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## Pharmacokinetics: Spearheading Advances and Delivering the Science

On the Occasion of Professor Malcolm Rowland's 70th Birthday

October 5 • 2009 • London • United Kingdom

The Royal Pharmaceutical Society of Great Britain hosted a very well attended meeting, which was co-sponsored by EUFEPS and the Academy of Pharmaceutical Sciences (APS). More than 150 pharmaceutical scientists gathered from all over the world to celebrate Professor Rowland's many contributions and achievements.

### Eureka moments – Clearance and PBPK

In the opening session of this international conference on pharmacokinetics, Les Benet (University of California, San Francisco) highlighted two seminal papers in the development of pharmacokinetics. The 1973 paper by Rowland, Benet and Graham, Clearance Concepts in Pharmacokinetics, defined the extraction ratio as a function of three parameters – the blood flow to the elimination organ, the intrinsic ability of the organ to eliminate the unbound drug if there were no flow and protein binding limitations, and the fraction of drug unbound in the blood. Clearance concepts then allowed the development of a basic understanding so as to be able to make predictions on how pathological and physiological changes would influence drug kinetics and drug dosing. This new concept of clearance was the first non-compartmental pharmacokinetic parameter. Malcolm Rowland's single-author paper in 1972, The Influence of Route of Administration on Drug Availability, contained the first physiologically-based quantitative prediction of first-pass hepatic elimination and paved the way for physiologically-based pharmacokinetics (PBPK).

### Extending the ideas

The theme of clearance concepts in pharmacokinetics was taken up by Yuichi Sugiyama (Tokyo University), particularly with respect to how hepatic uptake often



Professor Malcolm Rowland

becomes the rate-determining process of therapeutically important drugs, such as statins and ACE inhibitors. This can be accounted for by the clearance concept being extended to incorporate active transport processes. In vitro-in vivo correlation for those compounds should be performed based on the in vitro data of uptake, as well as metabolism, taking the rate-determining process into consideration. The in vitro metabolism data on statins underestimates in vivo clearance, but the prediction based on the hepatic uptake is much better.

Mike Roberts (University of Queensland) described how the activity of a drug can be related to transport and to other drug properties. This was illustrated in a wide-ranging review of recent work on the role of drug structure in the absorption, distribution and metabolism of drugs in normal and diseased states.

In a presentation entitled 'From PpH to PBPK' (say it out loud), Geoff Tucker (Sheffield University) gave a typically entertaining description of the early >>>

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*Professor Rowland and fellow educators at the conference*

>>> days of pharmacokinetics when urinary pH was recognized as being a crucial factor in the apparent variation in excretion of drug and metabolites. It was this work that led eventually to the application of PBPK, which is becoming so important in drug development and possibly in drug discovery.

Sandy Pang (University of Toronto) described PBPK modeling of metabolites. Transporters and enzymes for uptake and elimination may be included to describe the kinetics of the drug and metabolite in the liver, intestine, and kidney with PBPK models. The PBPK model, encompassing all the involved kinetic factors, is a useful tool to study transporter-enzyme interplay and predict drug-drug interactions.

### *Applied research*

Brian Houston (University of Manchester) described how the Centre for Applied Pharmacokinetic Research was set up in 1996 by Malcolm Rowland as a consortium between the University of Manchester, and AstraHassle, Glaxo and Zeneca (as they then were). It is an academic centre of excellence for research and training in metabolism and kinetics, engaged in problems of generic interest to the industry and is the platform for virtually all drug metabolism and pharmacokinetics in Manchester.

Medeval, a contract research organisation was founded in 1983 by Malcolm Rowland, said Steve Toon (SimCYP, Sheffield) and was initially owned by the University of Manchester. Phase 1 clinical development had been seen as a means to assess the safety and tolerability of a potential new medicine in the human animal, but under the direction of Malcolm Rowland, Medeval encouraged pharmaceutical companies to design their phase 1 studies in a way that they could extract more scientific knowledge and move away from the purely safety and tolerability mentality.

Donald R. Stanski (Novartis Pharma, Basel),

Switzerland extended the concepts of PBPK modeling to anatomy and drug development with impressive simulations of anatomical features involved in drug distribution.

Carl Peck (University of California, San Francisco) described how quantitative clinical pharmacology - that is, the application of the clearance concept and PBPK - has transformed drug regulation, describing how our modern understanding of drug clearance concepts has equipped drug development and regulatory scientists with key investigative tools to standardize approaches to pharmacokinetics and metabolism of new agents. Regulatory agencies have embraced these advances and incorporated them into regulatory requirements and decisions.

### *Educating the world*

In a final session, the importance of education in clinical pharmacology and therapeutics was highlighted. Jeffrey Aronson (Oxford University) said surveys in recent years show that the subject was inadequately covered in schools of medicine but steps have been taken by educational establishments and the future looks brighter. Peter Noyce described the evolution of pharmacy practice at Manchester during Malcolm Rowland's time as Dean or Research Director of Pharmacy and Pharmaceutical Sciences, highlighting the essential aspects of leadership, a clinical network and the academic infrastructure brought by Professor Rowland. Pharmacy practice was established as an academic discipline by the creation of the Boots Chair of Pharmacy Practice and by a Drug Usage and Pharmacy Practice Research Group. The group was commended in the 2001 and 2008 research assessment exercises and is acknowledged as a major influence on pharmacy policy and practice. It now includes the National Centre for Pharmacy Postgraduate Education, the Centre for Pharmacy Workforce Studies and

the Centre for Innovation in Practice. Appearing on a video film Tom Tozer, Professor Rowland's long time collaborator, detailed aspects of clinical pharmacokinetics teaching at the University of California and various international workshops.

### *Thank you and a vision*

'It is not the road that you travel on in life that is important but who you meet and interact with on the way' said Professor Rowland in a closing address, taking this as a theme to express his thanks to the many talented and generous individuals who had marked his own personal road. Much had been made of the development of physiologically-based pharmacokinetics in today's meeting and Professor Rowland believed that it has been such development that had brought pharmacokinetics from an academic subject to a real force in rational development of drug molecules. The more intuitive and informative whole body physiologically based models, which he called the natural face of pharmacokinetics, will be increasingly applied in clinical development to address the important therapeutic questions, aided by the increasing adoption and acceptance of such models by regulatory authorities. Pharmacokinetics will then have really come of age and, coupled with mechanistically based pharmacodynamics, will help transform the pharmaceutical industry from a largely empirically driven industry to a predictive and more efficient one. That indeed, he said, would give him a great sense of fulfilment and satisfaction. Finally, Professor Rowland pointed out it was the University that had retired him; and that he was serving notice that he had no intention of retiring from the work he so much enjoyed.

*J. Chamberlain  
Joint Pharmaceutical Analysis Group*

# Update on SafeSciMET

## European Modular Education and Training Programme in Safety Sciences for Medicines

This important training effort is part of the Innovative Medicines Initiative (IMI) under the 7th Framework Programme of the European Commission.

### IMI information

There were 18 topics (5 on research education and training) in this first round of IMI Joint Undertaking (JU) calls, announced in April 2008. After project proposals and the evaluation rounds, 15 of them are still there (4 on research education and training). For the full list of them, see e.g. the IMI JU Press Release of May 18, 2009 or the IMI website ([http://www.imi.europa.eu/index\\_en.html](http://www.imi.europa.eu/index_en.html)).

### SafeSciMET

The SafeSciMET Consortium Leadership (see below) delivered an updated and final Full Project Proposal, at the end of May 2009. This is now the basis for the project contract negotiations. It's envisaged that the contracting procedure will be finalized by November 2009, at the latest. All consortium partners will have to sign the Project Agreement, before the start of the Project.

### What is it about?

The project goals can be summarized as follows

- Develop and deliver a modular pan-European education and training program on drug safety emphasizing integrative and translational aspects lacking largely in today's educational programs.
- Combine and explore wide variety of training modalities and tools to enable a diverse audience to benefit from the training program.
- Enable formation of a new breed of safety scientists embracing new technologies to enhance innovative approaches to drug development.

- Achieve quality level in program unmatched by competing training programs.

What is now to be accomplished, in the next few years, is best summarized in the list of the SafeSciMET Work Packages – to keep us on track. It looks simple, but there will be a lot of work, of course. They are:

- WP1** Project management
- WP2** Development and harmonization of the training programme
- WP3** Quality assurance and accreditation
- WP4** Adaptation and support of an e-learning environment
- WP5** Development and running a student office
- WP6** Sustainable safety sciences education and training business model for long-term quality delivery and outcome

### Project presentations

We know that the SafeSciMET Project has been presented in a number of contexts. There was a presentation of it by Nico Vermeulen in the Safety Sciences Sessions of the Pharmaceutical Sciences Fair and Exhibition (PharmSciFair), on June 8-12, 2009, in Nice, France. Daniel Dietrich presented at EUROTOX 2009, on September 13-16, 2009, in Dresden, Germany.

### SafeSciMET Website

A website [www.safescimet.eu](http://www.safescimet.eu) has been established to give information the project mission and to facilitate communication within and about SafeSciMET, its plans and progress. There is still need for the addition of further content and updates on progress.

### Kick-off Meeting held in Alderley Park, UK 24/25Sept2009

After preparation work for the project lasting

more than a year, a first get-together of all the consortium members was badly needed. This kick-off meeting aimed at;

- building and firming up a common understanding of where the consortium members came from individually and where they wanted to go jointly
- getting each other to know –networking
- building relationships by face-to-face meeting, which will help in later remote interactions
- agreeing on how the group wants to work together
- understanding what has been achieved so far
- discussing the challenges in achieving overall goals; at developing a rough road map how to develop the Program.

### The Executive Committee

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## New Handbook edition

A new 6th edition of Handbook of Pharmaceutical Excipients is now available from Pharmaceutical Press, the publishing division of the Royal Pharmaceutical Society of Great Britain. The sixth edition is available in print and online and provides a systematic and uniform assessment of essential data relating to the physical and chemical properties, safety, handling and regulatory status of excipients. It has 340 fully-referenced monographs, written by over 140 expert pharmaceutical scientists, all individually reviewed and updated since the last edition. The detailed monographs are extensively illustrated, with SEMs and two-colour NIR spectra, line graphs, chemical structure diagrams and tables to support easy interpretation of the accompanying text.

## Jury for the NSMF Prize at work again

The jury for the New Safe Medicines Faster prize, sponsored by sanofi-aventis, have started their deliberations for 2009.

### The award topics in the last years have been;

2003	Microdosing concept
2004	New modelling and simulation tools
2005	Faster lead selection
2006	Predictive PK-PD relationship in scaling
2007	Process Analytical Technology
2008	Oral drug delivery

# Outcomes from EUMAPP

## – a Study Comparing In Vitro, In Silico, Microdose and Pharmacological Dose Pharmacokinetics

The European Microdosing AMS Partnership Programme (EUMAPP) as funded by the European Commission under Framework Programme 6.

The European Microdosing AMS Partnership Programme (EUMAPP), funded by the European Union, was a major international, multi-centre research study involving collaboration between industry and academia. There were 9 participating centres from 7 countries: Xceleron Ltd, (UK), Institut de Recherches Internationales Servier (France), Pharmaceutical Research Institute (Poland), University of Manchester (UK), Cyprotex Discovery Ltd (UK), University of Lund (Sweden), European Federation for Pharmaceutical Sciences, Foundation for the Review of Ethics in Biomedical Research (The Netherlands) and PRA-International (The Netherlands).

### The objectives of EUMAPP were:

- To assess if there was pharmacokinetic linearity following a microdose and a therapeutic dose for 7 drugs representative of situations where traditional pharmacokinetic predictive models (e.g. *in vitro* and animal species) are problematic.
- To compare the accuracy of the pharmacokinetic predictions made by microdosing to those made from physiologically based pharmacokinetic (PB-PK) computer models.

Table of Pharmacokinetic Parameters

Drug	Characteristic	t <sub>1/2</sub> (h) oral		t <sub>1/2</sub> (h) IV		CL (L/h)		V (L)		F	
		MD	TD	MD	TD	MD	TD	MD	TD	MD	TD
Paracetamol (acetaminophen)	Extensive phase II metabolism	5.8	2.0	4.6	2.0	19	21	123	66	88	80
Phenobarbital	Long plasma half-life	108	100	N/A							
Fexofenadine	PgP substrate	16	12	8.0	10	13	16	116	113	40	30
Propafenone	Saturable first pass metabolism	3.8	2.6	5.4	4.7	49	44	273	214	5.8	13
Sumatriptan	Cytosolic metabolism	1.9	1.4	6.5	5.6	46	50	426	397	20	7.6
Clarithromycin	PgP and CYP3A4 substrate	4.0	3.4	4.0	4.5	23	21	136	136	22	39

MD = microdose, TD = therapeutic dose

S-19812 is a compound dropped from development by Servier; results are not yet available.

In broad terms, the pharmacokinetics for oral doses of paracetamol, pentobarbital, fexofenadine, propafenone and clarithromycin scaled reasonably well to the therapeutic dose. There were some differences for the oral data with propafenone and sumatriptan. Propafenone is known to exhibit dose-dependent saturable first pass metabolism, primarily via CYP 2D6, which is the likely explanation for the observed difference in absolute bioavailability between the microdose and therapeutic dose. Other parameters such as clearance and volume of distribution scaled well. The microdose

of sumatriptan over-predicted the absolute bioavailability but, as with the other compounds, clearance and volume of distribution was well predicted. The pharmacokinetic results are summarized in the Table below. It is noteworthy that where inconsistencies between the pharmacokinetics at a microdose and a therapeutic dose are observed, they are for the oral dose. Where intravenous pharmacokinetics were examined, the data scale extremely well.

For all of the drugs tested in EUMAPP, intravenous microdose data predicted half-life (t<sub>1/2</sub>), clearance (CL) and volume of distribution (V) very well. Oral dose data did not scale as well as those from the IV doses but in general, the data obtained would have been useful in the selection of drug candidates for further development (or dropped from the development pipeline).

Where oral microdose data did not scale so well, the reasons can all be surmised from the known metabolic or chemical properties of the drug and therefore add to our understanding of the utility of microdosing.

EUMAPP has contributed to our knowledge of microdosing and has added to our understanding of where this technique can be best applied to drug selection.

For the full report of outcomes, please see [www.eumapp.com/pdfs/EUMAPP\\_SUMMARY.pdf](http://www.eumapp.com/pdfs/EUMAPP_SUMMARY.pdf)



Drug	Dose period 1	Dose period 2	Dose period 3
Clarithromycin	14C oral microdose	14C IV microdose	14C IV tracer dose + oral therapeutic dose (250 mg)
Paracetamol	14C oral microdose	14C IV microdose	None
Fexofenadine	14C oral microdose	14C IV microdose	14C IV tracer dose + oral therapeutic dose (120 mg)
Phenobarbital	14C oral microdose	None	None
Sumatriptan	14C oral microdose	14C IV microdose	14C IV tracer dose + oral therapeutic dose (50 mg)
Propafenone	14C oral microdose	14C IV microdose	14C IV tracer dose + oral therapeutic dose (150 mg)
S-19812	14C oral microdose	14C IV microdose	14C IV tracer dose + oral therapeutic dose (100 mg)



Tom Sam

## *PAT Highlights from the PharmSciFair, June 2009*

On the second day of the Nice PharmSciFair, the Netherlands Society for Pharmaceutical Sciences (NVFW) organized a well-attended session on the academic and industrial challenges of Process Analytical Technology (PAT). 150 Participants discussed how the new PAT tools and PAT philosophy will transform the way pharmaceuticals will be developed and manufactured. Tom Sam (Schering-Plough), organizer and moderator of the NVFW session, stressed that although better manufacturing of the same pharmaceutical products through PAT is directly advantageous for companies and therefore to society, the real benefit for the patient and society is to be found in using PAT to develop and manufacture better medicines, that deliver quality for the patient in terms of improved effectiveness and safety in real life, with higher levels of compliance and concordance. These better medicines should provide quality in terms of better access, improved stability, better handling, and more flexibility e.g. in relation to future individualised therapies. In principle, PAT can assist in developing the knowledge for this.

### *Analysis of Freeze Drying*

An example of how PAT can lead to enhanced knowledge of processes was provided by two presentations on freeze drying. Michael Wiggenhorn (Coriolis PharmaService) convincingly showed that a new non-invasive, wireless temperature measurement system can serve as a powerful PAT tool to accurately analyze the drying process. Thomas de Beer (Univ. of Ghent) demonstrated that the tandem

use of PAT tools leads to even better process understanding, for example by combining in the freeze drying process wireless temperature measurements with Raman, plasma emission or NIR spectroscopy.

### *NIR Spectroscopy*

Co-moderator Emil Ciurczak (Cadrai Group) demonstrated that Near InfraRed Spectroscopy (NIRS) can be used as a PAT tool in almost all steps of pharmaceutical product manufacture. Regis Cinier (Bruker Optics) explained the benefits of having blenders with the NIRS apparatus, measuring the increasing content uniformity of the powders, statically positioned at the rotation axis of the container. NIRS is not only applicable for process control, but also to determine product identity and estimate purity instantly. Most recent examples is the use of NIRS to detect oversulfated chondroitin in heparin and melamine in wheat gluten. NIRS is also powerful in determining physical parameters of dosage forms, which cannot easily be detected by more traditional analytical techniques. NIR chemical imaging was shown to be successful in root cause analysis investigations and process control.

### *Important New Science*

With the recognized need for PAT applications, new fundamental science is stimulated as well. In the PAT session examples were provided of advanced algorithms that claim to solve the calibration transfer problem for NIRS (Martijn Wiertz, Thermo Fisher Scientific),

and of a multispectral measuring system, that can be applied to the fast and accurate color classification of tablets (Ervin Nippolainen, University of Kuopio). With the current emphasis of many PAT applications on NIRS it is important to realize that other PAT tools may be more sensitive to the fundamental properties underlying the critical quality attributes and process parameters that allow for optimal process control and dosage form quality. In this context Axel Zeitler (University of Cambridge) referred to terahertz technology and magnetic resonance imaging as two promising techniques. Also non-spectroscopic PAT techniques show great promise for acquisition of material and process knowledge. Flowability of powders is a critical material attribute in many pharmaceutical manufacturing steps, including milling, filling, blending, compression, and granulation. This can be understood if one realizes that powder flowability is a complex function of the particles' size, shape, stiffness, porosity, surface texture, density, cohesion and adhesion. Tim Freeman demonstrated how the Freeman Technology powder rheometer can characterize powders, allowing flowability parameters, evaluated at the gram scale, to be correlated to large scale process parameters. This presentation was the last in a successful meeting.

A pdf of the hand-outs of this PharmSciFair PAT session including contact details of the speakers can be requested from [tom.sam@spcorp.com](mailto:tom.sam@spcorp.com).

*Tom Sam, Schering-Plough*

### *Application for the position of Dean (Director) of the Faculty of Pharmacy, University of Lisbon, (Portugal) (M/F)*

The Faculty of Pharmacy, University of Lisbon, Portugal, invites applications for the position of Dean (Director of the Faculty).

The Dean (Director) is elected by the Faculty's Assembly to serve for a period of 4 years on a full-time basis, acting as the institutional head of the Faculty and its external representation.

Applicants must be professors or researchers of recognized merit from the Faculty of Pharmacy, University of Lisbon,

or other national or foreign universities or research institutions, currently in full exercise of functions.

Applications must be written in Portuguese and sent to the Chair of the Assembly of the Faculty of Pharmacy, Av Prof. Gama Pinto, 1649-003 Lisbon, within the period from 5th to 25th September, 2009. Applications should also include the candidate's Curriculum Vitae and proposed Programme of Action.

The responsibilities of the Dean (Director)

are defined by the recently approved model for the government of the Faculty and its legal and statutory regime. These documents, the conditions of eligibility and the electoral regulations are available on line at [www.ff.ul.pt](http://www.ff.ul.pt)

University of Lisbon Faculty of Pharmacy, 30th June, 2009

The Chair of the Assembly of University of Lisbon Faculty of Pharmacy

# Medicinal Plant and Natural Product Research at PharmSciFair

At the second PharmSciFair, the GA - Society for Medicinal Plant and Natural Product Research was invited to organize a workshop on its general topic "Medicinal Plant and Natural Product Research". This took place on Fri morning, 12 June 2009

("Medicinal plant and natural product research: An introduction" by Brigitte Kopp, University of Vienna, Vienna, Austria; "Well known European herbal medicinal products: Still a pharmaceutical treasure trove?" by Michael Heinrich, University of London, London, United Kingdom; "Discovery of new pharmaceutical leads from TCM drugs" by Matthias Hamburger, Institute of Pharmaceutical Biology, Basel, Switzerland; "Systems biology: A new tool for understanding the pharmacology of herbal medicinal products" by Robert Verpoorte, Leiden University, Leiden, The Netherlands; "Molecular targets of natural drug substances" by Peter Imming, MLU Halle-Wittenberg, Halle, Germany)

## Talks, Speakers and their Affiliations

President Brigitte Kopp gave a general introduction for the audience, who were not only experts in the field but also other interested delegates at the PharmSciFair. She emphasized that still almost half of the worldwide used medicines are of plant and natural origin (Herbal Medicinal Products - HMPs) Furthermore natural products play a dominant role in the discovery of leads for the development of drugs for the treatment of human diseases.

## General Introduction

The four GA speakers presented the wide range of most modern medicinal plant and natural product research: Prof. Michael Heinrich could answer the opening question "Well known European Herbal Medicinal Products – still a pharmaceutical treasure trove?" with a clear yes and impressive examples such as the galanthamine story, today's cannabis research or the very new and very promising substance peplin with antikeratogenic and anti-skin cancer activity, that is now in the stage of clinical development.

## Therapies from Natural Products

Prof. Matthias Hamburger followed with "Discovery of new pharmaceutical leads from traditional Chinese medicine (TCM) drugs" and gave, at the same time, an overview on the recent developments of an ultra modern analytical instrumentarium – a technology platform for miniaturized activity-based assays for natural product discovery. Thus important compounds with antiplasmodial and angiogenesis-inhibitory properties were identified in TCM drugs among many others.

Prof. Robert Verpoorte showed the advantages of systems biology in his lecture "Medicinal plants and systems biology: a perfect holistic match" and demanded an urgent change of the current paradigm of "single compound, single target". Systems biology with the methods of metabolomics, proteomics and transcriptomics as well as physiological measurements might revolutionize drug development in the coming years.

## Systems Biology and Molecular Targets

Prof. Peter Imming gave an analysis of molecular targets and a survey of molecular target families that are addressed or not addressed by marketed natural product drugs. The reasons for the differentiation are various, connected with the history of drug discovery, typical chemical features (e.g. peptidomimetic alkaloids; hydrophilic protein-binders) of natural products, and other rationalisations. They appear to be well suited for mimetic, ideally "prosthetic" drug therapy.

## Summary

In summary, a multidisciplinary approach to drug discovery, involving the generation of truly novel molecular diversity from natural product sources, combined with total and combinatorial synthetic methodologies, and including the manipulation of biosynthetic pathways provides the best solution to improve productivity in drug discovery and development. European or Chinese herbal medicinal products can be regarded as excellent sources in the discovery of new pharmaceutical leads. Another aspect is that the interconnectivity of the herbal products with the physiological and biological systems combined in systems biology gives the possibility to control the quality for Herbal Medicinal Products in a novel way.

Professor Brigitte Kopp  
University of Vienna, Austria

## NVFW Sessions at PharmSciFair 2009



On the second day of the Nice PharmSciFair, the Netherlands Society for Pharmaceutical Sciences (NVFW) organized a well-attended session on the academic and industrial challenges of Process Analytical Technology (PAT). Please see separate article in this issue of the Newsletter.

On Thursday 11th June, the NVFW organised a successful session on Formulation and Characterization of Biopharmaceuticals chaired by Prof. Wim Jiskoot (University Leiden). In the first part of this session two main lectures were presented by Hans-Christian

Mahler (Hoffman-La Roche) and Wim Jiskoot on formulation and characterization, respectively. These lectures offered an excellent overview of these topics and were followed by lively discussions. Subsequently, interesting short presentations were given by Andrea Hawe (University Leiden) on aggregation profiling of freeze-thawed and thermally stressed monoclonal antibodies, Vinay Saluja (University Groningen) on the influence of buffers for influenza subunit vaccine during spray (freeze) drying and Wendy Hulse (University of Bradford) on

novel spectroscopic instrumentation for study of the aggregation state of proteins. All the lectures showed both fundamental aspects and applications. Also this session was well attended and the special interest of young scientists was remarkable. More information on this session can be requested from [w.jiskoot@lacdr.leidenuniv.nl](mailto:w.jiskoot@lacdr.leidenuniv.nl).

Prof. Ad de Jong  
Chairman of the Netherlands Society for  
Pharmaceutical Sciences  
University of Utrecht, The Netherlands

*Pharmacogenomics at the 2nd PharmSciFair 2009:*

## *Adverse drug reactions and clinical implementation*

### **Background**

*Two pharmacogenomics sessions were organized by the EUFEPS Network on Research in Pharmacogenetics/ Pharmacogenomics. The topics of the sessions were adverse drug reactions and clinical implementation. Important conclusions of the presentations were that there has been much progress in the field of pharmacogenomics and that implementation in clinical practice is not as easy as it was once thought. Large prospective trials may be necessary to prove clinical relevance.*

### Pharmacogenomics of Adverse Drug Reactions

The first presentation was given by Patricia van den Bemt (University of Utrecht, Utrecht, the Netherlands). She showed that adverse drug reactions are an important cause of hospitalizations. Her research group performed a prospective, multicenter study and found that 5.6% of all acute hospital admissions were medication related. Almost half of these admissions appeared potentially preventable. The top 3 groups of drugs involved in non-preventable Hospital Admissions Related to Medication (HARMs) were oncolytics (23%), coumarin derivatives (14%) and acetylsalicylic acid (8%). These non-preventable HARMs may become partly preventable in the future by including pharmacogenetic information. Fiona Brew (Affymetrix, Wooburn Green, United Kingdom) presented 'Modern tools of genotyping drug-related SNPs: the DMET chip'. The DMET chip contains 1936 polymorphisms in 225 genes of drug metabolism and transport as well as some receptors. Genotyping with the DMET chip takes, from start to finish, 48 hours and therefore provides a faster detection of genetic variations, compared to conventional methods. Ann Daly (Newcastle University, Newcastle upon Tyne, United Kingdom) linked liver injury caused by commonly prescribed drugs to a genetic basis. Drug-induced liver injury (DILI) is a rare but serious toxicity. To find genes that might be related to DILI she performed the DILIGEN study, which is a multicenter study across the UK focusing on co-amoxiclav and flucloxacillin. This case-control study showed that the major determinant of DILI is the genotype of HLA, for co-amoxiclav and flucloxacillin HLA-DRB1\*1501 and HLA-B\*5701 respectively. Iztok Grabnar (University of Ljubljana, Ljubljana, Slovenia) presented the influence of CYP2D6 genotype on the pharmacokinetics of risperidone in patients with schizophrenia. The active moiety arises from hydroxylation of risperidone by the

CYP2D6 and CYP3A4, the CYP2D6 genotype might be an important predictor for the steady-state plasma concentration of the risperidone active moiety and clinical outcome. In a second short presentation, Anke-Hilse Maitland-van der Zee presented the study design of the PACMAN (Pharmacogenomics of Asthma in Children: Medication with ANti-inflammatory effects) Cohort Study. About 10-15% of the children do not respond to the inhaled corticosteroid (ICS) asthma treatment. In the PACMAN study, the effects of genetic variation on treatment response will be studied in children using ICS therapy.

### **Clinical Implementation of Pharmacogenomics**

The first presentation of this second session was about the challenges and limitations of translating pharmacogenetics into clinical practice, presented by the co-chair Ingolf Cascorbi. Pharmacogenetic diagnostics are being developed to predict clinical response to a drug and to explain adverse drug reactions. Dr Cascorbi suggested that pharmacogenetic dosing may be applicable to drugs, such as those tumor therapies targeted to over-expressed or mutated proteins, or to drugs subject to polymorphic metabolism in various disease fields. However, implementation of pharmacogenetics for many drugs is not yet considered due to a lack of large prospective studies. Moreover, implementation of pharmacogenetics may take place only for drugs with a small therapeutic window and long lasting therapy. Candidate therapies which fulfill these criteria are coumarin derivatives on which Yoseph Caraco (Hadassah University Hospital, Jerusalem, Israel) and Rianne van Schie (University of Utrecht, Utrecht, the Netherlands) focused during their presentations. Yoseph Caraco talked about genetically based therapy of warfarin. Polymorphisms in genes encoding for CYP2C9, the metabolizing enzyme, and the target enzyme VKORC1 are major factors contributing to variability. His study group started the WSIDI-cohort. They recruited healthy volunteers between 20 and 40 years old and non-smoking. These volunteers received one single warfarin dose and subsequently the clearance was studied. He concluded that using the pharmacogenetic data for dosing adjustment is feasible. Rianne van Schie gave a short presentation on the study design of EU-PACT (European Pharmacogenomics Approach to Coumarin Therapy); the first large scale randomized controlled trial of a true pharmacogenomic strategy for coumarin derivative treatment ever performed in Europe.

This multi-center study will investigate the added value of genotyping before start of anticoagulation therapy with warfarin, acenocoumarol and phenprocoumon, of which the last two mentioned are predominantly prescribed in continental Europe. Matthias Schwab (Margarete Fischer-Bosch Institute of Clinical Pharmacology, Stuttgart, Germany) gave an overview of the improvement of leukemia treatment. Acute lymphoblastic leukemia (ALL) has a much higher cure rate now compared with several years ago. This success is a result of insight in clinical, immunological and genetic characteristics. Polymorphisms in genes encoding for TPMT, the metabolizing enzyme of 6-mercaptopurine, the drug used to treat ALL, lead to changes in drug response. This knowledge is not yet implemented in clinical practice. Finally, Jan Raaijmakers explained the view of the pharmaceutical industry in his presentation. Sometimes, it has been said that the pharmaceutical industry has no interest in pharmacogenetics and individualized medicines because the market may become smaller and therefore the revenues of the companies will also be lower. Fortunately, Jan Raaijmakers pointed out in his presentation that the pharmaceutical industry also sees a lot of opportunities by implementing the genetic information of the patient in the treatment. Some medicines that did not reach the market in the past may have done so if they had been only prescribed to patients with a certain genetic profile.

### **Conclusion**

Although there are many non-genetic factors that play a role in lack of drug efficacy or the development of adverse drug reactions, it has been shown that pharmacogenomics contributes significantly. In this pharmacogenomics session, it was shown that much progress has been made. Pharmacogenomics will play a role in the future both in predicting efficacy of drugs and in predicting or explaining adverse drug reactions. Some large prospective randomized controlled trials have recently been initiated to test the clinical benefit of inclusion of pharmacogenomic information into drug prescription and to translate pharmacogenomic findings into clinical practice.

*Rianne M.F. van Schie<sup>1</sup>*

*Ingolf Cascorbi<sup>2</sup>*

*Anke-Hilse Maitland-van der Zee*

*<sup>1</sup>Utrecht University, Utrecht, the Netherlands*

*<sup>2</sup>University Hospital Schleswig-Holstein, Kiel, Germany*

# Report from EAPB at PharmSciFair, Nice, 2009

*PharmSciFair is the premier European Platform for Advancing Pharmaceutical Sciences, initiated by EUFEPS. The second Fair took place in Nice from June 8 - 12, 2009. The European Association of Pharma Biotechnology (EAPB) was responsible for the sessions 'Biotech derived Products' and 'Nano Delivery Systems'.*

## **Biotech derived Products**

Jan van de Winkel focused in his keynote lecture on Therapeutic Antibodies: trends & future developments: 25% of all drugs in development are presently based on antibodies. 24 monoclonal antibodies (mAbs) have currently been FDA-approved for a wide range of diseases. Improvement of the therapeutic potential goes along with the modification of antibody effector function and the development of novel antibody formats, e.g. fully human therapeutic antibodies derived from human Ig-transgenic mice.

Carina Sonnega reported in the subsequent Minisymposium: CMC Aspects of First-In-Human (FIH) Studies with Biopharmaceuticals. She provided an overview of the current global regulatory climate and focused on particular quality aspects of pharmaceutical products derived from biotechnological processes. This was illustrated with a case study, accompanied

by practical hints based on own experience.

Stefan Bassarab concentrated on the aspects of formulation and process development for first-in-human biological products. Predictability for small molecules is generally better than for biologics. The effective strategy for first-in-human formulation goes along with the analytical methods development, standard characterization methods and risk reduction by choice of reliable process equipment.

Key note lecture and minisymposium were well attended. On the basis of the excellent lectures, intensive discussions and interactions with the participants followed.

## **Nano Delivery Systems**

Cornelia Keck gave an overview about the physicochemical characterization of nanoparticles, i.e. size, charge and surface hydrophobicity. These characteristics determine the protein adsorption pattern in the body, and therefore e.g. tolerability and organ distribution. Optimized analytical procedures and characterization methods were introduced and evaluated.

Rainer Mueller reviewed nanocrystals versus lipid nanoparticles as delivery systems so far accepted on the market. Nanocrystals are the formulation of choice for biotechnological or

plant derived molecules being poorly soluble in water or organic media. The lipid nanoparticles are suitable for drugs which are lipophilic or soluble in lipophilic media and for peptides which can be dissolved in the lipid matrix by solubilisation.

Robert Landsiedel reported about the safety assessment of nanomaterials, toxicity testing and the importance of understanding their uptake and distribution in the body indicating effects of the agglomeration state, surface area and the surface chemistry of uptake, distribution and effects of nanomaterials.

The final EAPB presentation by Cornelia Keck and Rainer Mueller presented strategies how to enter the market, using as examples solid lipid nanoparticles and drug nanocrystals. Particularly addressed aspects were intellectual property, transfer to industry, state of excipients, large scale production and first product realization.

All abstracts of the conference you get at <http://www.pharmscifair.org/summer09060812.html>. If you want more detailed information about special EAPB presentations, please send your request to [managing.director@eapb.org](mailto:managing.director@eapb.org).

*Marion Kronabel  
Managing Director EAPB*

## PharmSciFair Session organized by the EUFEPS Safety Sciences Network

*On behalf of the Safety Sciences Network, Ole J. Bjerrum organized a session entitled "Safety Sciences Aspects of Biologics".*

The rationale for this session, where Ole J. Bjerrum acted as chairman, was that the number of biologics among newly registered drugs is steadily increasing. The safety aspects of new biologic entities (NBEs) during drug development differ from those of new chemical entities (NCEs). The clinical outcome may, for example, be seriously disturbed by antibody formation. However, the experience on how to handle biologics is accumulating and the session dealt with these aspects. Currently negotiation within ICH about the revision/updating of the "S6

Guideline Preclinical Testing of Biotechnology Derived Proteins" takes place.

### **Three major safety aspects for the biologics were presented;**

- An overview of the current preclinical regulatory framework (by Gabrielle Reichman)
- The important role which species selection plays in the preclinical safety testing (by Lars Wichmann Madsen)
- The clinical aspects of the unwanted immune response of anti-drug antibodies that are linked to the majority of therapeutic proteins (by Christian Ross Pedersen)

These three main lectures were supplemented with a short communication on how to characterize the potential safety risk of IgG aggregation in antibody preparations by means of addition of fluorescent dyes (by Andrea Howe).

From the length of discussion raised by the audience (about 35 participants) it seems that the choice of topics was good.



**11th joint conference on the Qualified Person**  
 3 November 2009, London, UK  
**Meeting the needs of patients**  
 – pharmacy and mental health care  
 12 November 2009

**The role of natural products in drug discovery and development in the new millennium**  
 4 December 2009  
**Contact:** Gabriella Highfield  
 Tel +44 207 5722640 Email [events@rpsgb.org](mailto:events@rpsgb.org)  
[www.rpsgb.org/pdfs/sciconf091103.pdf](http://www.rpsgb.org/pdfs/sciconf091103.pdf)

**Second Open Scientific EIP Symposium: Immunogenicity of Biopharmaceuticals**  
 17-19 November, Leiden, The Netherlands  
**Contact:** Prof Dr Wim Jiskoot, Leiden/ Amsterdam Center for Drug Research (LACDR)  
 P.O. Box 9502, Einsteinweg 55, 2300 RA Leiden The Netherlands. Tel +31 71 5274314  
 Fax +31 71 5274565  
 Email [wjiskoot@lacdr.leidenuniv.nl](mailto:wjiskoot@lacdr.leidenuniv.nl)  
[www.brpl.nl](http://www.brpl.nl)

**EMA Workshop on In vitro Cytokine Release Assays**  
 19 November, London, UK  
**Contact:** Dr. Jean-Marc Vidal, 7 Westferry Circus, Canary Wharf, London, E14 4HB, UK  
 Tel (44-20) 74 188400 Fax (44-20) 74 188613  
 Email [mail@emea.europa.eu](mailto:mail@emea.europa.eu)  
[www.emea.europa.eu/meetings/conference.htm](http://www.emea.europa.eu/meetings/conference.htm)

**Dutch-Danish Workshop on Modeling and simulation approaches in drug discovery and development**  
 19 November 2009 Carlsberg Academy, Copenhagen, Denmark  
 24 November 2009 Naturalis, Leiden, The Netherlands  
**Contact:** Prof. Daan Crommelin, TI Pharma  
 Tel + 31(0) 71 3322030  
[www.tipharma.com/workshop](http://www.tipharma.com/workshop)  
 Registration is free of charge

**7th World Meeting on Pharmaceutics, Biopharmaceutics and Pharmaceutical Technology**  
 8-11 March, 2010, Valetta, Malta  
**Contact:** Isabella Treser, APV  
 Arbeitsgemeinschaft für Pharmazeutische Verfahrenstechnik e.V.  
 International Association for Pharmaceutical Technology  
 Tel +49 6131 9769 85 Fax +49 6131 9769 69  
 Email [it@apv-mainz.de](mailto:it@apv-mainz.de)  
[www.worldmeeting.org](http://www.worldmeeting.org)  
 Deadline for abstract submission:  
 15th November 2009

**8th International Conference and Workshop on Biological Barriers - in vitro Tools, Nanotoxicology, and Nanomedicine**  
 21 March - 1 April 2010, Saarbrücken, Germany  
**Contact:** KWT - Conference Office  
 Tel +49 681 3022656 Fax +49 681 3024270  
 Email [biological-barriers2010@mx.uni-saarland.de](mailto:biological-barriers2010@mx.uni-saarland.de)  
[www.uni-saarland.de/biological-barriers2010](http://www.uni-saarland.de/biological-barriers2010)

**International Probiotic Conference 2010 – IPC 2010**  
 15 - 17 June, 2010, Kosice, Slovakia  
**Contact:** Maria Kasmanova, Organizing Secretariat  
 Tel +421 904 837153  
 Fax +421 41 4000123  
 Email [info@probiotic-conference.net](mailto:info@probiotic-conference.net)  
[www.probiotic-conference.net](http://www.probiotic-conference.net)

**16th World Congress in Basic and Clinical Pharmacology**  
 17-23 July 2010, Copenhagen, Denmark  
**Contact:** Professor Kim Brösen  
 Tel +45 6550 3751 Fax +45 6591 6089  
 Email [kbroesen@health.sdu.dk](mailto:kbroesen@health.sdu.dk)  
[www.worldpharma2010.org](http://www.worldpharma2010.org)

**FIP Pharmaceutical Sciences World Congress & AAPS Annual Meeting and Exposition**  
 14-18 November, 2010, New Orleans, USA  
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[www.pswc2010.org](http://www.pswc2010.org)

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