



APV Focus Group Biotechnology

Pharmaceutical Biotechnology from Production to Application

INTERNATIONAL ASSOCIATION FOR PHARMACEUTICAL TECHNOLOGY

NEWSLETTER

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Dear colleagues,

With the spring season knocking on our doors we are in the right mood to start the new adventures of this year with a positive attitude. Sadly though, the news reaching us from Japan and the implications on environmental policies worldwide are casting their shadows. Despite the human and environmental disaster it appears that the causes are more and more instrumentalized in politics that distracts us to think of the fate of so many Japanese people. As I have many friends in this region I would like to state that we are deeply touched by this combined natural and human-made disaster and hope that regarding the circumstances further harm can be avoided as much as possible.

One lesson learned from all this is probably that we are very vulnerable and forces of Nature will always bear a potential threat that cannot be limited to a regional problem. Health, the field we are professionally concerned with, does not know borders and can affect anyone of us at any unexpected time. We can either just close our eyes or try to prepare for such situations. Therefore, I am grateful to Prof. Borchard to report from the IFPMA and GAVI alliance on bringing improved vaccine solutions to patients, also to those regions that normally cannot afford adequate treatments. Infectious diseases will most likely be continue to be a major threat to our global community in the not-so-far future, and certainly not limited to pandemic influenza.

Our featured article provided by Claudia Müller and Gerrit Borchard discusses the recent status on protein PEGylation research. For those that are interested to follow-up on this subject we would also like to kindly reference to a full review of this topic in the recently published book: "Protein Pharmaceuticals" by the ECV publisher house (www.ecv.de).

The outlook on seminars in 2011 offers a highlight with a course on "Immunogenicity and aggregation of therapeutic proteins" that will be held on October 4 & 5. This course will offer the possibility to a highly reputed panel of international speakers. Based on the very successful organized basic course repeatedly held by Beppo Schubert and Rolf Daniels over the past years it was time to organize a follow-up advanced course. This will be organized by Michael Wiggenhorn in Q4/2011.

We also would like to provide a warm welcome to our new group members Karoline Bechtold-Peters, Carsten Olbrich and Mathias Schroedter. You find their CV's in this Newsletter and I also can say that they brought a lot of fresh energy and ideas to the group.

Finally, I wish everyone that you experience the content of this Newsletter interesting and like to follow-up on our work as a group in your interest area. Please do not hesitate to provide feedback to us.

Henrik Luessen, April 21st, 2011

BIOTECHNOLOGY GROUP EVENTS

Course: Immunogenicity and aggregation of therapeutic proteins, 4th to 5th October 2011 in Berlin, Germany

Therapeutic protein candidates are increasingly entering the pipelines of pharmaceutical companies and the marketplace in spite of production, formulation and safety challenges encountered. This 2-day conference held under the auspices of APV and AAPS will focus on issues in immunogenicity and protein aggregation by gathering opinion leaders from academia, industry and regulatory authorities for an update on the state-of-the-art. The conference will also offer to students the presentation of their latest results in poster format, and the display of advanced analytical technology to suppliers in an industrial exhibition.

Highly recognized experts in the field like John Carpenter, Mary Cromwell and Huub Schellekens have been recruited as keynote speakers. If you are interested please visit the website of APV.

Course: Advanced Lyophilization

This course is planned for Q4 2011 and will be cover recent innovation in process and formulation development.

Reserve your time and If you are interested please visit the website of APV for further information's and dates.

BIOTECHNOLOGY EVENTS

AAPS - NBC - National Biotech Conference in San Francisco

16-18th May 2011

Deutsche Biotechnologietage 2011 Munich

25-26th May 2011

BIO in Washington DC

27-30th June 2011

CPHi Frankfurt

25-27th October 2011

BioEurope Duesseldorf

31st October-02nd November

Suggest a meeting to be announced!

BIOTECH PRODUCTS

US: Recent BLA Approvals (January 2010 - July 2010)

Brand name	Proper name	Company	Date of Approval	Indication
Glassia	Alpha1-Proteinase Inhibitor	Kamada Ltd.	July 1, 2010	Emphysema due to congenital deficiency of alpha-1-proteinase inhibitor
Provenge	Sipuleucel-T	Dendreon Corp	April 29, 2010	Metastatic prostate cancer
TachoSil	Fibrin Sealant Patch	Nycomed Danmark ApS	April 5, 2010	Adjunct to hemostasis in cardiovascular surgery
Hizentra	Immune Globulin	CSL Behring AG	March 4, 2010	Treatment of primary immunodeficiency

Source: www.fda.gov, new BLA Approvals

EU: Recent MAA Approvals for Biologicals (January 2010 - December 2010)

Brand name	INN	Company	Date of Approval	Indication
Arzerra	Ofatumumab	Glaxo Group Ltd	Jan 2010 (conditional)	CLL

Source: www.ema.europa.eu, CHMP Monthly Reports

BIOTECH – IFPMA and GAVI Alliance

Two partners in Providing Access to Vaccines to the Developing World

On November 17, 2010, the International Federation of Pharmaceutical Manufacturers and Associations (IFPMA) organized a podium discussion on the contribution of vaccines, and vaccine manufacturers, on achieving the Millennium Development Goals (MDG) 4 and 5 at the Geneva Conference Center. The podium was joined by Eduardo Pisani, Director General of IFPMA, Dr. Jean-Marie Okwo-Bele, Director at WHO Dept. of Immunization, Vaccines and Biologicals, Mr. Jean Stéphenne, Chairman and President of GSK Biologicals, Mr. Mark Swindell, President Pfizer Vaccines, and Dr. Michael Watson, who heads the Global Immunisation Policy at Sanofi Pasteur. The panel discussion was moderated by Prof. Gerrit Borchard, Vice President School of Pharmaceutical Sciences at the University of Geneva.

Preceding the panel discussion, Dr. Okwo-Bele presented on the WHO's perspective of the "*Power of Vaccines and Immunization*". He reminded that the World Health Assembly in 2008 urged the member states to implement a strategy to reduce measles mortality, achieve equitable coverage of at least 80% by 2010, and to stimulate rapid introduction of new vaccines and to expand coverage of these vaccines. While the first goal is close to its target, the other two are not on track to meet health-related MDG goals, in particular the goal to

reduce under-five mortality rate (MDG 5). As an example, the pneumo conjugate vaccine, introduced in 2000 in 42 countries, and the rotavirus vaccine (23 countries) have both only reached 11% of the 2009 global birth cohort. Challenges with new vaccines are easily identified. Costs are a major hurdle, as well as the absence of a National Immunization Advisory Committee in many countries and unsuitable logistics to deal with new antigens and to "reach the hard to reach".

In his presentation, Jean Stéphenne discussed the role of the R&D based vaccine industry, represented in IFPMA, in achieving Millennium Development Goals. Firstly, the industry is investing in R&D, to maintain efforts in commonly used vaccines, and makes significant investments in the development of new breakthrough vaccines. The IFPMA vaccine pipeline has more than 20 candidates in different stages of development, addressing diseases such as Dengue fever, HIV, malaria and tuberculosis. Secondly, the industry is already supplying large quantities of vaccines worldwide. Some of the IFPMA companies are allocating up to 75% of their production to developing countries. For example, the R&D industry was a major supplier of hepatitis B, Haemophilus Influenza B, and Yellow fever vaccines from 2000 to 2005.

This effort was made possible through the interaction with the GAVI Alliance, a non-for-profit organisation based in Geneva. GAVI brings together the partners in vaccine development and distribution, including governments of developing and donor countries, WHO, UNICEF, the World Bank, vaccine industry in industrialized and developing countries, research and technical agencies, as well as the Bill & Melinda Gates Foundation. With a budget of US\$ 4 billion for the period of 2000 to 2015, raised mostly by issuing bonds in the capital market, GAVI funds immunization programs in developing countries.

In accordance with Dr. Okwo-Bele, Mr. Stéphenne also stressed the issue of developing new technology to facilitate the distribution and administration of vaccines, which would include implementation of vaccine vial monitoring (VVM), the introduction of auto-disabling syringes, and the technical education and support of vaccine producers in developing countries.

Last not least, the R&D vaccine industry must engage in actively improving access to vaccines (affordability) and education (clinical trials, training of healthcare professionals, educational grants). In all of this, however, a favorable environment with regard to IP and return on investment for the industry needs to be maintained. New financing models such as represented by the GAVI Alliance, may be very helpful in this.

Further information on IFPMA and GAVI are found on their respective websites at www.ifpma.org and www.gavialliance.org.

Non-covalent PEGylation for the stabilisation of protein drug formulations**Claudia Müller^{1,2} and Gerrit Borchard¹**

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Protein therapeutics

With the approval of insulin by the FDA in 1982, the first recombinantly produced protein therapeutic became commercially available [1] and represented a major breakthrough for the therapy of diabetes mellitus. Since then, the application of recombinant protein based therapeutics and diagnostics increased tremendously. Biopharmaceuticals became of major importance in the treatment of severe diseases, such as cancer, infectious diseases or autoimmune diseases [2]. However, formulation scientists are confronted with various problems when developing a safe and stable protein formulation that is accepted also by the patients: i) proteins suffer from short plasma half-lives due to fast enzymatic degradation and renal filtration, ii) proteins were observed to be immunogenic, although human homologues are preferably used today, iii) biopharmaceutical formulations are affected by the poor stability and shelf-lives of the API due to physical and chemical degradation processes [2, 3].

Protein aggregation - pathways and inducing factors

Recently, Philo has described different possible mechanisms causing protein aggregation as a major physical degradation process [4]. In principle, conformational changes, partial unfolding, chemical degradation or modification of the native protein may lead to oligomerization and result in aggregation [4, 5]. Furthermore, the adsorption of native protein monomers at container surfaces or air-liquid interfaces may result in partial unfolding, leading to aggregation, whether directly at the surface or interface or even in solution after liberation of the altered protein [6, 7]. These processes are mostly called „non-native“ aggregation, since an altered protein structure is involved. In addition, native proteins may also self-associate and aggregate [4].

Regardless of the mechanism, non-covalent interactions of electrostatic and hydrophobic nature are most often implicated [8]. Unfolded intermediates are highly flexible and expose hydrophobic patches usually buried in the native protein. Though present only to a very low extent, these intermediates are supposed to trigger aggregation by attracting hydrophobic interactions [5, 9]. When a native protein possesses sticky patches on its surface, aggregation may proceed by attractive forces of hydrophobic, electrostatic or van der Waals nature [8, 10].

Aggregation may be induced by a myriad of "stress" conditions occurring during the production, purification, and formulation processes of a biopharmaceutical. The protein structure itself, protein concentration, temperature changes, freezing/thawing cycles, changes in pH or ionic strength, additives such as preservatives or polyols, shaking or shearing processes all may induce aggregation [5, 8, 10]. Thus, stabilization of a biopharmaceutical against aggregation is most often an empirical process testing various processing and formulation conditions.

Protein formulation – covalent PEGylation

PEGylation represents the covalent conjugation of poly(ethylene glycol) to biopharmaceuticals and might be employed in order to obtain either one or several of the following effects: i) prolongation of the *in vivo* circulation half-life, ii) decrease of *in vivo* immunogenicity, and iii) decrease of aggregation [3]. However, several challenges in covalent PEGylation remain: i) after synthesis, heterogeneous products are obtained in need of separation and characterization, ii) the chemistry employed to attach the PEG may represent additional stress for the protein, which might lead to increased aggregation and partial or complete loss of activity, iii) because of steric shielding by the PEG, reduced *in vivo* bioactivity is most often obtained resulting from decreased interactions of the drug with its receptor.

Development of novel PEGylation approaches based on non-covalent interactions

In order to address the need of PEGylation approaches circumventing one or several remaining drawbacks of covalent PEGylation, we opted for the development of non-covalent PEGylation techniques based on hydrophobic interactions, since the latter have been predominantly described in literature to be a key parameter during aggregation.

At first, we synthesized PEG-based excipients of different molecular weight bearing dansyl- as hydrophobic headgroup. Although dansylamide (the underlying structure for the headgroup employed) is not approved for use in humans, it offered the advantage of having a further diagnostic tool by following changes in its fluorescence characteristics. The successful conjugation of the dansyl-headgroup to PEG and the purity degree were analyzed using ¹H-NMR and ¹³C-NMR, FTIR, MALDI-TOF and UV-Vis spectroscopy. Thus, three different PEG-based excipients were obtained: monovalent dansyl-mPEGs of 2 kDa (93 % conjugation degree) and 5 kDa (96 % conjugation degree) and a bivalent bis-dansyl-PEG of 3 kDa (91% conjugation degree). The sensitivity of the dansyl-fluorescence towards the polarity of its environment was maintained after PEG-conjugation. This property and dynamic light scattering measurements (DLS) were employed to check for the ability to associate (micellization). Both techniques suggested the absence of micelles. Furthermore, neither cytotoxic nor hemolytic effects were observed for any of the dansyl-PEGs at all concentrations tested. By fluorimetric titration DNSA was found to bind to human serum

albumin (HSA) while for dansyl-mPEG 2 kDa binding to HSA was absent.

Dansyl-mPEG 2 kDa was added to a stable solution of salmon calcitonin (sCT). Reduction of the 90° light scatter and an increase in dansyl-fluorescence of this mixture may suggest possible interactions between sCT and dansyl-mPEG 2 kDa. Subsequently, the influence of all excipients on the aggregation of sCT in various buffer systems was analyzed by following changes in Nile Red fluorescence (added as an extrinsic fluorophore to follow aggregation of sCT) and turbidity in time.

Dansyl-mPEG 2 kDa reduced sCT aggregation best at a 1:1 molar ratio, although stabilization was observed down to molar ratios of sCT:dansyl-mPEG 2 kDa of 100:1. Bis-dansyl-PEG 3 kDa also stabilized sCT against aggregation at a 1:1 molar ratio, though less effectively than dansyl-mPEG 2 kDa. Dansyl-mPEG 5 kDa deteriorated aggregation of sCT. Furthermore, we were able to show that the changes in dansyl-fluorescence of the dansyl-PEGs may also be used to detect and follow aggregation of sCT.

In another approach, Tryptophan-mPEGs (Trp-mPEGs) of 2 and 5 kDa were synthesized and physicochemically characterized, before their influence on sCT aggregation was evaluated. Trp is approved for use as a nutritional supplement offering furthermore the advantage of its fluorescence being susceptible to environmental polarity. Successful conjugation and purification were analyzed using the same methods as described for the dansyl-PEGs. A conjugation degree of 98 % was obtained for both Trp-mPEGs. The susceptibility of Trp fluorescence intensity to polarity of its environment was maintained after PEG-conjugation. Again, this property and DLS were used to evaluate possible association. Following the fluorescence intensity vs concentration suggested a possible association of few Trp-mPEG 2 kDa molecules resulting in complexes too small to include hydrophobic dyes like Nile Red. No association was observed for Trp-mPEG 5 kDa. Furthermore, the hemolytic and cytotoxic potentials were analyzed for both excipients. Only Trp-mPEG 2 kDa at a concentration of 20 mg/ml was shown to be cytotoxic *in vitro*.

With increasing Trp-mPEG 2 kDa concentration, sCT aggregation was decreased in 10 mM sodium citrate buffer pH 6, being a harsh environment, wherein sCT in the absence of the excipient aggregated very fast. A 10-fold molar excess even suppressed aggregation of sCT up to 64 hours under these conditions. Again, Trp-mPEG 5 kDa was less effective than Trp-mPEG 2 kDa. With a 10-fold molar excess of Trp-mPEG 2 kDa in presence of sCT, a very low aggregation tendency was measured after ~10 days in 10 mM sodium citrate buffer pH 5 by various techniques such as 90° light scattering, Nile Red fluorescence, Nile Red fluorescence microscopy, fluorescence lifetime and fluorescence anisotropy. Trp-mPEG 2 kDa significantly reduced sCT aggregation in harsh environments, wherein sCT alone aggregated fast. Trp-mPEG 2 kDa was superior to dansyl-mPEG 2 kDa in reducing the aggregation of sCT.

We also tested commercially available benzyl-mPEGs (2 and 5 kDa) and cholesteryl-PEGs (2 and 5 kDa). The excipients were physicochemically characterized and subsequently analyzed for their influence on sCT aggregation. Furthermore, phenylbutylamino-mPEG 2 kDa was synthesized and characterized as described above for the dansyl-PEGs. DLS measurements

indicated the absence of micelles for phenylbutylamino-mPEG 2 kDa and benzyl-mPEGs 2 and 5 kDa. For the cholesteryl-PEGs increased count rates of scattered light and hydrodynamic radii indicated the presence of micelles. The critical micelle concentrations (CMCs) for cholesteryl-PEG 2 kDa and 5 kDa were determined to be at 0.007 mg/ml and 0.01 mg/ml from measurements following the changes in fluorescence intensity and emission maximum after inclusion of the hydrophobic Nile Red fluorophore.

The aggregation of sCT was increased after the addition of equimolar amounts of phenylbutylamino-mPEG 2 kDa, benzyl-mPEGs 2 and 5 kDa, and cholesteryl-PEGs 2 and 5 kDa. Based on the observations of the varying efficacy of all the PEG-based excipients on the aggregation of sCT, it is proposed that electrostatic interactions between sCT and the dansyl- or Trp-headgroup are of importance for the observed stabilization against aggregation. Due to these interactions, the PEG gets attached non-covalently to sCT and can perform a sterical shielding of the latter resulting in decreased aggregation.

Furthermore, the different excipients were evaluated for their influence on the aggregation of hen egg white lysozyme (HEWL) by following turbidity. Benzyl-PEGs aggravated HEWL aggregation, while phenylbutylamino-mPEG 2 kDa prolonged the lag phase of HEWL aggregation with increasing concentration. Both cholesterol-PEGs suppressed HEWL aggregation over 20 hours. Trp-mPEG 2 kDa reduced the aggregation velocity, Trp-mPEG 5 kDa had no effect on HEWL aggregation. After addition of the dansyl-PEGs HEWL aggregation was decreased, the aggregation velocity reduced, and the lag time of aggregation increased to a varying degree.

From the different studies performed we can draw several conclusions: i) in most cases the stabilization of the PEG-based excipients against aggregation is dependent on the molecular weight of the PEG chain, ii) the headgroup and the biopharmaceutical itself are of significance, iii) the molar ratio of biopharmaceutical to PEG-based excipient used is important. Concerning conclusion number i) it was observed that 2 kDa excipients bearing the same headgroups were most often more efficient than 5 kDa excipients. With regards to conclusion ii) it was noticed that Trp-mPEG 2 kDa was superior to dansyl-mPEG 2 kDa at a 1:1 molar ratio of sCT to PEG-based excipient. Phenylbutylamino-mPEG 2 kDa, benzyl-mPEGs 2 and 5 kDa, and cholesteryl-PEGs 2 and 5 kDa all aggravated sCT aggregation at equimolar amounts. By contrast, equimolar amounts of phenylbutylamino-mPEG 2 kDa prolonged the lag time of HEWL aggregation and cholesteryl-PEGs both even suppressed HEWL aggregation completely.

Conclusion iii) renders the matter even more complicated. A two-fold molar excess of dansyl-mPEG 2 kDa deteriorated sCT aggregation, while a 10-fold molar excess of Trp-mPEG suppressed sCT aggregation for over 64 hours. Similar tendencies were observed concerning the influence of phenylbutylamino-mPEG 2 kDa on HEWL aggregation velocity and HEWL aggregation lag time: a ten-fold molar excess of the excipient was superior than an equimolar amount.

Covalent PEGylation is performed in order to prolong the *in vivo* circulation half-life, to

decrease *in vivo* immunogenicity, and/or to decrease aggregation [4]. The excipients described here were able to weakly interact with biopharmaceuticals based on non-covalent interactions. By this approach chemical reactions needed to attach the PEG to the biopharmaceutical are circumvented. Simple addition to a liquid formulation is sufficient in order to obtain stabilization. We were further able to show that aggregation of biopharmaceuticals can be reduced and in some cases even suppressed over a certain period of time by the described PEG-based excipients in accelerated stress tests. However, depending on the headgroup, the biopharmaceutical and the molar ratio of excipient to biopharmaceutical used, stabilization or even destabilization might be obtained. Therefore, these influencing factors need to be carefully investigated and evaluated.

Prolongation of the *in vivo* circulation half-life and decrease of *in vivo* immunogenicity are further benefits obtained by covalent PEGylation. Most probably, these characteristics will not be delegated on the biopharmaceuticals by the described PEG-based excipients. This conclusion may be drawn from fluorescence titration measurements of the dansyl-mPEG 2 kDa with human serum albumin (HSA), where only a marginal binding strength was detected. Interaction of the dansyl-headgroup with the hydrophobic binding pocket on HSA was probably reduced due to steric interactions by the PEG. In order to obtain prolonged pharmacokinetics and decreased immunogenicity *in vivo* by non-covalent PEGylation, specific interactions need to be employed resulting in a high binding affinity of the excipient to the biopharmaceutical although the PEG might sterically interfere.

A further application of phenylbutylamino-, benzyl- or cholesteryl-PEGs in the future might be the possible stabilization of human calcitonin (hCT). The efficient use of hCT as a drug is limited due to its marked tendency to fibrillate and precipitate in aqueous solutions [11, 12]. It has been speculated that the enhanced tendency of hCT aggregation and fibrillation might be due to aromatic contributions from phenylalanine side chains [11, 13, 14]. Interaction of these phenylalanine rings with benzyl- or phenylbutylamino-mPEGs might be possible, which might result in a reduced hCT aggregation.

The studies described here have laid the basis for a patent application [15] recently submitted to the US patent office.

References

- [1] Leader, B., Baca, Q. J., Golan, D. E. Protein therapeutics: a summary and pharmacological classification. *Nature Reviews* 7 21-39 (2008).
- [2] Frokjaer, S., Otzen, D. E. Protein drug stability: a formulation challenge. *Nature Reviews* 4 298-306 (2005).
- [3] Veronese, F. M., Pasut G. PEGylation: Posttranslational bioengineering of protein biotherapeutics. *Drug Discov. Today: Technology Article in Press*. doi:10.1016/j.ddtec.2009.02.002 (2009).
- [4] Philo, J. S., Arakawa, T. Mechanisms of protein aggregation. *Curr. Pharm. Biotechnol.* 10 348-351 (2009).
- [5] Wang, W. Protein aggregation and its inhibition in biopharmaceuticals. *Int. J. Pharm.* 289 1-30 (2005).
- [6] McLeod, A. G., Walker, I. R., Zheng, S., Hayward, C. P. Loss of factor VIII activity during storage in PVC containers due to adsorption. *Haemophilia* 6 89-92 (2000).
- [7] Sluzky, V., Klibanov, A. M., Langer, R. Mechanism of insulin aggregation and stabilization in agitated

aqueous solutions. *Biotechnol. Bioengin.*: 40 895-903 (1992).

- [8] Wang, W., Nema, S., Teagarden, D. Protein aggregation--pathways and influencing factors. *Int. J. Pharm.* 390 89-99 (2010).
- [9] Chi, E. Y., Krishnan, S., Randolph, T. W., Carpenter, J. F. Physical stability of proteins in aqueous solution: mechanism and driving forces in nonnative protein aggregation. *Pharm. Res.* 20 1325-1336 (2003).
- [10] Mahler, H. C., Friess, W., Grauschopf, U., Kiese, S. Protein aggregation: pathways, induction factors and analysis. *J. Pharm. Sci.* 98 2909-2934 (2009).
- [11] Andreotti, G., Motta, A. Modulating calcitonin fibrillogenesis: an antiparallel alpha-helical dimer inhibits fibrillation of salmon calcitonin. *J. Biol. Chem.* 279 6364-6370 (2004).
- [12] Arvinte, T., Cudd, A., Drake, A. F. The structure and mechanism of formation of human calcitonin fibrils. *J. Biol. Chem.* 268 6415-6422 (1993).
- [13] Reches, M., Porat, Y., Gazit, E. Amyloid fibril formation by pentapeptide and tetrapeptide fragments of human calcitonin. *J. Biol. Chem.* 277 35475-35480 (2002).
- [14] Zanuy, D., Haspel, N., Tsai, H. H., Ma, B., Gunasekaran, K., Wolfson, H. J., Nussinov, R. Side chain interactions determine the amyloid organization: a single layer beta-sheet molecular structure of the calcitonin peptide segment 15-19. *Physical Biol.* 1 89-99 (2004).
- [15] G. Borchard, C. Müller, T. Arvinte, M. Capelle. Stabilized protein formulations and use thereof. PCT/IB2010/054927, November 1, 2010.

New Group Members

Karoline Bechtold-Peters

Karoline Bechtold-Peters is pharmacist and holds a Ph.D. degree from the University of Munich as well as a degree as "Fachapotheker" for Pharmaceutical Technology.

She began her industrial career in 1994 at Boehringer Ingelheim in Ingelheim developing solid dosage forms with the focus on powders for inhalation (e.g. Spiriva Inhalet). In 2000 she changed from the small molecule world to biopharmaceuticals building up Formulation Development at Boehringer Ingelheim's Biberach site. In 2003 Karoline took over the responsibility for global clinical supplies, aseptic process development and process transfer within Boehringer Ingelheim Biopharmaceuticals.

In January 2011 Karoline joined F. Hoffmann-La Roche AG in Basel, Switzerland, where she will be Head of Clinical Manufacturing, Process Science and Business Excellence from February.

Karoline is active in various associations and organizations and contributes frequently to conferences in the EU as well as in the US.

Her vision as regards the APV Fachgruppe Biotechnology is to support international orientation whilst collaborating with European and American Associations such as the EAPB and the AAPS and organize/initiate co-sponsored conferences and co-sponsored papers.

Carsten Olbricht

Dr. Carsten Olbricht has studied Pharmacy at the University of Heidelberg and continued his qualification at the Free University Berlin preparing a PhD thesis in pharmaceuticals. Dr. Olbricht joined Schering AG in 2000 as a laboratory head in diagnostic research working on antibody attachment onto i.v. injectable polymeric particles and quality methods for target specific imaging agents. In 2004 Dr. Olbricht joined the Pharmaceutical Development Department of Schering AG where he acted as an associated director in the CMC Technology Office and Drug Delivery Systems department as a scout for new technologies for CMC. In 2006 he joined the Parenteral Development Group of Bayer Schering Pharma AG and has now a senior scientist position in the Liquid Dosage Form development department, where he is responsible for drug product development of parenterals and especially biologics. Dr. Olbricht is a member of APV, CRS and the PDA.

Mathias Schroedter

Dr. Mathias Schroedter studied Biotechnology at the Technical University of Berlin and made his PhD in bioprocess engineering. He founded the Alpha Bioverfahrenstechnik GmbH, a contract development and production organisation for biopharmaceutical APIs in 1996. In 2003 he sold the company to swiss Siegfried holding and further developed it in his position as CEO and COO to a full fledged CMO for mammalian cell cultures. The main projects were biosimilar product developments and API production for clinical phases. In 2007 Siegfried sold the company to indian Avesthagen where Dr. Schroedter staid as CEO/COO and developed biosimilar antibodies. In 2009 he changed to IDT Biologika GmbH in Dessau to work as Director Strategic Technology Development Biopharmaceuticals in a business development role. Since 2011 Dr. Schroedter works as COO for Adrenomed AG in Hennigsdorf.

ABOUT OUR FOCUS GROUP

The APV Biotechnology Focus Group (APV BT) 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 Biotechnology was established in 2000 in response to the increasing importance of Biotechnology within modern pharmaceuticals. [Read more...](#)

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