigens are integrated in the phosphatidylcholine bilayer of the liposomes. Virosomes can improve the immune response by specific targeting of the antigen to APCs and B lymphocytes, channeling of antigens to specific subcellular locations and other non-specific immunostimulant effects unrelated to the respective antigen [10, 25, 29, 30]. Virosomes may penetrate mucosal membranes and therefore could be suitable for mucosal administration routes.

In 2019 the market situation of these influenza vaccines is rather unclear. Invivac® was introduced on the market in 2004. In 2008 the product was still marketed in Austria by Abbott. This product was developed by Solvay, went then to Abbott, and then to BGP Products and finally to Mylan. The trademark is still valid in various countries (e.g. in Italy [31]). In 2019, Invivac®, Inflexal® and Epaxal® are not available anymore in Austria. Inflexal V IN seems to be still on the market in Switzerland (J&J).

Shingrix® the vaccine of GSK against herpes zoster was introduced on the market in 2018. The adjuvant used AS01 comprises DOPC/Cholesterol liposomes mixed with QS21 and MPL. The phospholipid/liposome-based herpes zoster vaccine of Glaxo, Shingrix®, had revenues of £700-750 million in 2018. Considering the further use of AS01 for many other diseases like malaria (see clinical research section) the market potential of this adjuvant is very high. This product and technology are therefore of great importance for the future use of phospholipids and liposomes in vaccine products.

2.3 ISCOMs

ISCOMs of the company Novavax, Inc., USA, are designed as nanoparticulate adjuvants. ISCOMs are made of *Quillaja saponins*, cholesterol and phospholipid (phosphatidylcholine). Basically, the ISCOM formulations are similar to the AS01 formulations of GSK but without MPL. They also have another QS-21 to phospholipid ratio (as example: one dose of the Equilis West Nile suspension for injection for horses contains 250 µg purified saponin, 83 µg cholesterol and 42 µg phosphatidylcholine [32]). If these raw materials are mixed together at a specific stoichiometry (see above), they spontaneously form open cage-like structures. The particles typically have diameters of ca. 40 nm.

Novavax is in Phase III with their ResVax – Respiratory Syncytial Virus (RSV**)** F vaccine (infants via maternal immunization) and in Phase II to vaccinate older adults (60+ yrs) and Phase I for pediatric (6 mos-5 yrs) use. Their NanoFlu vaccine (Nanoparticle Seasonal Influenza Vaccine for older adults (65+ yrs) is in Phase II. Their Ebola GP vaccine is in Phase I. Novavax believes that the RSV F Vaccine represents a multi-billion dollar commercial opportunity. Currently, there is no approved RSV vaccine available.

3 Phospholipids in veterinary vaccines

Liposomes could be used as adjuvants in veterinary vaccines. Some studies with liposomes as adjuvants in veterinary vaccines are summarized in [33], but no product specifically using liposomes is on the market for veterinary vaccination so far. But this is irrelevant with respect to the use of phospholipids because a few animal vaccines contain phospholipids as component of ISCOMS (which are not liposomes but open cage-like lipid particles with 40 nm size) are on the market (see Table 4).

Table 4: Animal vaccines containing ISCOMs

Product	Antigen	Indication	Company	Formulation	Phospholipid
Equip® FT	Infuenza A and tetanus toxoid	Influenza / Tetanus	Essex	ISCOM	Phosphatidylcholine/ Cholesterol
Equilis® Prequenza	Horse influenza A virus	Equine influenza	MSD	ISCOM (Matrix-C™)	Phosphatidylcholine/ Cholesterol
Equilis® Prequenza Te	Horse influenza A virus and tetanus toxoid	Equine Influenza / Tetanus	MSD	ISCOM (Matrix-C™)	Phosphatidylcholine/ Cholesterol
Equilis West Nile suspension for injection	Inactivated chimeric flavivirus	West Nile virus	MSD	ISCOM-Matrix	Phosphatidylcholine/ Cholesterol
Strangvac®		Equine strangles	Intervacc	ISCOM (Matrix-C™)	Phosphatidylcholine/ Cholesterol

MSD = Merck Sharp & Dohme

4 Conclusions

To date the number of vaccines delivered by phospholipid containing adjuvants is still limited, but since the advent of the Shingrix® vaccine of GSK for prophylaxis of herpes zoster (shingles) using liposomes with DOPC/chol in their AS01 adjuvant, the use of liposomal adjuvants may become substantial. In fact, Shingrix® is nowadays the largest selling liposome product in the pharmaceutical market. This market potential will be considerably increased if the other vaccines of GSK under development with the AS01 adjuvant become successful. In addition, there are quite a few more adjuvant formulations presently being clinically tested comprising a phospholipid /liposome component, with different antigens.

Vaccines containing virosomes as adjuvants are other liposomal vaccines that have been marketed so far. These formulations have been proven to be safe for conventional administration routes, but for intranasal administration the product NasalFlu® had to be taken from the market as it was thought to cause Bell's palsy. The vaccines based on virosomes have been more or less been discontinued.

ISCOMs are used as adjuvants in many different vaccine formulations investigated for human and animal use and are in veterinary vaccines on the market. They have been proven to exhibit good immune responses with many antigens and they are safe for application as they have been used in veterinary applications for many years.

The drive towards phospholipid-based adjuvants will be further stimulated by the tendency to avoid in future products the classical aluminum containing adjuvants to eliminate any risks of neurodegenerative diseases.

5 Literature/References

[1] Jain D, Jain V, and Singh R, Novel antigen delivery technologies: a review. *Drug Delivery and Translational Research*, (2011). 1(2): p. 103-112.

[2] Seven Key Reasons Why immunization must remain a priority in the WHO European Region. http://www.euro.who.int/__data/assets/pdf_file/0017/84302/Seven_Key_Reasons.pdf

[3] Amorij J-P, et al., Towards tailored vaccine delivery: Needs, challenges and perspectives. *Journal of Controlled Release*, (2012). 161(2): p. 363-376.

[4] Greenwood B, Salisbury D, and Hill A V S, Vaccines and global health. *Philos Trans R Soc Lond B Biol Sci*, (2011). 366(1579): p. 2733-42.

[5] Hook S, Lipid Delivery of Vaccines by the Oral Route, in *40th Annual Meeting & Exposition of the Controlled Release Society*. (2013): *Honolulu, Hawaii, U.S.A.*

[6] Meeusen E N T, et al., Current status of veterinary vaccines. *Clin Microbiol Rev*, (2007). 20(3): p. 489-510, table of contents.

[7] Burakova Y, et al., Adjuvants for Animal Vaccines. *Viral Immunology*, (2018). 31(1): p. 11-22.

[8] MerckVaccines.com. [cited 2019 February 11]; Available from: https://www.merckvaccines.com.

[9] Kaddar M, Global Vaccine Market Features and Trends, in *Workshop on Business Modeling for Sustainable Influenza Vaccine Manufacturing, Washington, DC*. (2013), World Health Organization.

[10] Brito L A, Malyala P, and O'Hagan D T, Vaccine adjuvant formulations: A pharmaceutical perspective. *Seminars in Immunology*, (2013). 25(2): p. 130-145.

[11] Trovato M, et al., Delivery strategies for novel vaccine formulations. *World J Virol*, (2012). 1(1): p. 4-10.

[12] Aucouturier J, Dupuis L, and Ganne V, Adjuvants designed for veterinary and human vaccines. *Vaccine*, (2001). 19(17–19): p. 2666-2672.

[13] Cox J C and Coulter A R, Adjuvants—a classification and review of their modes of action. *Vaccine*, (1997). 15(3): p. 248-256.

[14] Aiyer H P, et al., An Overview of Immunologic Adjuvants - A Review, in *Journal of Vaccines & Vaccination*. (2013). p. 167.

[15] Audibert F M and Lise L D, Adjuvants: current status, clinical perspectives and future prospects. *Immunology Today*, (1993). 14(6): p. 281-284.
[16] Jellinger K A, The relevance of metals in the pathophysiology of neurodegeneration, pathological considerations. *Int Rev Neurobiol*, (2013). 110: p. 1-47.
[17] Exley C, Aluminum Should Now Be Considered a Primary Etiological Factor in Alzheimer's Disease. *Journal of Alzheimer's Disease Reports*, (2017). 1(1): p. 23-25.
[18] Shaw C A, Li D, and Tomljenovic L, Are there negative CNS impacts of aluminum adjuvants used in vaccines and immunotherapy? *Immunotherapy*, (2014). 6(10): p. 1055-1071.
[19] Wang Z, et al., Chronic exposure to aluminum and risk of Alzheimer's disease: A meta-analysis. *Neuroscience Letters*, (2016). 610: p. 200-206.
[20] Common Ingredients in U.S. Licensed Vaccines. 04/30/2018 [cited 2019 February 11]; Available from: https://www.fda.gov/BiologicsBloodVaccines/SafetyAvailability/VaccineSafety/ucm187810.htm.
[21] Fox C B, et al., Effects on Immunogenicity by Formulations of Emulsion-Based Adjuvants for Malaria Vaccines. *Clinical and Vaccine Immunology*, (2012). 19(10): p. 1633-1640.
[22] Plotkin S A, Offit P A, and Orenstein W A, Vaccines expert consult. (2013), Saunders: *Edinburgh*.
[23] Allison A C and Gregoriadis G, Liposomes as immunological adjuvants. *Nature*, (1974). 252(5480): p. 252-252.
[24] Barnier-Quer C, et al., Adjuvant Effect of Cationic Liposomes for Subunit Influenza Vaccine: Influence of Antigen Loading Method, Cholesterol and Immune Modulators. *Pharmaceutics*, (2013). 5(3): p. 392-410.
[25] Romero E L and Morilla M J, Topical and mucosal liposomes for vaccine delivery. *Wiley Interdiscip Rev Nanomed Nanobiotechnol*, (2011). 3(4): p. 356-75.
[26] Haensler J, Liposomal adjuvants: preparation and formulation with antigens. *Methods Mol Biol*, (2010). 626: p. 73-90.
[27] Perrie Y, et al., Designing liposomal adjuvants for the next generation of vaccines. *Advanced Drug Delivery Reviews*, (2016). 99: p. 85-96.
[28] Garçon N and Di Pasquale A, From discovery to licensure, the Adjuvant System story. *Human vaccines & immunotherapeutics*, (2016). 13(1): p. 19-33.
[29] Herzog C, et al., Eleven years of Inflexal® V—a virosomal adjuvanted influenza vaccine. *Vaccine*, (2009). 27(33): p. 4381-4387.
[30] Inflexal V - Product Monograph. (2009).
[31] Dr. Green. Invivac Sospensione Iniettabile. (2018) [cited 2019 February 11]; Available from: https://www.schedefarmaci.it/schede-tecniche/invivac.
[32] Intervet International B.V., Equilis West Nile suspension for injection for horses p. 18.
[33] Sadozai H and Saeidi D, Recent Developments in Liposome-Based Veterinary Therapeutics. *ISRN Vet Sci*, (2013). 2013(Article ID 167521): p. 8 pages.

DRUG DELIVERY LITERATURE

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Provided by Dr. Carsten Timpe

Peptide, Protein-based Drug Delivery

Versatility of cell-penetrating peptides for intracellular delivery of siRNA. Singh T, Murthy ASN, Yang HJ, Im J. Drug Deliv. 2018 Nov;25(1):1996-2006.

This review is focused on the versatility of cell-penetrating peptides (CPPs) and advanced approaches for siRNA delivery.

Dermal and Transdermal Drug Delivery

Hydrogels and Their Applications in Targeted Drug Delivery. Narayanaswamy R, Torchilin VP. Drug Delivery. Molecules. 2019 Feb 8;24(3).

The versatility and diversity of the hydrogels extend their applications beyond targeted drug delivery also to wound dressings, contact lenses and tissue engineering to name but a few. They are 90% water, and highly porous to accommodate drugs for delivery and facilitate controlled release. This review discusses hydrogels and how they could be manipulated for targeted drug delivery applications.

Transspinal delivery of drugs by transdermal patch back-of-neck for Alzheimer's disease: a new route of administration. Lehrer S, Rheinstein PH. Discov Med. 2019 Jan;27(146):37-43.

This review describes possibilities to administer NSAIDS, or the anticancer, paclitaxel *transdermally: e.g. a high dose of paclitaxel might be administered to the brain by transdermal patch over the back of the neck/cervical spine while avoiding the systemic side effects. A transdermal patch over the cervical spine could revolutionize the drug therapy of AD, and probably other neurodegenerative/neuropsychiatric diseases as well.*

Gene Drug Delivery, Gene Therapy, siRNAs

Pharmacokinetics and Clinical Pharmacology Considerations of GalNAc(3)-Conjugated Antisense Oligonucleotides. Wang Y, Yu RZ, Henry S, Geary RS. Expert Opin Drug Metab Toxicol. 2019 Jun;15(6):475-485.

In this review, the ADME (absorption, distribution, metabolism, and excretion) characteristics of GalNAc$_3$-conjugated ASOs in animals and in humans are summarized, and their clinical relevance is evaluated from the clinical pharmacology perspectives.

Nanosystem-based Drug Delivery

Emerging blood-brain-barrier-crossing nanotechnology for brain cancer theranostics. Tang W, Fan W, Lau J, Deng L, Shen Z, Chen X. Chem Soc Rev. 2019 Jun 4;48(11):2967-3014.

The detailed elucidation of BBB-crossing nanotechnology in this review is anticipated to attract broad interest from researchers in diverse fields to participate in the establishment of powerful BBB-crossing nanoplatforms for highly efficient brain cancer theranostics.

Solid lipid matrix mediated nanoarchitectonics for improved oral bioavailability of drugs. Banerjee S, Pillai J. Expert Opin Drug Metab Toxicol. 2019 Jun;15(6):499-515.

This article specifically focuses on the biopharmaceutical and pharmacokinetic aspects of solid lipid matrix based nanoformulations and possible mechanisms for better drug absorption and improved bioavailability (BA) following oral administration. It also briefly reviews methods to access the efficacy of LNFs for improving oral BA of drugs, regulatory aspects and some interesting lipid-derived commercial formulations, with a concluding remark.

Nanocarriers and nonviral methods for delivering antiangiogenic factors for glioblastoma therapy: the story so far. Clavreul A, Pourbaghi-Masouleh M, Roger E, Menei P. Int J Nanomedicine. 2019 Apr 9;14:2497-2513.

The review describes the nonviral methods, including convection-enhanced delivery devices, implantable polymer devices, nanocarriers, and cellular vehicles, to deliver antiangiogenic factors.

Nanomedicine in Alzheimer's disease: Amyloid beta targeting strategy. Tosi G, Pederzoli F, Belletti D, Vandelli MA, Forni F, Duskey JT, Ruozi B. Prog Brain Res. 2019;245:57-88.

The review outlines the most talented approaches in AD treatment with a specific focus on the main advantages/drawbacks and future possible translation to clinic application.

The glyconanoparticle as carrier for drug delivery. Zhang X, Huang G, Huang H. Drug Deliv. 2018 Nov;25(1):1840-1845.

This review describes in how far the glyconanoparticle (GlycoNP) has multiple effects and has important applications in drug delivery and bioimaging. It not only has the advantages of nano drug delivery system but also utilizes the characteristics of multivalent interaction of sugar, which greatly improves the targeting of drug delivery. Herein, the application of GlycoNP in drug delivery was analyzed and discussed, the solution to its problem was proposed, and its prospects were forecasted

Ocular Drug Delivery

Updates on thermosensitive hydrogel for nasal, ocular and cutaneous delivery. Wang Q, Zuo Z, Cheung CKC, Leung SSY. Int J Pharm. 2019 Mar 25;559:86-101.

The current review aims not only to provide an update on the recent developments in thermosensitive hydrogel formulations for nasal, ocular and cutaneous deliveries, but also identify the relationship between the drug characteristics and the loading strategies, and their impacts on the release mechanisms and the in vivo performance. This update for the first time highlights the essential features for successful development of in situ thermosensitive hydrogels to facilitate nasal, ocular or cutaneous drug deliveries.

Parenteral Drug Delivery

In Situ Forming Depot as Sustained-Release Drug Delivery Systems. Kanwar N, Sinha VR. Crit Rev Ther Drug Carrier Syst. 2019;36(2):93-136.

The present paper is an overview of the various in situ gelling polymers and their application in the preparation of depot formulations. Numerous products based on in situ forming systems such as Eligard®, Atridox® are available in market.

Oral Drug Delivery

A review on 5-aminosalicylic acid colon-targeted oral drug delivery systems. Shahdadi Sardo H, Saremnejad F, Bagheri S, Akhgari A, Afrasiabi Garekani H,

Sadeghi F. Int J Pharm. 2019 Mar 10;558:367-379.

In the current review, the different strategies utilized in the design and development of an oral colonic delivery dosage form of 5-ASA are presented and discussed.

Oral Nano-Delivery Systems for Colon Targeting Therapy. Zhang T, Zhu G, Lu B, Peng Q. Pharm Nanotechnol. 2017;5(2):83-94.

The review aims to provide a comprehensive understanding of the recent progress in the area of colon targeting delivery in combination with introduction of the pathophysiological changes of diseased colon sites and the obstacles for drug delivery.

Pulmonary drug delivery

Future of nanomedicines for treating respiratory diseases. Scherließ R Expert Opin Drug Deliv. 2019 Jan;16(1):59-68.

This review will look into the promises and opportunities of the use of nanoparticles in the treatment of respiratory diseases. Important aspects to discuss are the fate of nanoparticles in the lung and mechanisms for reproducible delivery of nanoparticulate formulations to the lungs. Examples are given where nanoparticles may be advantageous over for traditional formulations and further aspects to explore are mentioned.

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Critical Parameters for Particle-Based Pulmonary Delivery of Chemotherapeutics. Dabbagh A, Abu Kasim NH, Yeong CH, Wong TW, Abdul Rahman N. J Aerosol Med Pulm Drug Deliv. 2018 Jun;31(3):139-154.

This review aims at investigating the parameters that significantly drive the clinical outcomes of various particle-based pulmonary delivery systems. This should aid clinicians in appropriate selection of a delivery system according to their clinical setting. It will also guide researchers in addressing the remaining challenges that need to be overcome to enhance the efficiency of current pulmonary delivery systems for aerosols.

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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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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