

VCU HANDS-ON PK/PD MODELING WORKSHOP 2017

PK/PD Research Laboratory
Department of Pharmaceutics
Virginia Commonwealth University

*June 12 – June 15, 2017
Richmond, VA*

TARGET WORKSHOP AUDIENCE:

This workshop is designed for drug development scientists in pharmaceutical industry, regulatory agencies and academia who want to understand and master PK/PD (pharmacokinetic/pharmacodynamic) modeling techniques to assist in the clinical pharmacological evaluation of drug products.

This interactive hands-on workshop has been given successfully on numerous occasions to diverse professional/scientific audiences at Virginia Commonwealth University (VCU) and to more than 100 clinical pharmacology fellows, reviewers and team leaders at FDA (OCP), NIH and Walter Reed Army Research Institute (WRAIR); it is part of a graduate-level Advanced PK course at VCU for M.S. and Ph.D. students in the Pharmaceutical Sciences.

WORKSHOP OVERVIEW:

This workshop is designed to review and extend key pharmacokinetic (PK) and pharmacodynamic (PD) concepts, and to apply them to basic PK/PD data analysis. In particular, it discusses and emphasizes the validity, limitations, interpretation and usefulness of different approaches to PK data analysis during drug development, i.e., compartmental PK/PD modeling and parameter estimation using nonlinear regression programs (Scientist[®] for Windows), noncompartmental PK analysis, and fundamentals of physiologically-based PK modeling (PBPK). New PK/PD concepts will be introduced, e.g., capacity-limited PK models, mean residence times and non-steady-state PK/PD models. The course entails extensive hands-on computer-based analysis of PK and PD data using spreadsheets (MS Excel[®]-based public domain) and Scientist[®] for Windows in order to apply the concepts discussed in the classroom. Active participation in discussions in class is essential in addition to graded homework assignments and a final examination. Participants taking the course are expected to have acquired a basic understanding of PK concepts.

The class will be taught as an intensive four-day workshop: morning sessions will be held in a regular classroom (Smith, 129 A/B) with presentations by the course instructors and provide ample opportunity for interaction. Afternoon sessions will be held in a computer room (Thomsom McCaw Library, 2-006) with each student assigned a computer with appropriate PK/PD software installed. These hands-on computer sessions are designed to reinforce important concepts by means of computer simulations and to allow students to explore "what-if" scenarios on their own.

In-class handouts and additional pertinent references will deepen and apply understanding of fundamental concepts and real-world applications; the required textbook (for graduate students only) serves as repository for review of class material. A set of (public domain) PK/PD modeling and analysis spreadsheets along with a manual (developed by the course coordinator) will be provided to the students for self-study; these spreadsheets are also used to illustrate important PK/PD concepts in the computer room and are applied extensively in the homework assignments. In addition, the students will receive a set of (public domain) PK/PD models using Scientist[®] for Windows from real-life applications; some of these applications will be reviewed and discussed in the afternoon hands-on computer sessions.

WORKSHOP FACULTY:

Jürgen Venitz, MD, Ph.D. (Course Coordinator and Instructor)
 Professor, Dept. of Pharmaceutics
 Room 450 Smith, (804) 828-6249
jvenitz@vcu.edu

Dr. Venitz is a clinical pharmacologist with more than thirty years of experience in preclinical/clinical drug development. He is currently Professor, Depts. of Pharmaceutics, and Director of the PK/PD Laboratory at the VCU School of Pharmacy; he is also Affiliate Professor in the Departments of Pharmacotherapy and Outcomes Sciences, Medicinal Chemistry and Pharmacology and Toxicology as well as a Fellow with the VCU Center for the Study of Biological Complexity. He received his M.D. in 1981 from the Universität des Saarlandes in Saarbrücken, Germany where he also received his Ph.D. in physiology in 1986. From 1981 to 1985, he was Director of Clinical Research and Development at the Institut für Klinische Pharmakologie (IKP) Bobenheim in Grünstadt, Germany. He was in charge of a Phase I Clinical Pharmacology Unit and responsible for design, implementation and data analysis of phase I and PK/PD studies. From 1985 to 1987, he completed a postdoctoral fellowship with Dr. E.R. Garrett at the Beehive, School of Pharmacy, University of Florida, Gainesville, FL. In 1988, he joined the faculty at the VCU School of Pharmacy, where he has been teaching and mentoring numerous B.S., Pharm.D., Ph.D. and postdoctoral students. He has published more than 180 abstracts, more than 65 peer-reviewed articles and six book chapters; he presented to various scientific audiences in the area of quantitative pharmacology in early clinical drug development. He serves on multiple university, AAPS, ACCP, ASCPT, NIH, and FDA committees. He is scientific expert consultant in clinical pharmacology with several pharmaceutical companies, as well as the FDA Office of Clinical Pharmacology. He currently chairs the Pharmaceutical Compounding Advisory Committee and is *ad-hoc* member of the Clinical Pharmacology Advisory Committee with CDER. For his professional accomplishments, he has been awarded Fellowship status with ACCP and AAPS.

Satjit S. Brar, Pharm.D., Ph.D. (Instructor)
 Associate Director of Clinical Pharmacology, Pfizer Oncology Business Unit, San Diego, CA
 Affiliate Associate Professor, Dept. of Pharmaceutics, VCU
satjit.brar@pfizer.com

Dr. Brar is a clinical pharmacologist who received his combined Pharm.D./Ph.D. degree from the VCU School of Pharmacy in 2008. After graduation, he joined FDA initially as postdoctoral research fellow in Pharmacometrics (PM). He has been involved for more than 8 years in teaching various PK/PD topics to pharmacy students, graduate students and OCP reviewers; he was also instructor at a PERI PK/PD workshop for industrial scientists. His previous position was as Clinical Pharmacology Team Leader - supporting Pulmonary, Rheumatology and Allergy products - in the Office of Clinical Pharmacology (OCP) at the FDA. His current position is Associate Director of Clinical Pharmacology at Pfizer, specializing in immuno-oncology and PK/PD of large molecules.

SPECIFIC WORKSHOP OBJECTIVES:

1. Develop and use computer spreadsheets to implement simple pharmacokinetic models and to analyze pharmacokinetic plasma and urine data.
2. Apply ready-made computer spreadsheets to simulate different pharmacokinetic/dynamic models and perform noncompartmental PK analysis.
3. Identify rate-limiting processes in complex pharmacokinetic models (e.g., absorption and metabolism) and define flip-flop phenomena. Estimate rate constants for rate-limiting steps.
4. Graphically determine half-lives and (hybrid) rate constants from plasma and urine concentration-time data as initial parameter estimates for PK modeling of linear compartmental PK models.
5. Understand the assumptions and concepts of the nonlinear regression approach (using Scientist[®] for Windows) for PK modeling. Apply nonlinear regression to simple PK and PK/PD models. Understand the significance of PK/PD parameter estimation. Assess goodness-of-fit (residuals, CI of parameter estimates, SSR, r^2 , MSC).
6. Define and calculate clearances (CL_{tot} , CL_{ren} , CL_{nonren} , and CL_{met}) from PK (plasma, urine and metabolite) data and discuss their assumptions, validity and underlying physiological significance; understand the concept of mass balance.

7. Discuss quantitatively the PK variables (Q_{hep} , f_u , CL_{int} ; GFR, CL_{sec} , CL_{reabs}) determining hepatic and renal clearance (CL_{hep} , CL_{ren}). Define high and low hepatic-extraction-ratio (ER_{hep}) drugs. Understand metabolic and biliary clearance conceptually.
8. Discuss the validity, significance and interrelationship of the different volumes of distribution ($V_{d_{\text{cc}}}$, $V_{d_{\text{pss}}}$, $V_{d_{\text{ss}}}$, and $V_{d_{\text{extra}}}$) for multi-compartment PK models. Understand the effects of plasma protein and tissue binding (f_u^p , f_u^t) on their physiological interpretation.
9. Explain the concept and clinical relevance of depth and capacity of peripheral compartments in multi-compartment body models.
10. Discuss the method of noncompartmental PK analysis and apply it to pharmacokinetic data. Interpret the PK parameter estimates. Compare the approach to compartmental PK modeling.
11. Understand and apply the concepts of mean residence times in PK (MRT_{sys} , MAT, MDT).
12. Identify drug absorption, distribution processes and elimination pathways in the body that exhibit saturation and provide examples.
13. Discuss Michaelis-Menten pharmacokinetics, and understand its implications for PK. Identify plotting methods to estimate Michaelis-Menten parameters (v_{max} , K_m) and compare them to nonlinear regression methods.
14. Understand the assumptions and use of physiologically -based PK modeling (PBPK). Be familiar with physiological parameters (Q , V , R). Compare the approach to compartmental PK modeling methods.
15. Explain the concept of allometric scaling in quantitatively extrapolating PK information across species; understand the contribution of *in-vitro-in-vivo* extrapolation (IVIVE) to interspecies scaling.
16. Define pharmacodynamics (PD), relate observed effect and observed plasma concentration, and differentiate between different effect-concentration models. Discuss the issue of PD parameter estimation (E_0 , E_{max} , EC_{50} , n).
17. Using compartmental modeling approaches, understand and apply the concept of a biophase linking plasma concentration and effect, as well as active metabolites. Understand the principles of the indirect effect model.
18. Discuss different strategies of PK/PD data analysis and their usefulness in drug development and regulatory decision making.

WORKSHOP SCHEDULE:

Time	(Room)	Topic(s)	Handouts
<u>Monday, June 12, 2017</u>			
8:30a-10:00a	(129 A/B)	<u>Clearance I</u> (General Concepts)	(Chapters 8 and 9) Spreadsheet Manual/Disk
10:00a-11:00a	(129 A/B)	<u>Clearance II</u> (Renal Clearance)	Physiol. Model Handout
11:00a-12:00n	(129 A/B)	<u>Clearance III</u> (Hepatic Clearance)	
1:00p-4:30p	(2-006, TML)	<u>Computer Simulations</u>	
<u>Tuesday, June 13, 2017</u>			
8:30a-9:30a	(129 A/B)	<u>Volume of Distribution I</u> (General Concepts)	(Chapter 5)

9:30a-10:00a	(129 A/B)	<u>Volume of Distribution II</u> (Protein and Tissue Binding)	
10:00a-11:30a	(129 A/B)	<u>Noncomp. PK Analysis I</u> (General Concepts)	(Chapter 11)
11:30a-12:30p	(129 A/B)	<u>Noncomp. PK Analysis II</u> (Mean Residence Times)	Brockmeier et al.
1:00p-4:30p	(2-006, TML)	<u>Computer Simulations</u>	

Wednesday, June 14, 2017

8:30a-9:30a	(129 A/B)	<u>Nonlinear PK Models</u> (General Concepts)	(Chapter 7) Jusko et al.
9:30a-11:00a	(129 A/B)	<u>Nonlinear Regression I</u> (General Concepts)	(Scientist handbook) PK/PD Model Manual/Disk
11:00a-12:30n	(129 A/B)	<u>Nonlinear Regression II</u> (Goodness of Fit)	Scientist Output Sheiner and Beal
1:00p-3:00p	(2-006, TML)	<u>Computer Simulations and Exercises, Scientist®</u>	

Thursday, June 15, 2017

8:30a-9:30a	(129 A/B)	<u>PK Data Modeling Analysis</u> (PK Analysis Strategies)	(Chapter 10) Summary, Garrett et al., Derendorf et al.
9:30a-10:30a	(129 A/B)	<u>Pharmacodynamics I</u> (DDR, integrated models)	(Chapter 6) PD book chapter
10:30a-12:00n	(129 A/B)	<u>Pharmacodynamics II/PK Scaling</u> (PK/PD Examples, PBPK, Allometric PK Scaling, IVIVE)	
1:00p-4:30p	(2-006, TML)	<u>Computer Exercises, Scientist®</u>	

TUITION:

Tuition for the workshop is \$3,000, and includes attendance of all lectures, hands-on interactive participation of the computer exercises as well as extensive course handouts/binder and a CD ROM with public domain PK/PD software (see above) and electronic copies of most handouts.

Checks should be made payable to **VCU School of Pharmacy** and mailed along with the registration to:

Ms. Victoria Savoy
Director, Fiscal Operations
VCU School of Pharmacy
410 N 12th Street
P. O. Box 980581

Richmond, VA 23298-0581

We also accept all major credit cards. If you want to charge the course tuition and/or need an invoice, please contact Ms. Keyetta Tate by e-mail at kstate@vcu.edu or by phone at (804) 828-6102.

Please complete and return the attached registration form first (no later than May 19, 2017) to make sure that there is still room available. After your registration is confirmed, please mail in your remittance.

ACCOMODATIONS:

Workshop participants are kindly asked to make their own hotel reservations. The following hotels are in reasonably close vicinity of the VCU School of Pharmacy and have special VCU rates (current as of January 2016):

Commonwealth Park Suites Hotel (3 blocks)

901 Bank Street
(804) 343-7300
VCU Rate: \$113 plus tax

Omni Richmond Hotel (6 blocks)

100 S 12th Street
(804) 344-7000
VCU Rate: \$113 plus tax

Marriott

500 E Broad Street
(804) 643-3400
VCU Rate: \$113 plus tax

Berkeley Hotel

1200 E Cary Street
12th and Cary Street
(804) 780-1300
VCU Rate: \$113 plus tax

Linden Row Inn

100 E Franklin Street
(804) 783-7000
VCU Rate: \$99 plus tax (Garden Room), \$119 plus tax (Main House Room)

Crowne Plaza

555 E Canal Street
(804) 344-2973
VCU Rate: \$113 plus tax (free breakfast buffet, free parking, complimentary shuttle to all VCU offices)

When you make your reservations, please mention that you will be with a VCU-sponsored event to obtain the above quoted rates.

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REGISTRATION FORM

Please e-mail to Dr. J. Venitz at jvenitz@vcu.edu

NO LATER THAN MAY 19, 2017

Name, Degree(s): _____

Job Title: _____

Organization: _____

Address: _____

City, State, ZIP: _____

E-mail address: _____

Phone Number: _____

Fax Number: _____