



# APV FOCUS GROUP DRUG DELIVERY

COMBINING SCIENCE & TECHNOLOGY TO CREATE ADVANCED DRUG DELIVERY SYSTEMS

INTERNATIONAL ASSOCIATION FOR PHARMACEUTICAL TECHNOLOGY

NEWSLETTER

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## TABLE OF CONTENTS

- ◇ DRUG DELIVERY EVENTS: Upcoming seminars and conferences
- ◇ APV COURSE SUMMARY Intensive Patent Workshop; Berlin, Germany 25<sup>th</sup>-26<sup>th</sup> February 2014
- ◇ DRUG DELIVERY PRODUCTS: Bunavail™ / Qudexy® XR
- ◇ DRUG DELIVERY PEOPLE: Nicola Tirelli, Ph.D. (University of Manchester)
- ◇ FEATURED ARTICLE: Parenteral Injectable Liposomal Products Anno 2014, Status and Prospects  
*By Peter van Hoogevest*
- ◇ ABOUT OUR FOCUS GROUP: Who are we and what do we do?

## DRUG DELIVERY EVENTS

Provided by Christoph Blümer

[BACK TO TABLE OF CONTENTS](#)

**The 41<sup>st</sup> Annual Meeting & Exposition of the Controlled Release Society**  
July 13-16, 2014, Chicago, IL, USA

[Details](#)

**Skin Forum 14<sup>th</sup> Annual Meeting (APV 6557)**  
September 04-05, 2014, Prague, Czech Republic

[Details](#)

**1st European Conference on Pharmaceutics: Drug Delivery (organized by ADRITELF, APGI and APV)**  
April 13-14, 2015, Reims, France

[Details](#)

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

## APV COURSE SUMMARY

Provided by Dr. Karsten Cremer

[BACK TO TABLE OF CONTENTS](#)

### INTENSIVE PATENT WORKSHOP: HOW TO DRAFT, ANALYSE AND CIRCUMVENT A FORMULATION PATENT

Berlin, Germany 25<sup>th</sup>-26<sup>th</sup> February 2014

The course was jointly organized by the APV Drug Delivery Focus Group and Pharma Concepts GmbH. It was chaired by Dr. Karsten Cremer (Pharma Concepts GmbH, CH-Basel), who had developed it and has conducted the workshop once or twice per year since 2011.

Each of the two days of the course was dedicated to one of the two sides of the IP coin: FREEDOM TO OPERATE (Day 1) and OBTAINING PATENT PROTECTION (Day 2). The individual sessions focussed on the patent know-how that is essential for professionals in pharmaceutical product development. The primary objective was to enable the participants to collaborate effectively with IP experts and to understand what contribution is required from them to tackle patent issues effectively. Day 1 included sessions on the essential knowledge on FTO (freedom to operate), patent searching, and evaluation of third party patents with an eye on FTO, and the development of viable circumvention options. The main topics of day 2 dealt with protecting pharmaceutical innovations, identifying inventions and determining their scope, and the making of a patent application. The last session gave an overview of the patenting process, starting from idea to patent grant, and eventually to the generation of a portfolio of global patent families.

There are probably three major factors which have contributed to the great success of this course: (1) A systematic approach with thorough discussions of those aspects of patent law whose understanding is crucial in pharma development; (2) Numerous examples and illustrations which are all from the field of pharmaceutical dosage forms, drug formulations, and pharmaceutical processing, and (3) Several case studies and workshop exercises to confer an in-depth understanding of how the patent know-how is applied to real-life situations.

Since this intensive patent course has been so well received, Karsten Cremer and the APV Drug Delivery Focus Group are now evaluating the development of an advanced patent course targeted at those pharmaceutical professionals that require a substantial level of patent knowledge, such as those working in drug delivery innovation, team leaders in formulation development, and managers with a liaison function between R&D and IP. Any suggestions or enquiries are welcome; please contact Karsten directly ([cremer@pharma-concepts.com](mailto:cremer@pharma-concepts.com)).

## DRUG DELIVERY PRODUCTS

Provided by Dr. Louise Rosenmayr-Templeton

[BACK TO TABLE OF CONTENTS](#)

### BUNAVAIL™ (buprenorphine/naloxone buccal film)

On 6 June 2014 the FDA approved Bunavail™ a buccal film containing the partial mu-opioid receptor agonist and kappa-opioid receptor antagonist, buprenorphine, and the mu-receptor antagonist, naloxone [1, 2]. The product is indicated for the maintenance treatment of opioid dependence and should be used in conjunction with a program involving counseling and psychosocial support. The clinical effects of the product are due to buprenorphine with the naloxone discouraging dissolution and injection of the product.

Bunavail is available in three strengths: buprenorphine:naloxone 2.1mg:0.3mg; 4.2 mg:0.7 mg and 6.3 mg:1 mg. The films are 2.2 cm<sup>2</sup>, 4.4 cm<sup>2</sup> and 6.5 cm<sup>2</sup> respectively. The recommended daily dose is 8.4 mg/1.4 mg applied once daily but maintenance dosing can range from 2.1 mg buprenorphine to 12.6 mg depending on the amount required to suppress withdrawal symptoms.

The product employs BioDelivery Sciences International's BioErodible MucoAdhesive (BEMA®) technology and consists of a bi-layer film which adheres within 5 seconds of application, delivers the medication across the buccal mucosa and then dissolves. The mucoadhesive layer contains the buprenorphine and the backing layer the naloxone. Diffusion of the buprenorphine into the mucosa and not into the mouth cavity is promoted through manipulation of the pH in the two layers in order to maximize the drug's absorption and bioavailability [3].

The need for products to treat opiate dependence is growing especially in the USA where the market for such products is said to be worth more than US\$1.7 billion. Bunavail, which is expected to be launched in Q3 2014, will compete in this market with Suboxone® sublingual films from Reckitt Benckiser which in 2013 had US sales of greater than \$1.3 billion. The buccal film formulation has a number of differentiating features from the current market leader [1]. Firstly, as a result of improved bioavailability from the BEMA formulation, only half the dose of buprenorphine is required compared with Suboxone (Bunavail 4.2/0.7 mg gives the same buprenorphine exposure as a Suboxone 8 mg/2 mg sublingual tablet). This dose decrease may result in a reduction in the abuse potential of the product and lessen the risk of side-effects. Secondly, the company cites the improved ease of administration and convenience of the buccal film product in comparison with the sublingual dosage form that must be held under the tongue.

### QUDEXY® XR (Topiramate extended-release capsules)

Qudexy® XR from Upsher-Smith was approved on 11 March 2014 by the FDA [4]. The capsules contain the anti-epileptic, topiramate, and are indicated for the monotherapy of partial onset seizures and primary generalized tonic-clonic seizures in patients 10 years of age and older and as adjunctive therapy in those of 2 years and above. The capsules can also be used in patients of 2 and over suffering from Lennox-Gastaut Syndrome (LGS), a rare, severe, and difficult-to-treat form of childhood-onset epilepsy. The capsules are available in different strengths: 25 mg, 50 mg, 100 mg, 150 mg, and 200 mg. The recommended dose for monotherapy in patients older than 10 is 400 mg once daily titrated upwards from 50 mg daily for 6 weeks. This is compared to twice daily dosing for the intermediate release formulation. The capsules can be swallowed whole or opened and sprinkled onto a spoonful of soft food. The controlled release formulation is based on ethyl cellulose.

Qudexy is the second controlled release formulation of topiramate that has recently reached the US market. In August 2013 the FDA approved Trokendi XR™ from Supernus Pharmaceuticals [5]. This product has proved popular with patients with the number of prescriptions growing on average by 1000 per month since launch [6]. It will be interesting to see what the impact of the arrival of Qudexy® XR on the market will have on Trokendi XR™ sales.

### References and Further Reading

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## DRUG DELIVERY PEOPLE

Provided by Prof. Dr. Karsten Mäder

[BACK TO TABLE OF CONTENTS](#)

**NICOLA TIRELLI** graduated in Chemistry and then obtained a PhD in Industrial Chemistry at the University of Pisa (Italy), in 1992 and 1996 respectively, in both cases under the supervision of F. Ciardelli. He then moved to Switzerland (ETH Zurich, Department of Materials) where he was first post-doc in the Institute for Polymers (U.W. Suter), and later Oberassistent in the Institute of Biomedical Engineering headed at the time by J. Hubbell (12/98-12/02). He joined the School of Pharmacy and Pharmaceutical Sciences of the University of Manchester in 2003, being promoted to Chair of Polymers and Biomaterials in 2005. Since Aug 2010 he has been part of the School of Materials and of that of Medicine/Inst. of Inflammation and Repair of the University of Manchester.



Since 2005 Nicola has been part of the Executive Advisory Board of all Macromolecular journals of Wiley-VCH and in 2006-2012 he was editor-in-chief of Reactive and Functional Polymers for Elsevier. He received a Bessel award from the Humboldt foundation in 2004 and was EPSRC Advanced Research Fellow 2005-2010. He has been Visiting Professor at the Max Planck Institute for Colloids and Interfaces (Golm, Germany; 2004) and at the Helmholtz Centre of Biomaterials Development (Teltow, Germany; 2012). Nicola has published 107 research papers (excluding proceedings), 69 as corr. author, 5 reviews and 6 patents.

## FEATURED ARTICLE

[BACK TO TABLE OF CONTENTS](#)

### Parenteral Injectable Liposomal Products Anno 2014, Status and Prospects

*By Peter van Hoogevest*

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#### Abbreviations

DEPC:	1,2-dierucoylphosphatidylcholine
DMPC:	1,2-dimyristoylphosphatidylcholine
DOPC:	1,2-dioleoylphosphatidylcholine
DOPS:	1,2-dioleoylphosphatidylserine
DPPG:	1,2-dipalmitoylphosphatidylglycerol
DSPC:	1,2-distearoylphosphatidylcholine
DSPG:	1,2-distearoylphosphatidylglycerol
HSPC:	Hydrogenated soybean phosphatidylcholine
MPEG-DSPE:	1,2-distearoyl-phosphatidylethanolamine-methyl-polyethyleneglycol conjugate-2000 sodium salt
MTP-PE:	Muramyltripeptide-phosphatidylethanolamine
PC:	Phosphatidylcholine
PG:	Phosphatidylglycerol
POPC:	1-palmitoyl-2-oleoylphosphatidylcholine
SM:	Sphingomyelin

#### 1. Introduction

In the APV Newsletter, Issue 1/2006 the properties of the marketed liposomal products in the USA and EU were reviewed [1]. Since then, the interest in using nanotechnology in drug delivery has increased tremendously. This trend can also be observed for research into liposomes as carriers for therapeutics as can be seen from the many publications devoted to this subject. Liposomes are a sub-set of nanotechnology and can be considered as the "gold standard" for nano-particulate delivery systems.

This article summarizes the changes in marketed parenteral injectable liposome products compared to eight years ago and discusses the clinical and technical development lessons learned from these products. Finally, trends that will affect the future use of liposomes are briefly discussed.

## 2. Marketed Products

Nowadays, liposomal products for intravenous injection and for local depot injection are on the market.

### *Intravenous products*

In addition to the products mentioned in 2006 [1], Abelcet\*, AmBisome, DaunoXome, Doxil/Caelyx, Myocet, Visudyne and Mepact, one additional intravenous liposomal product, Marqibo, has entered the market. The characteristics of all marketed liposomal products are provided in Table I [2, 3].

Table 1: Characteristics of marketed intravenous liposomal products, anno 2014.

Product	Drug substance	(Phospho)lipid composition	Indication
Abelcet	Amphotericin B	DMPC DMPG	Invasive fungal infections
AmBisome	Amphotericin B	HSPC DSPG Cholesterol Alpha-tocopherol	Aspergillus -, Candida- and/or Cryptococcus species infections Visceral leishmaniasis
DaunoXome	Daunorubicin citrate	DSPC Cholesterol	Advanced HIV-associated Kaposi's sarcoma
Doxil/Caelyx	Doxorubicin HCl/sulphate	DSPE-MPEG HSPC Cholesterol	AIDS-related Kaposi's sarcoma Ovarian cancer Multiple myeloma
Marqibo	Vincristine sulphate	Egg SM Cholesterol	Philadelphia chromosome-negative (Ph-) acute lymphoblastic leukemia
Mepact	MTP-PE, Mifamurtide	POPC DOPS	Osteosarcoma
Myocet	Doxorubicin HCl/citrate	Egg PC Cholesterol	Metastatic breast cancer
Visudyne, Verteporfin for injection	Benzoporphyrin	DMPC Egg PG Ascorbyl palmitate (Butylated-hydroxytoluene)	Exudative (wet) age-related macular degeneration (AMD) with predominantly classic subfoveal choroidal neovascularisation (CNV) Subfoveal choroidal neovascularisation secondary to pathological myopia.

Marqibo (Spectrum Pharmaceuticals, Inc.) was approved by the FDA in 2012 [4]. Marqibo is a result of the usual line extension development strategy to combine a rather toxic generic drug with liposomes in order to suppress toxicity and/or enhance the efficacy of the encapsulated drug [5, 6].

Marqibo uses liposomes comprising Egg SM and cholesterol, which are stable and non-leaky in the blood circulation and have long circulating characteristics. The alternative approach using PEG-ylated phospholipids to make long circulating liposomes, failed because the liposomes comprising PEG-ylated phospholipids appeared to be too leaky for the encapsulated vincristine sulphate [7].

From this list of products (Table 1) several interesting observations can be made. The products

- are based on generic drugs as well as NCEs (MTP-PE, Benzoporphyrin),
- are mainly developed for life-threatening diseases (exception Visudyne)
- are used as solubilizers for lipophilic drugs (AmBisome and Visudyne) or to increase the therapeutic index (all products with exception of Visudyne),
- use natural (HSPC, Egg SM, Egg PC) as well as synthetic phospholipids.

The selection of natural or synthetic phospholipids is an important issue for the development of future liposomal products. Natural phospholipids are derived from renewable sources e.g., soy beans or egg yolk, and produced with more ecologically friendly processes and are available in larger scale at relatively low costs. They comply with all requirements of the regulatory authorities and are safe to use for any administration route and any dosage form. Synthetic phospholipids contain chemically specific, defined polar head groups and fatty acids but are synthesized with various chemicals and solvents. They may contain intermediates or by-products and unnatural enantiomers may be formed. Synthetic phospholipids are only available in relatively small amounts at high prices [3].

Another interesting observation is that various formulation approaches seem to be possible to increase the therapeutic index of cytostatic drugs mainly through stable (non-leaky) long circulating liposomes: these are the inclusion of PEG-ylated lipids (Doxil), use of DSPC/cholesterol (DaunoXome) or Egg SM/cholesterol (Marqibo). It is claimed that the long circulating properties are required to get an enhanced permeability retention (EPR) of the entrapped cytostatic at leaky

epithelial tumor sites, yielding higher efficacy and/or lower toxicity of the cytostatic. However it is interesting to note that the Myocet doxorubicin liposomes, which do not possess long circulating properties, but in contrast are mainly taken up by macrophages of the mononuclear phagocytotic system [8] show an increased therapeutic index in cancer treatment compared to doxorubicin HCl injectable. In addition, Myocet does not show the hand-and-foot-syndrome (palmar-plantar erythrodysesthesia) a dose limiting side effect of Doxil. Based on these product characteristics, it can be concluded that besides the stealth approach other formulation principles may be explored to increase the therapeutic index of anti-cancer drugs. Clearly, there is more research needed to understand the action and toxicity mechanism of these various liposomal formulations in more detail.

A further interesting clinical use aspect of some parenteral liposomal products (Doxil and AmBisome) is the occurrence of mild-to-severe hypersensitivity (infusion) reactions, which are referred to as complement (C) activation-related pseudo-allergy (CARPA) [9]. Although in most cases CARPA is inconsequential, a main symptom, cardiopulmonary distress, may be life threatening in some hypersensitive individuals. Many options, however, exist to reduce the risk for occurrence of CARPA after infusions of liposomes [10]. In addition, these infusion reactions have been known for decades for other (non-liposomal) drugs and parenteral excipients like Cremophor EL and Tween 20 and 80 causing far more severe infusion reactions [11].

#### Local depot injections

Liposomal products based on DepoFoam technology were found to be suitable as local slow release depot injectables for low MW (molecular weight) water-soluble drugs and entered the market in the past decade. Two products, Exparel [12] and DepoCyt [13] marketed by Pacira Pharmaceuticals Inc., are based on this technology and contain various types of phospholipids. A previous product DepoDur [14-16] was withdrawn from the market. The characteristics of these products are provided in Table 2. DepoCyt is distributed in the USA by SigmaTau Pharmaceuticals Inc. and in Europa by Mundipharma GmbH.

The DepoFoam technology, based on multivesicular liposomes, was developed to reduce the injection volume by maximizing the encapsulation efficiency of water soluble drugs [17]. These multivesicular liposomes comprise discontinuous internal aqueous chambers, bounded by a continuous, non-concentric network of lipid membranes. This structure renders a higher aqueous volume to lipid ratio and much larger particle diameters (e.g. median diameter for Exparel (bupivacaine DepoFoam) 24 to 31  $\mu\text{m}$  [12] compared to MLVs [18]). The multivesicular liposomes are prepared by a two-step water-in-oil-in-water double emulsification process [18, 19].

Table 2: Characteristics of slow release injectable products based on DepoFoam technology

Product	Drug Substance	Lipid Excipients	Administration Route	Duration of Action/Release	Indication
Exparel	Bupivacaine	DEPC DPPG Tricaprylin	At surgical site after e.g. Bunionectomy or Hemorrhoidectomy	Up to 96 h	Postsurgical analgesia
DepoDur	Morphine sulphate	DOPC DPPG Cholesterol Tricaprylin Triolein	Epidural at lumbar level	Dose dependent: $t_{1/2}$ 4-26 h	Pain treatment prior to surgery or after clamping the umbilical cord during caesarean section
DepoCyt	Cytarabine	DOPC DPPG Cholesterol Triolein	Intrathecal	$t_{1/2}$ of cytarabine in CSF 6-82 h	Lymphomatous meningitis

### 3. Discussion

Since 2006 liposomes have been established for local depot injections and two additional liposomal products entered the market. However, only one additional intravenous liposomal product was launched. The reasons for this may be related to the fact that the small pharmaceutical companies that try to develop these complex intravenous products may not have the resources to develop such products independently in an expeditious manner. In addition, the clinical research may be challenging. Typically major pharmaceutical companies only show limited interest in such products and consider them mostly as licensing-in candidates at a late stage of clinical development. The approval procedures of such products by regulatory authorities may also be longer compared to less complex formulations. Based on the many orphan drug designations for intravenous liposomal drugs (see [www.orpha.net](http://www.orpha.net)) new liposomal product are, in spite of these difficulties, continuously being developed. In addition, it is to be expected that liposomes as well-established nano-drug carriers will profit from the continuous interest in nanotechnology.

As illustration of these ongoing development efforts, examples of intravenous liposomal products which are in Phase II or Phase III clinical testing are provided in Table 3.

Table 3: Examples of intravenous liposomal products in Phase II or Phase III clinical research.

Product	Drug Substance(s)	Company
CPX-351	Cytarabine:Daunorubicin	Celator Pharmaceuticals
CPX-1	Irinotecan HCl:Floxuridine	Celator Pharmaceuticals
EndoTag-1	Paclitaxel	Medigene AG
LEP-ETU	Paclitaxel	Insys Therapeutics, Inc.
Lipoplatin	Cisplatin	Regulon Inc.
MBP-426	Oxaliplatin	Mebiopharm Co.,Ltd.
MM-398/ PEP02	Irinotecan	Merrimack Pharmaceuticals
Telintra	Ezatiostat HCl, TLK 199	Telik, Inc.
ThermoDox	Doxorubicin	Celsion Corporation

The products listed in the Table show clearly that the development trend to combine existing drugs with liposomes is being continued. The mentioned products are mainly developed for various cancer indications. Telintra was clinically investigated up to Phase IIA for the myelodysplastic syndrome indication in a liposomal form but is now explored in an oral dosage form [20-22].

The product ThermoDox is a first generation of thermosensitive liposomes. Thermosensitive liposomes comprise phospholipid blends which are more permeable for the entrapped cytostatic at temperatures slightly above body temperature. Systemic treatment with such liposomes (with or without PEG-ylated phospholipids) is combined with selective heating of tumor tissue. In this way it is hoped that the cytostatic is also selectively released at the site where it is needed, so giving rise to a more efficacious therapy and lower systemic toxicity of the used cytostatic. The local heat generation can be achieved by high-intensity-focused-ultrasound guided by MRI (magnetic resonance imaging) [23-25].

In cancer research, further future use of liposomes focuses on the increase of anti-tumor efficacy of liposomal cytostatic by 1) using immuno-liposomes to increase the selectivity of the liposomes for tumor cells [26, 27] 2) exploring combinations of cytostatic drugs simultaneously encapsulated in liposomes [28].

Together with the thermosensitive liposome approach, these future research directions aim to potentiate liposomes which, through a stealth effect and the EPR mechanism, have targeting properties to the tumor sites. In addition, based on the successful use of liposomes with the lipophilic photosensitizer benzoporphyrin, there is a continuous interest to use liposomes as solubilizers in photodynamic therapy for poorly water soluble photosensitizers like zincphthalocyanine [29] and temoporfin [30].

#### 4. Conclusions

Since 2006 parenteral injectable liposomal drugs have been further shown to be valuable medicines especially in life threatening indications like cancer and systemic fungal infections. One new intravenous and two additional liposomal depot injections were introduced on to the market. Although the development of new liposomal products proceeds at low pace, it is to be expected, considering the ongoing preclinical and clinical efforts in nanotechnology and the acceptance of liposomal dosage forms by regulatory authorities, that more interesting liposomal products will gradually reach the market.

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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 pharmaceuticals.

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## COMBINING SCIENCE AND TECHNOLOGY TO CREATE ADVANCED DRUG DELIVERY SYSTEMS

### OUR MISSION STATEMENT:

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

### Our mission includes in particular the following tasks:

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

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

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

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