

## 2008 LRIG Workshop on ADMET/PK

**Date – November 12, 2008**

**Location – Crowne Plaza Hotel - Somerset, NJ**

[www.cpsomerset.com](http://www.cpsomerset.com)

**Schedule:**

**4:30 to 5:45PM Social Hour with Appetizers;**

**5:45 to 6:30 PM dinner**

**6:30 to 9:00 PM seminars**

***There is no cost to attend.***

On-line registration is mandatory at <http://www.lab-robotics.org/>

### Program

4:30-5:45 pm Registration

6:30-6:35 pm **Program Introduction:**

**Dr. Zhengming (Jimmy) Chen**  
Vice President, Chemistry and Pharmaceutial R&D  
DOV Pharmaceutical, Inc.  
[zchen@dovpharm.com](mailto:zchen@dovpharm.com)

6:35-7:10 pm **Dr. Handan He**  
Director and Head of Preclinical PK/PD  
Novartis Pharmaceuticals Corporation.

**Topic: Practical human PK prediction approaches using in silico, in vitro and in vivo animal data**

**Bio:**

Dr. Handan He is Director and Head of Preclinical PK/PD at Novartis Pharmaceuticals Corporation. She received a B.S. in Pharmacy and M.S. in Medicinal Chemistry from the Second Military Medical University in Shanghai, China. She earned her Ph.D. in Drug Metabolism and Pharmacokinetics at the University of Saskatchewan, Canada, under the supervision of Dr. K. K. Midha, a former Chairman of the International Pharmaceutical Federation. From 1994 to 1997, Dr. He was a Senior Scientist at Wyeth-Ayerst Research, where she worked in the field of biotransformation in drug development. In 1997, she joined the Drug Metabolism and Pharmacokinetics Department at Novartis. Dr. He's primary responsibility has been to direct preclinical ADME studies for early development projects with a special emphasis towards human PK predictions based on preclinical data. She was instrumental in establishing an in silico absorption support group at Novartis, and has led a number of global and local scientific initiatives there. Dr. He is the principal contributor or author of IND documents and NDA submissions for more than a dozen compounds, and is the recipient of numerous Novartis Business Excellent Awards. She has published more than 20 scientific papers and over 30 abstracts, and is a frequently invited lecturer in the area of pharmacokinetics and drug metabolism.

**Abstract:**

The accurate prediction of human pharmacokinetic parameters based on early in vitro and in vivo preclinical data remains a major challenge in drug development. Various approaches have been published, each having their own advantages and limitations.

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The predictability of these approaches varies significantly and is largely dependent on individual compound properties and interspecies differences. There is an increased focus to use more mechanistic approaches, e.g. physiologically based pharmacokinetics, in addition to empirical methods, e.g. allometric scaling. Although mechanistic models (PBPK) allow an understanding of the effect physiological variables on pharmacokinetic parameters, the successful development and implementation of routine PBPK models is still limited, as significant experience, and resource intensive data are often required,. Thus, allometric scaling approaches have remained and expanded their uses as valuable tools in drug development. Of course, many theories and different approaches have been proposed for improving the predictive performance of allometry for CL,  $V_{ss}$  and  $t_{1/2}$ . Besides prediction of PK parameters, attempts have also been made to predict plasma concentration profiles. This presentation is to share our experience with you in predicting human PK parameters, e.g. CL,  $V_{ss}$ ,  $t_{1/2}$ , ka and F% as well as oral PK profiles in plasma and tissues. To predict human CL, it is suggested to use multiple approaches to assess prediction confidence, e.g. IVIVC using microsomal or hepatocyte data, allometric scaling (rule of exponent), single species allometric scaling and fraction unbound corrected intercept method (FCIM). To predict  $V_{ss}$ , 3 multiple species approaches e.g. Oie-Tozer, allometric scaling (1-3 species) and PBPK will be discussed. Moreover, many approaches for  $t_{1/2}$ , ka, F% will also be recommended. In terms of PK profile prediction, PBPK, Wajima and two-compartmental allometric scaling will be among the choices. This presentation will not only describe scaling techniques using Novartis examples, but also highlight how to address interspecies differences to improve prediction confidence in the anticipation of human doses.

7:10-7:45 pm

**Dr. Simon Thomas**  
**Head of Scientific Computing**  
**Cyprotex Discovery Ltd**

**Topic: Improving Candidate Quality Through the Prediction of Clinical Outcome**

**Bio:**

Simon Thomas studied Chemistry at Oxford University, followed by several years in the fledgling computer software industry as a scientific programmer and consultant. His Ph.D. training and postdoctoral research were conducted in the fields of Metabolic Control Analysis, and computer simulation of the behaviour of biochemical pathways: fields that are today part of the discipline known as Systems Biology. This was followed by a year as a lecturer in Biochemistry at Brunel University. Since joining Cyprotex in 1999, he has been responsible for the development of predictive in silico methods in the company, predominantly in the area of physiologically based pharmacokinetic modeling for the prediction of PK. Recent developments in the area of PK/PD modeling have been fostered by his experience in the Systems Biology field.

**Abstract:**

Despite ever-increasing discovery and preclinical budgets, and data generation for new compounds, most new compounds that enter clinical trials fail in Phases I or II. In essence, this is due to the difficulty of predicting fundamental pharmacological behaviour in human a priori. This prediction requires the combination of data from in vitro efficacy, ADME and toxicity screens, as well as the results obtained in animal models. The combination of all relevant data is necessary to help to predict the clinical outcome of the administration of a novel compound, and to guide lead optimisation and candidate selection.

One means of achieving this combination of data is by simulation modelling. Physiologically-based pharmacokinetic (PBPK) modelling is becoming a widely established means of predicting pharmacokinetics, including the crucial aspects of target and non-target tissue exposure. Combining tissue dosimetry predictions from PBPK modelling with the modelling of drug action at target sites enables lead optimisation to be guided rationally by optimising on in vivo therapeutic effect. Incorporating toxicity data in the same manner increases the value of the approach.

I shall present results of an ongoing study on PK/PD modelling of the statins, a group of

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compounds that reduce plasma LDL-cholesterol levels by inhibition of HMG-CoA reductase, an enzyme of the cholesterol synthesis pathway. I shall describe the use of ADME data generated in HT in vitro screens, activity data generated in receptor and cell-based in vitro screens, and PK and response data from preclinical species (and even from humans for the special case of 'me-too' drug development). The interplay between activity and ADME/PK data will be discussed, as will the continuing challenge of developing cost-effective alternatives to in vivo animal PK screens.

7:45-8:10 pm

**Dr. Hong Wen**  
**Pharmaceutical Development,**  
**Novartis Pharmaceuticals Corporation.**

**Topic: Formulation approaches in addressing PK Related Issues**

**Bio:**

Dr.Hong Wen is a part time project leader and formulation expert in PHAD, East Hanover. His responsibilities include project management, formulation/process development, and a core member of Novartis TRD S&T committee. His expertise spans from discovery support and preformulation to late phase development of solid oral dosage forms with a special focus on bioavailability enhancement for water insoluble drugs, oral sustained release (SR) formulations and Combination products (FDC).

Hong joined Novartis in 2006 after working four years in pharmaceutical development at Wyeth Research. During his tenure in pharmaceutical industry, Hong has contributed to more than 10 INDs/IMPDs filing as well as several NDAs filing. Hong received his Ph.D. in Industrial and Physical Pharmacy from Purdue University. His doctoral research focused on "Effects of Additives on Dissolution and Growth of Drug Crystals", focusing on the influence of polymers on drug crystallization and dissolution, especially critical for stabilizing supersaturated solutions and amorphous forms.

Hong is an internationally recognized scientist that is a reviewer for eight journals in the field of pharmaceutical sciences, has 7 patents, 12 research publications, 5 presentations and 3 book chapters in various areas of formulation development. He is currently editing/co-authoring a book on Oral Controlled Release Formulation Design and Drug Delivery, Theory to Practice to be published by John Wiley and Sons by 2009.

**Abstract:**

For each compound, its PK profile is affected by not only its physico-chemical and biopharmaceutical properties, but also the formulation design. Based on drug solubility and permeability, drugs have been classified into four classes. For those drugs with poor water solubility or low permeability, lots of research has been done to improve their bioavailability. Considering the Lead compound screen process, most new compounds are poorly water soluble, and most pharmaceutical development are focusing on improving their dissolution in the human GI tract.

Besides, some drugs with narrow adsorption window, i.e. narrow adsorption region in human GI tract, some special delivery systems can help to improve the bioavailability by overcoming the short transit time of drug in those specific GI regions. Furthermore, some special delivery system like controlled release formulations can be useful for those drugs with short half, or narrow therapeutic window. Those controlled release formulation can improve patient compliance, as well as reduce side effects related to high Cmax.

8:10-8:45 pm

**Bob O'Hara**  
**Managing Partner at ResultWorks, LLC**

**Topic: R&D Knowledge Assessment Shapes Scientific Information Strategy**

**Bio:**

An accomplished senior executive with more than 20 years experience in building and leading organizations including sales, professional services, product management and

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development, Bob O'Hara co-founded ResultWorks to apply this knowledge and expertise specifically as it relates to the Life Sciences and Healthcare industries.

Mr. O'Hara has managed a number of organizations that have provided information technology solutions including laboratory information management systems (LIMS), chromatography, e-procurement, and compound management.

Prior to co-founding ResultWorks, Mr. O'Hara was Vice President of Product Management at SciQuest, Inc. a software and services company providing e-procurement and materials management solutions to the pharmaceutical and biotechnology industries. At SciQuest, Mr. O'Hara oversaw the product strategy, product methodology and solution sales support for all product lines.

At EMAX Solution Partners, a privately held company focused on research materials management, Mr. O'Hara served as Vice President of Operations, Professional Services and Product Management. Under his leadership, EMAX transformed from a custom software business to a standard product software business, creating added value for EMAX clients.

While at Hewlett-Packard Company, Mr. O'Hara held various management positions in both the Chemical Analysis Group and the Computer Business Group. While with the HP Chemical Analysis Group (now Agilent), Mr. O'Hara was the National Business Manager for LIMS and Chromatography systems where he built a successful consulting services business leveraging a project management methodology approach to all aspects of the business. He developed an analytical instrumentation training business to support the needs of major pharmaceutical and chemical clients. He also held various management roles in the HP Computer Systems Business Group in the professional services operation and the systems support operation.

**Abstract:**

At the highest level, Pharmaceutical R&D is supported by a number of formal and well developed scientific information systems that are carefully managed. These systems and the inherent scientific knowledge they support are quite visible to upper management. Yet over time, R&D communities employ of a variety of informal systems from spreadsheets to commercial systems that are often implemented "under the radar" of the formal IT support channels.

Several pharmaceutical companies recently undertook an effort to assess the scientific information systems being used throughout their organizations, including formal as well as informal systems. They contracted with ResultWorks to perform a collaborative assessment of R&D knowledge assets from discovery through early development. These projects lead to better prioritization of R&D scientific information system needs, key knowledge assets and a roadmap of system initiatives for the future.

This presentation will outline the business problems recognized by several clients, the approach undertaken to uncover and catalog scientific knowledge assets and the resulting strategic roadmap that became the foundation for guiding R&D scientific information system investments.

8:45-8:50 pm

**Closing Remarks:**  
**Mel Reichman, Ph.D.**  
**Pharmacophore Discovery Consulting**

**Organization  
Committee**

**Drs. Zhengming (Jimmy) Chen and Mel Reichman**