ACOP 2009

American Conference On Pharmacometrics

October 4-7, 2009

The Grand Pequot at Foxwoods Resort

Mashantucket, CT

Welcome to the 2009 American Conference on Pharmacometrics!

ACoP is a U.S. national meeting focusing on all aspects of modeling and simulation in pharmacology and therapeutics. The first ACoP meeting in Tucson last year proved to be the premiere U.S. event for excellence and knowledge sharing in pharmacometrics, with international participation from academia, industry, and government sectors.

While our first ACoP was a resounding success, we are excited by the tremendous growth we've experienced for the 2009 meeting:

	2008	**2009**
Participants	320	426
Organizations	108	125
Posters	100	164
Exhibitors	6	12
Students/Post-docs	29	70

We are especially pleased that, thanks to the generosity of our sponsors, we have been able to make the registration cost lower for students, allowing us to more than double their numbers from last year! In addition, we'll have some special student programming this year for the first time, which we hope to make a regular part of future ACoP meetings.

We look forward to sharing an exciting, educational, and entertaining 3 days with you!

The ACoP 2009 Organizing Committee:

Kyle Baron
Dick Brundage
David D'Argenio
Marc Gastonguay
Raymond Miller
Marc Pfister
Stacey Tannenbaum

Special Thanks to BMSR for their support of ACoP 2009!!

BMSR | Biomedical Simulations Resource

bmsr.usc.edu

To ACoP Participants,

The Biomedical Simulations Resource in the Department of Biomedical Engineering at the University of Southern California is delighted to serve as a sponsor for ACoP 2009.

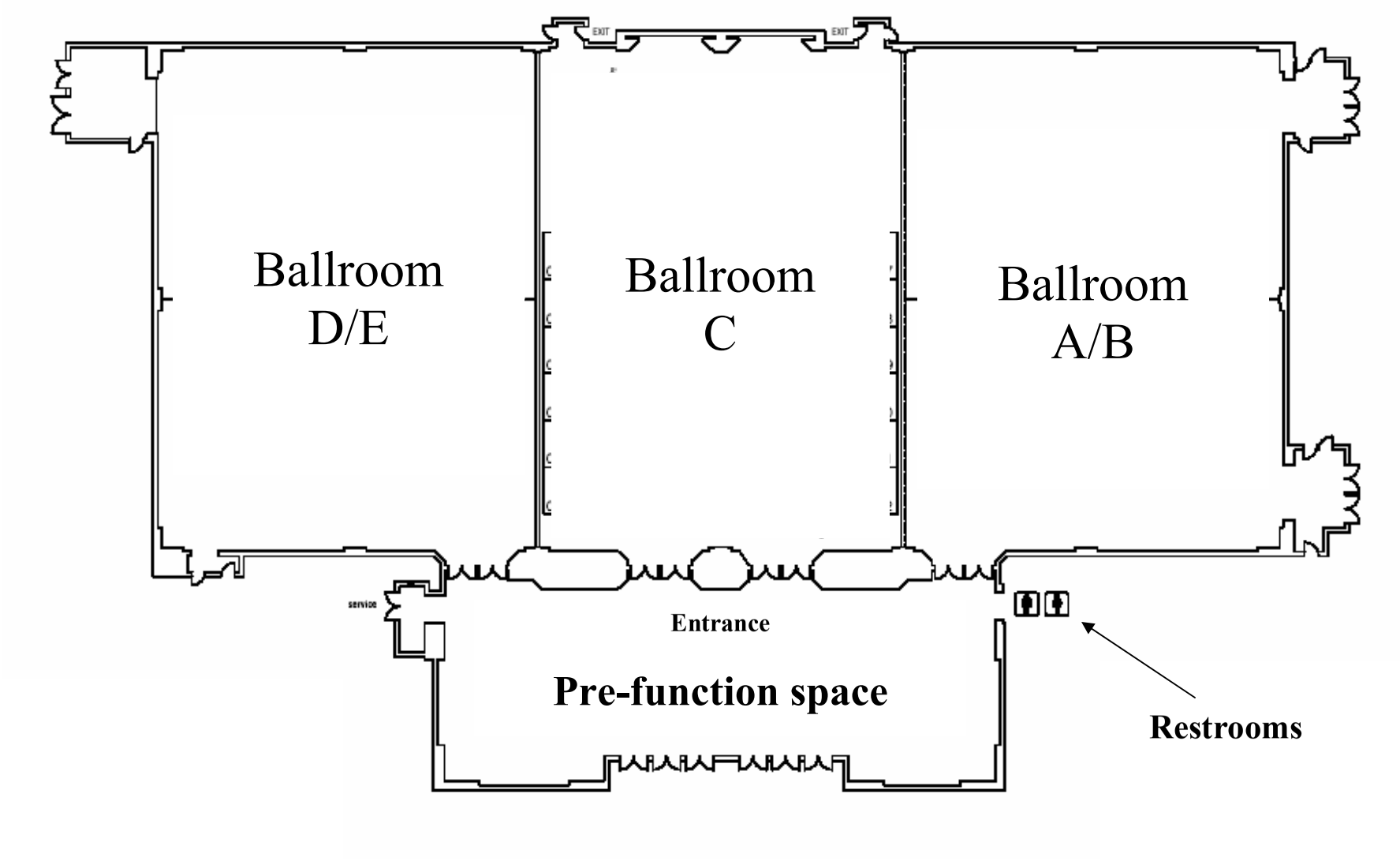
Since 1987, the BMSR has sponsored 12 workshops on Advanced Methods of PK/PD Systems Analysis as part of the service, dissemination and training activities of its NIH/NIBIB center grant. These meetings, held in Marina del Rey, California, brought together pharmaceutical scientists, clinical pharmacologists, clinical pharmacists, mathematicians, statisticians, engineers, chemists, physicists, biological scientists and others in a forum designed to facilitate the exchange of ideas between basic and clinical research scientists, experimentalists and modelers, for the purpose of advancing the study of pharmacokinetics and drug response.

The BMSR's continuing mission to promote the development and application of systems modeling in biomedicine is also shared by ACoP, and we look forward to working with its members to insure the success of this essential mission.

Best wishes for a stimulating meeting from the BMSR,

David Z. D'Argenio, PI
Vasilis Z. Marmarelis, Co-PI
Michael C.K. Khoo, Project Leader
Theodore W. Berger, Project Leader
Marcos Briano, Administrator

GRAND PEQUOT BALLROOM



Main Conference: Ballrooms D/E (left)
Posters and Exhibitors: Ballroom C (middle)

Meals and Breaks: Ballroom A/B (right)
Registration: Pre-function Space

SUNDAY OCT 4

12:00 PM	5:00 PM	Registration	
5:00 PM	9:00 PM	ACoP Opening Reception	

MONDAY OCT 5

7:30 AM	8:30 AM	Breakfast/Registration	
8:30 AM	8:45 AM	**Opening remarks**	**Stacey Tannenbaum**
8:45 AM	10:15 AM	**Applications of Modeling over the Development Life Cycle of Biologics** **Session Chairs: David D'Argenio and Don Mager**	
		Predicting human PK/PD of biologics from animal data	Peiming Ma
		Modeling and simulations for assessment of PK and PD of a G-CSF biosimilar	Wojciech Krzyzanski
		Population PK-PD Modeling of Biological Agents: When Modeling Meets Reality	Diane Mould
10:15 AM	11:00 AM	Break/Poster set up/Software Demos	
11:00 AM	12:30 PM	**Model and Data Sharing Initiatives** **Session Chairs: Klaus Romero and Brian Corrigan**	
		TIPharma mechnism-based PKPD modeling platform	Meindert Danhof
		The Coalition Against Major Diseases: Review of goals, accomplishments and future plans	Klaus Romero
		OpenDiseaseModels.org: An Open Forum for Collaborative Model Building and Evaluation	Bill Gillespie
		FDA Disease Models	Christoffer Tornøe
12:30 PM	2:00 PM	Lunch	
2:00 PM	3:30 PM	**Dealing with Missing Data in Pharmacometrics** **Session Chairs: Marc Gastonguay and Jonathan French**	
		Introduction to Missing data and issues in pharmacometrics	Jonathan French
		When Should We Be Concerned About Nonignorably Missing Data?	Dan Heitjan
		The Impact of Missing Data on Model Evaluation	Marc Gastonguay
3:30 PM	5:00 PM	Break/Posters/Software Demos	
5:00 PM	6:00 PM	**Lewis B. Sheiner Memorial Lecture: Connecting to the Other Side**	Mats Karlsson
6:00 PM	7:00 PM	**Where will the pharmacometricians of the future come from?** **Session Chairs: Bernd Meibohm and Hartmut Derendorf**	
		Panel discussion	Sandra Allerheiligen, David Cadieu, Amita Joshi, Richard Lalonde
7:00 PM	11:00 PM	ACoP Social Event	

TUESDAY OCT 6

8:00 AM	9:00 AM	Breakfast	
9:00 AM	10:30 AM	**Development and utilization of disease models** **Session Chairs: Mats Karlsson and Marc Pfister**	
		A Mechanism-Based Disease Model for SGLT2 Inhibitors in Type 2 Diabetes (T2DM) Subjects	Chee Ng
		Empirical Disease Progression Model for Ranibizumab in Age-Related Macular Degeneration	Satyendra Suryawanshi
		The Antiviral Information Management System (AIMS): Leveraging prior knowledge to inform dose selection of new hepatitis C therapies	Lauren Neal
		A Modeling Framework to Simulate Motesanib Efficacy in Thyroid Cancer	René Bruno
10:30 AM	11:00 AM	Break	
11:00 AM	12:30 PM	**New Directions in Cardiovascular Modeling: From Biomarkers to Clinical Outcomes and Comparative Effectiveness** **Session Chairs: Christine Garnett and Richard Lalonde**	
		The RAAS Hypertension PhysioLab platform: A Systems Modeling Approach to Hypertension	Ramprasad Ramakrishna
		Conceptual Framework for Evaluating The CV Risk Manifested By Drug-Induced Elevations in Systolic Blood Pressure	Raj Madabushi
		Quantitative Approaches for Comparative Effectiveness and Pharmacoeconomics	Jens Grueger
12:30 PM	2:00 PM	**Student Session: Troubleshoot your project with M&S experts** **Diane Mould, David D'Argenio, Leonid Gibiansky, William Gillespie, Luann Phillips**	
12:30 PM	7:00 PM	Afternoon off (on your own)	
7:00 PM	8:30 PM	**KEYNOTE PRESENTATION: Beautiful Evidence**	**Edward Tufte**
8:30PM	10:00 PM	Buffet dinner, posters, and exhibitors	

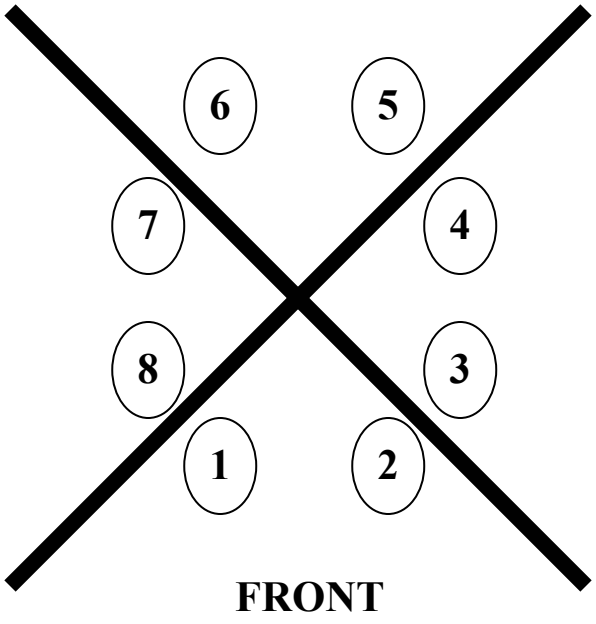
WEDNESDAY OCT 7

7:00 AM	8:00 AM	Breakfast	
8:00 AM	9:30 AM	**Communication Through Graphics: Looking at Data, Models, and Results** **Session Chair: Andreas Krause**	
		Exploratory Data Visualisation: Taming the Technology	Richard Pugh
		Visualizing PK/PD Models using Berkeley Madonna	Andreas Krause
		Simulation Graphics to Enable Model-Based Decision Making	Kevin Dykstra
9:30 AM	11:00 AM	Break/Posters/Software Demos	
11:00 AM	1:00 PM	**Event Driven/Non-continuous Data Models** **Session Chairs: Raymond Miller and Celine Dartois**	
		Exposure-Response Analysis for Spontaneously Reported Dizziness in Pregabalin Treated Patients with Generalized Anxiety Disorder	Kaori Ito
		Impact of Dosing Regimens on Dropout Across Pregabalin Trials in the Treatment of Generalized Anxiety Disorder	Bojan Lalovic
		Apnea of prematurity: A mixed effects modeling approach to disease resolution and pharmacologic intervention modeling	Christopher J Godfrey
		Estimation of Mixed Hidden Markov Models with SAEM. Application to daily seizures data	Marc Lavielle
1:00 PM	2:00 PM	Lunch	
2:00 PM	3:30 PM	**Who Wants to Be the First to Dose this Drug in Children? Approaches to Use Knowledge to Inform Dosing Choices** **Session Chair: Steven Kern**	
		The Design and Analysis of Informative Pediatric Clinical Pharmacology Trials Based on Integrating Modeling and Simulation With Available Prior Knowledge	Jeff Barrett
		No Experience, No Problem: Using Bottom-up Approaches to Guide First-in-Children Dosing	Andrea Edginton
		Evaluation of Performance of a Pediatric Pharmacokinetic Study Using a Simulation Based Design	Manisha Lamba
3:30 PM	4:30 PM	Break/Posters/Software Demos	
4:30 PM	5:45 PM	**PhRMA working group updates** **Session Chairs: Julie Stone and Amit Roy**	
		Adaptive Dose-Ranging Studies: An Update from the PhRMA Working Group	Jose Pinheiro
		Optimizing TQT Studies through PK-PD: An OQT Working Group	Larisa Reyderman
		Model-Based Drug Development PhRMA Initiative: Mapping the current status and future state for modeling and simulation in the pharmaceutical industry	Julie Stone
5:45 PM	6:00 PM	**Closing remarks**	**ACoP committee**

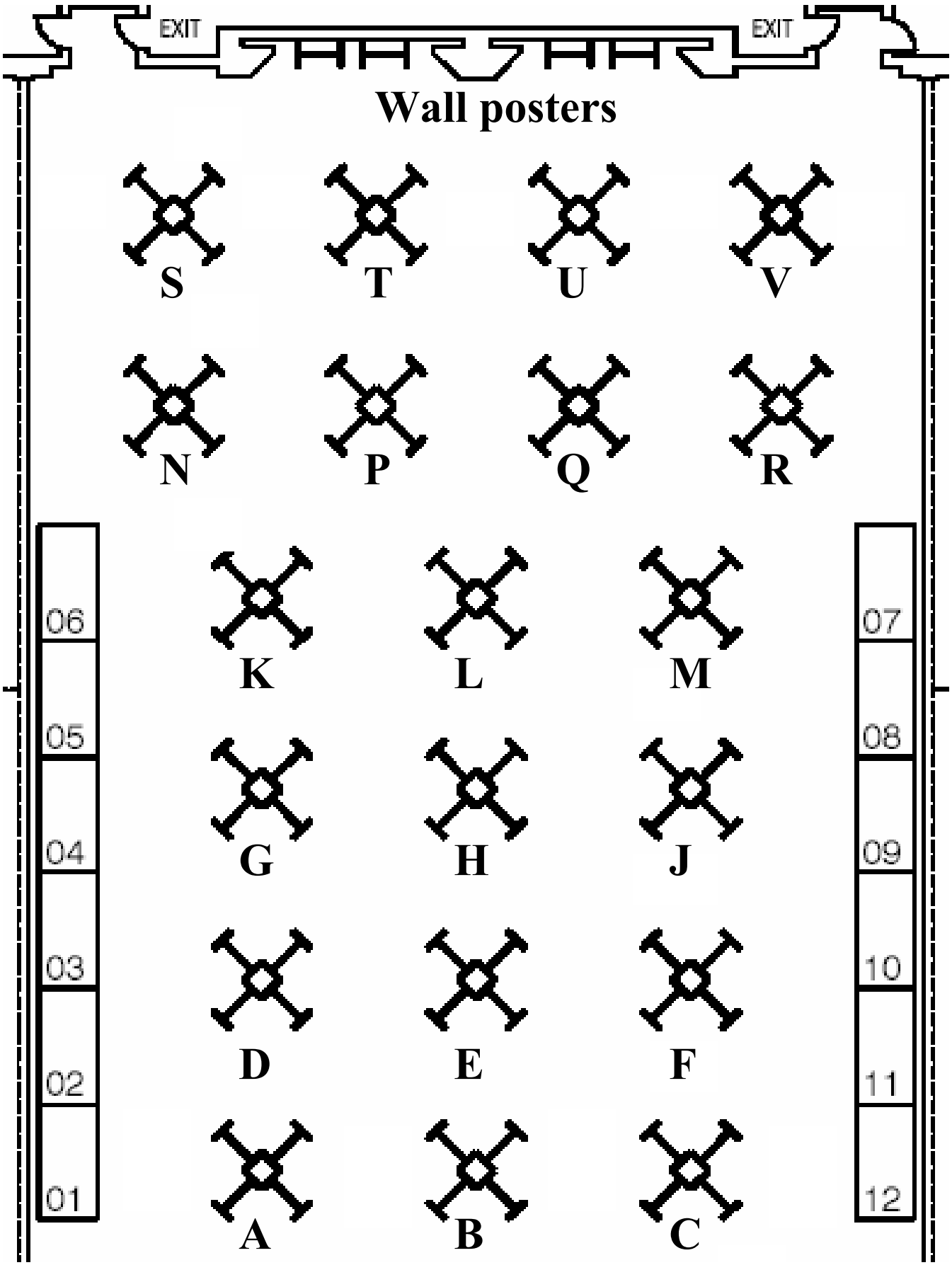
ACoP posters

Posterboards will be set up in clusters of 4 double-sided poster boards in an "X" formation. Each X is designated with a letter (A,B,C) as in the map on the next page.

Posters are located by the letter of the X cluster as well as the number (1-8), designating the location on the cluster, in the formation shown below.



There are also 4 posters against the side and back walls designated Wall 1 – Wall 4.


EXIT
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Wall posters
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FRONT

Posters are listed by day of presentation, then sorted by main topic

MONDAY AFTERNOON			
Name	**Abstract Title**	**Topic**	**Location**
Kenneth T. Luu	A Pharmacokinetic and Tumor-Immune Interaction Model for Immunomodulating Antibodies	Biologics	D1
Ramprasad Ramakrishna	Meta-analysis of Summary-level Literature Data Integrated with Sponsor Data to Support Model Based Drug Development.	Clinical Outcome Modeling	C2
Pascal Chanu	Decisive support of Modeling & Simulation for getting drug approval in the context of safety concern on the drug class	Clinical Outcome Modeling	E7
James Dunyak	Modeling Enterohepatic Recirculation and Intestinal Lumen Exposure for a Compound with Substantial Accumulation	Clinical PK	G7
Wei Liu	Time-Dependent, Dual First and Zero-Order Absorption Model for Characterizing the Delayed Absorption Profile in Subjects with Acute Pain	Clinical PK	P7
France Varin	Clinical Pharmacokinetics of Ropivacaine after Femoral Nerve Block in Patients Undergoing Total Knee Arthroplasty: Preliminary results.	Clinical PK	Q7
Srividya Neelakantan	Population Pharmacokinetic Analysis of Dalbavancin in Patients with Skin and Skin Structure Infections	Clinical PK	R1
Lauren Neal	Theoretical and experimental comparison of hepatitis C viral dynamics models and parameter estimates	Disease Modeling	H7
Sima Ahadieh	Model-Based Meta-Analysis of Young Maniac Rating Scale in Bipolar Patients	Disease Modeling	T7
Elodie Plan	Repeated Time-to-Categorical Events analysis	Event Driven Non-continuous Data Models	J1
Fatemeh Akhlaghi	Blood and Plasma Pharmacokinetics of Bortezomib in Relation to Blood 20S Proteasome Activity after Single and Multiple Dosing in Cynomongolus Monkeys.	Exposure-Response	A1
Amit Khatri	Evaluation of Drug Administration Sequence Effects on Tumor Cell Kill Using WBDiff in WinBUGS	Exposure-Response	J7
Susan Zhou	Feasibility of Characterizing Time and Concentration Dependent Binary Response Data by Time-To-Event Analysis	Exposure-Response	N7
Nitin Kaila	A Methodological Approach For Projecting Blood-Pressure Dose Response For A Backup Compound Using Clinical And Biomarker Data From A Previously Studied Agent In The Same Class	Exposure-Response	P1

MONDAY AFTERNOON			
Name	**Abstract Title**	**Topic**	**Location**
Ihab G. Girgis	Pharmacokinetic-Pharmacodynamic Assessment of Topiramate Adjunctive Therapy in Epilepsy	Exposure-Response	T1
Pratap Singh	Mixed Effects Model Analysis of the QTc Interval-concentration Relationship of SC-080 in Healthy Subjects	Exposure-Response	U7
Xiaoning Wang	Dasatinib Exposure-Efficacy/Safety Analyses to Support Dose Regimen Recommendation for Patients with Chronic Myeloid Leukemia	Exposure-Response	Wall1
Fatemeh Akhlaghi	Development of an Integrated Pharmacokinetic and Pharmacodynamic Model for Bortezomib to Allow Predication of 20S Proteasome Activity from Plasma Concentrations	Mechanistic Modeling/ Systems Biology	A2
Sunny Chapel	Semi-mechanistic Model for Characterizing the Effect of Rifampin Co-administration on the Pharmacokinetics of Efavirenz	Mechanistic Modeling/ Systems Biology	B7
Jürgen Bulitta	Mechanism-based Modeling of Beta-lactam Antibiotics Binding to Specific Penicillin-Binding Proteins of Pseudomonas aeruginosa at Several Initial Inocula	Mechanistic Modeling/ Systems Biology	K1
Jun Li	A new estimation approach for in vivo antimicrobial drug efficacy accounting for variability in pharmacokinetics	Mechanistic Modeling/ Systems Biology	U1
Yasong Lu	Modeling-Aided Human-to-Animal Translation of the Anticonvulsant Retigabine, a Kv7.2-5 Channel Opener	Mechanistic Modeling/ Systems Biology	Wall4
Rocio Lledo-Garcia	A New Whole Body Clinical Physiologically-Based Pharmacokinetic Model (WB-PBPK) for Estimation of PK Parameters with Informative Prior Distribution in Nonmem	PBPK modeling	R7
Michael Tagen	Population Pharmacokinetic and Pharmacogenetic Analysis of Gefitinib in Pediatric Cancer Patients	Pediatrics	D7
Hyewon Kim	Population Pharmacokinetics of Unbound Mycophenolic Acid in Patients Undergoing Allogeneic Hematopoietic Cell Transplantation (HCT)	Pediatrics	F1
Fang Li	Pharmacometrics-Based Dose Selection of Levofloxacin as a Treatment for Post-Exposure Inhalational Anthrax in Children	Pediatrics	L7
Christoffer W Tornoe	Impact of Pharmacometric Reviews on New Drug Approval and Labeling Decisions—a Survey of 65 NDAs Between 2006 and 2008	Pharmacometrics review, Regulatory impact	S1
Andrea Edginton	Physiologically-based Modeling for Predicting Pharmacokinetic Changes under Physiological Stressors	Special populations	G1

MONDAY AFTERNOON			
Name	**Abstract Title**	**Topic**	**Location**
Sihem Ait-Oudhia	Comparison of Pharmacokinetics of Epoetin Alfa Following Multiple Subcutaneous Administrations in Healthy Volunteers and Anemic Cancer Patients	Special populations	S7
Joo-Yeon Lee	Evaluation of Bayesian adaptive designs for dose-finding studies via computer simulations	Study Design/Conduct	V1
Tim Bergsma	Development and Pilot Evaluation of a High-Performance Computing System for Web-Based Deployment of Pharmacometrics Applications in a Multi-User Training Environment.	Tools and Techniques	B1
Ramprasad Ramakrishma	Evolving an Infrastructure to build and maintain indication- specific summary-level literature databases to support model based drug development	Tools and Techniques	C1
Huafeng Zhou	A Bayesian Approach to Handle Pharmacodynamics (PD) Data Below Limit of Quantification (BLOQ) in PK/PD Modeling	Tools and Techniques	E1
Martin Bergstrand	Prediction Corrected Visual Predictive Checks	Tools and Techniques	F7
David A James	ABPM: A statistical package for the visualization, analysis and modeling of ambulatory blood pressure data	Tools and Techniques	H1
Michael Heathman	Interactive Simulation and Visualization of Drug/Disease Models	Tools and Techniques	K7
Chee M Ng	Simulated Annealing Monte-Carlo Parametric Expectation Maximization Estimation Method for Population Pharmacokinetic/Pharmacodynamic Data Analysis	Tools and Techniques	L1
Stefan Willmann	Mechanism-based Prediction of Particle-Size Dependent Dissolution and Absorption Kinetics with PK-Sim®	Tools and Techniques	M1
France Mentré	Evaluation of different tests based on observations for external model evaluation of population analyses	Tools and Techniques	M7
Stacey Tannenbaum	Sharing Experiences of a Dedicated SAS Programming Group in a M&S Department	Tools and Techniques	N1
Anita Grover	Determination of the Operational Multiple Dosing Half Life	Tools and Techniques	Q1
Paul Baverel	Informativeness of Internal and External Validation Techniques in Various Simulation Settings and Across Algorithms	Tools and Techniques	V7

TUESDAY EVENING			
Name	**Abstract Title**	**Topic**	**Location**
Varun Goel	Application of Active-Comparator Based Benefit-Risk Assessment in Evaluating Clinical Trial Design Features of a New Chemical Entity in a Bayesian Decision Theoretic Framework	Benefit/Risk Assessment	B2
Immanuel Freedman	Feasibility of Immunogenicity Assessment Based on Models of Polyclonal Anti-Drug Antibody Immunodynamics	Biologics	P4
Hanbin Li	Pharmacokinetics Nomograms For The Onset And Offset Of Postoperative Dental Pain Relief with Ibuprofen	Clinical Outcome Modeling	B4
Sameer Doshi	Clinical Trial Simulations to Evaluate Non-Inferiority of Hemoglobin Response Comparing Once Monthly to Every Two Week Dosing of Darbepoetin Alfa	Clinical Outcome Modeling	G2
Timothy Nicholas	Preliminary Population Pharmacokinetic Modeling of PF-04360365, a Humanized Anti-Amyloid Monoclonal Antibody, in Patients with Mild-to-Moderate Alzheimer's Disease	Clinical PK	F4
John Carl Panetta	A Mathematical Model of Intracellular Methotrexate Accumulation and the Inhibition of Folate Pathway Enzymes in Acute Lymphoblastic Leukemia	Clinical PK	M4
Parviz Ghahramani	Population Pharmacokinetic Analysis of Milnacipran in Fibromyalgia Patients and Healthy Volunteers	Clinical PK	V2
Zhaoyu (Amy) Meng	Pharmacokinetic Modeling of Etomidate: A Randomized Comparison of Two Formulations	Clinical PK	Wall3
Mahesh N. Samtani	Paliperidone Palmitate Dosing in Special Patient Populations Including the Elderly and those with Renal Impairment or Differing Body Mass Index: Guidance Based on Pharmacokinetic Modeling and Simulation	Clinical PK, Special Populations	K4
Song Mu	Modeling longitudinal tumor metrics in NHL patients treated with Rituximab: Application of the Norton-Simon Hypothesis incorporating Gompertzian growth	Disease Modeling	F2
Julie Stone	Viral Dynamics Modeling of Viral Load and Resistance Data from Short-term Monotherapy with the HCV Protease Inhibitor, MK-7009	Disease Modeling	G4
Nitin Kaila	A Pharmacodynamic Model for the Long Term Effects of Galvus, Metformin and a combination therapy of Galvus with Metformin on Fasting Plasma Glucose (FPG) and Glycosylated Hemoglobin A1c (HbA1c) in patients with Type II Diabetes Patients (T2DM)	Disease Modeling	P2
Klas Johan Fredrik Petersson	Comparisons of modeling dropout as Time-to-Event data or Binary data using logistic regression.	Event Driven Non-continuous Data Models	H4

TUESDAY EVENING			
Name	**Abstract Title**	**Topic**	**Location**
Tae Eun Kim	The evaluation of the impact of in vitro dose-response curve slope on the clinical antiviral activity prediction of an HIV drug using PK-PD-Disease model-based simulation	Exposure-Response	A4
Rujia Xie	Population Pharmacokinetic/Pharmacodynamic (PK/PD) Analysis for the Effect of Tanezumab on Overall Daily Pain Score Data in Adults with Moderate-to-Severe Pain due to Osteoarthritis of the Knee	Exposure-Response	D4
Wonkyung Byon	Exposure-Response Analyses of the Effects of Pregabalin Administration in Patients with Fibromyalgia using Daily pain Score and Patient Global Impression of Change	Exposure-Response	J4
Farkad Ezzet	A Mixed-Effects Hazard Model to Compare the PK/PD of Armodafinil and Modafinil in Patients with Excessive Sleepiness Associated with Shift Work Disorder	Exposure-Response	Q4
Jian-Feng Lu	Population Pharmacokinetic (PK)/Pharmacodynamic (PD) Modeling and Simulations for Exposure–Tumor Response Relationships: Motesanib in a Phase 2 Thyroid Cancer Study	Exposure-Response	S4
Arne Ring	Delayed Effects in the Exposure-Response Analysis of Clinical QT-Studies	Exposure-Response	T2
Emma Hansson	Correlations Between Fatigue, Hand-foot syndrome and the Angiogenic Factors VEGF, sVEGFR-2, sVEGFR-3 and sKIT in Patients Receiving Sunitinib	Exposure-Response	V4
Ramprasad Ramakrishna	The RAAS PhysioLab model of hypertension: Development and parameterization of normotensive and hypertensive virtual patients (VPs), and generation of virtual populations (Vpops).	Mechanistic Modeling/ Systems Biology	C3
Ramprasad Ramakrishna	The RAAS Hypertension PhysioLab platform: A computer modeling platform to support design and analysis of clinical studies of novel antihypertensive therapies in a variety of clinical hypertensive phenotypes: Concepts and methodology.	Mechanistic Modeling/ Systems Biology	C4
Gabriel Helmlinger	Inference of imatinib (IM) effects on leukemic stem cell (SC) compartment via mathematical modeling of IRIS treatment response data	Mechanistic Modeling/ Systems Biology	D2
Jurgen Bulitta	Population Pharmacodynamic Modeling of the Mechanism of Action and Emergence of Sub-populations of Pseudomonas aeruginosa for a Wide Range of Colistin Dosage Regimens	Mechanistic Modeling/ Systems Biology	K2
Matthew M. Riggs	A Systems Biology Model To Describe Long-Term Bone Remodeling Effects Of Estrogen In Menopausal And Postmenopausal Women.	Mechanistic Modeling/ Systems Biology	N2
Cornelia Landersdorfer	Pharmacodynamic Modeling of the Effects of Tetraiodothyroacetic Acid (Tetrac) on Human Cancer Cell Proliferation	Mechanistic Modeling/ Systems Biology	N4
Frédérique Fenneteau	Physiologically based predictions of the impact of inhibition of intestinal and hepatic metabolism on human pharmacokinetics of CYP3A substrates	Mechanistic Modeling/ Systems Biology	R4

TUESDAY EVENING			
Name	**Abstract Title**	**Topic**	**Location**
Rui Zhu	Isoniazid Pharmacokinetics in HIV Perinatally Exposed Infants: The Role of NAT-2 Enzyme Maturation	Pediatrics	E4
Stefan Willmann	A Generic Translational Approach to Pediatric Study Design Relying on Whole-Body Physiologically-Based Pharmacokinetic Modeling	Pediatrics	M2
Robert Bies	Public Health Model For The Evaluation Of The Management Of Hypertension – A Proposal	Public Health Outcomes	E2
Diane R Mould	Population Pharmacokinetic Modeling and Simulation in Treatment of Seizures in Infants with Topiramate	Special populations	R2
Scott Van Wart	Impact of Dose Selection and Assay Sensitivity on Target Mediated Drug Disposition (TMDD) Population Pharmacokinetic Model Parameter Estimation: A Case Study Using Interferon-beta	Study Design/Conduct	J2
James A. Rogers	Clinical Trial Simulation to Compare Adaptive and Fixed Designs for a Phase 3 Clinical Trial of Nacystelyn® (L-Lysine-N-acetyl-L-cysteinate) for Cystic Fibrosis	Study Design/Conduct	L4
Caroline Bazzoli	Prediction of power of test of discrete covariates in population analyses and influence of design: application to gender effect in joint pharmacokinetic models of nucleoside analogs and their active metabolites	Study Design/Conduct	T4
Mohamed A Kamal	Application of Bayesian Feedback Analysis to Test Competing Hypotheses of Discrepancy between Single and Multiple Ascending Dose Pharmacokinetic Data	Tools and Techniques	A6
Ping Ji	Modeling of Rich Pharmacokinetic Datasets Using SAEM Algorithm Implemented in MONOLIX 2.4	Tools and Techniques	H2
Chee M Ng	Global Optimization and Pattern Search-based Optimization Algorithms for Parameter Estimation in Complex Pharmacokinetic/Pharmacodynamic Data Analysis	Tools and Techniques	L2
Anne Dubois	Model-based analyses of crossover trials: extension of the SAEM algorithm in MONOLIX software and evaluation of Wald and likelihood ratio tests	Tools and Techniques	S2
Bill Gillespie	BUGSModelLibrary: A Prototype Model Library for Bayesian PKPD Modeling in WinBUGS	Tools and Techniques	U2
Demiana William Faltaos	Estimation of Population Pharmacokinetic Parameters Using MLXTRAN Interpreter in MONOLIX 2.4	Tools and Techniques	U4
Yaming Hang	Comparison of Generalized Additive Model and Wald's Approximation Method for Covariate Selection in Population Pharmacokinetic Analysis	Tools and Techniques	Wall2

WEDNESDAY MORNING			
Name	**Abstract Title**	**Topic**	**Location**
Anson Kunjachan Abraham	Role of Receptor Dimerization and Specific Tissue Distribution in Target-Mediated Drug Disposition Models.	Biologics	C8
Joerg Lippert	Development of a generic physiologically-based pharmacokinetics model for protein therapeutics in PK-Sim®	Biologics, Mechanistic Modeling	A7
Chunlin Chen	Modeling of The Intravascular Mixing Phase of Neuromuscular Blocking Agents Following Intravenous Bolus Injection	Clinical PK	G8
Joy C. Hsu	Population Pharmacokinetics of PLX4032, a highly selective V600E BRAF kinase inhibitor, in Healthy Volunteers	Clinical PK	L6
Kyle Baron	Pharmacometric Basis for a Fludarabine Test Dose Strategy in Nonmyeloablative Hematopoietic Stem Cell Transplantation	Clinical PK	N8
Patanjali Ravva	Population pharmacokinetic model of sulopenem and an oral prodrug, sulopenem etzadroxil, in man, including interaction with probenecid	Clinical PK	Q2
Parag Garhyan	Poster: Population Pharmacokinetic Modeling of Enzastaurin and its Major Metabolite in Healthy Subjects and Cancer Patients	Clinical PK	Q6
France Varin	In vivo-In vitro correlation between early systemic exposure and delivered dose of inhaled milrinone using two types of nebulizers.	Clinical PK	Q8
Tushar Garimella	Population Pharmacokinetic Analysis of ABT-089, a Neuronal Nicotinic Receptor Agonist, in Elderly Subjects with Alzheimer's Disease and in Healthy Adult Subjects	Clinical PK	R8
Sandeep Dutta	Population Pharmacokinetics of ABT-594 in Subjects with Diabetic Peripheral Neuropathic Pain	Clinical PK	S5
Susan Willavize	Disease Progression of Cognitive Impairment in Alzheimer's Disease: A Model-Based Approach	Disease Modeling	B8
Lars Lindbom	A Drug Independent Tumor Size Reduction-Survival Model in Advanced Ovarian Cancer to Support Early Clinical Development Decisions	Disease Modeling	E6
Satjit Brar	Hemodynamic Determinants of Clinical Endpoints in Pulmonary Arterial Hypertension Trials	Disease Modeling	F8
Kaori Ito	Disease Progression Analysis from ADNI Database in Normal, MCI and Alzheimer's Disease Patients.	Disease Modeling	J6

WEDNESDAY MORNING			
Name	**Abstract Title**	**Topic**	**Location**
Kristin Karlsson	Performance of the LAPLACE method in repeated time-to-event modeling	Event Driven Non-continuous Data Models	D8
Wei Liu	Modeling “Pain Memory” is Central to Characterizing the Hazard of Dropping Out in Acute Pain Studies	Event Driven Non-continuous Data Models	P8
Ruolun Qiu	Modeling and Simulation of Plasma Abeta in Human After Multiple Oral Doses of PF-3084014, A Potent Gamma Secretase Inhibitor	Exposure-Response	B6
Juan Jose Perez Ruixo	Characterization of Platelet Cell Turnover in Thrombocytopenic Adults with ITP using a KPD model	Exposure-Response	H6
Xiujiang (Susie) Li	Population PK/PD Modeling of Efficacy and Safety of CB1R Inverse Agonist Taranabant in Obese Patients	Exposure-Response	J8
Christine Garnett	Influence of Gender and Study Design on Moxifloxacin Concentration-QT Relationship	Exposure-Response	P6
Sandeep Dutta	Population Analyses of Efficacy and Safety of ABT-594 in Subjects with Diabetic Peripheral Neuropathic Pain	Exposure-Response	S6
Gianluca Nucci	Model-Based Meta-Analysis of Concentration-D2 Occupancy in Healthy Volunteers and Schizophrenic Patients	Exposure-Response	T8
TJ Carrothers	Population Models Correlating Exposure to Efficacy and Safety Markers following Oral Administration of a Novel Fructose-1,6-Bisphosphatase Inhibitor in Type 2 Diabetic Subjects	Exposure-Response	V8
Micha Levi	A mechanistic target mediated drug disposition (TMDD) model is required to correctly estimate the bioavailability of a subcutaneous formulation of Tocilizumab (TCZ), a monoclonal antibody with non-linear kinetics	Mechanistic Modeling/ Systems Biology	D6
Zheng Lu	Pharmacokinetic – Pharmacodynamic modeling of Tumor Growth Data from Mice Following Administration of Drug Candidate	Mechanistic Modeling/ Systems Biology	E8
Jean R. Lavigne	Simultaneous Modeling and Simulation of Glucagon, Glucose and Insulin	Mechanistic Modeling/ Systems Biology	H8
France Mentré	Parameter estimation of long-term HIV dynamic model in the COPHAR2 – ANRS 111 trial using MONOLIX	Mechanistic Modeling/ Systems Biology	M8
William M. Sallas	Population Pharmacokinetics for Penciclovir in Infants and Children for Famciclovir Dosing Recommendations	Pediatrics	K8

WEDNESDAY MORNING			
Name	**Abstract Title**	**Topic**	**Location**
Craig M Comisar	Determination of Operating Characteristics and Performance Requirements for a Vancomycin Forecasting Algorithm Used for Clinical Decision Support in Pediatric Patients.	Pediatrics	U6
Thaddeus Grasela	Forensic Pharmacometrics: Part 1 - Data Assembly	Quality Assurance, Forensic Pharmacometrics	U8
Frank Jen	Characterizing Nelfinavir Pharmacokinetic Changes During Pregnancy in HIV-Infected Women – Modeling and Simulations in Study Design	Special populations	S8
Jakob Ribbing	Use of a Non-Parsimonious Model for Study Design	Study Design/Conduct	G6
Tarek A. Leil	Trial Simulation to Assess the Effect of Patient Compliance on Potential Outcomes in Population PK Studies	Study Design/Conduct	R6
Joerg Lippert	Unified statistical and physiologically-based modeling with PK-Sim® and MoBi®: PBPK meets NLME and MCMC	Tools and Techniques	A8
Sachin Sanduja	Interactive, scalable and modular framework for data analysis: An application to population pharmacokinetic modeling.	Tools and Techniques	C6
Margherita Bennetts	Simulation Methodology for Quantitative Study Decision Making with R/NONMEM6	Tools and Techniques	F6
Jae Eun Ahn	Longitudinal Model-Based Meta-Analysis with NONMEM	Tools and Techniques	K6
Fang Li	Implementation of Computer Cluster for Pharmacometric Analyses at FDA	Tools and Techniques	L8
Joseph Kahn	Simulation Manager in R for Modeling and Decision Analysis	Tools and Techniques	M6
Helen Moore	Mathematical optimization of therapies for chronic hepatitis C virus (HCV) infection	Tools and Techniques	N6
Bill Poland	Optimal Sequencing of Interdependent Drug Development Programs	Tools and Techniques	T6

WEDNESDAY AFTERNOON			
Name	**Abstract Title**	**Topic**	**Location**
Timothy Waterhouse	Using Uncertainty in Exposure-Response Modeling and Simulation to Select Phase II Doses	Benefit/Risk Assessment	A3
Jing Liu	Semi-Mechanism Based Nonlinear PK Modeling and Scaling of a Fully Human Antibody in Cynomolgus Monkeys Predicts the Nonlinear PK in Healthy Volunteers	Biologics	C5
Leonid Gibiansky	Mechanistic Interpretation of Indirect-Response Models for Drugs with Target-Mediated Disposition	Biologics	V5
Leonid Gibiansky	Target-Mediated Drug Disposition Model for Drugs with Multiple Targets	Biologics	V6
Stacey Tannenbaum	A Methodology for Model-Based Bioequivalence of Two Manufacturing Variants of a Monoclonal Antibody	Biologics, Tools and Techniques	J3
Mark Lovern	Use of a Short-Term Viral Dynamic Model to Predict Long-Term Clinical Outcome in Patients Receiving Anti-Retroviral Therapy for HIV-1 Infection	Clinical Outcome Modeling	E3
Michelle Green	Quantitative Understanding of the Impact of Evolving Rescue Criteria in the Assessment of Anti-diabetic Compounds	Clinical Outcome Modeling	F5
Yoon Gyoon Kim	Population pharmacokinetics of PD 0200390, a new calcium channel alpha-2-delta subunit-binding compound	Clinical PK	D3
Seong Bok Jang	The Use of Truncated Area under the Curve as a Measure of Relative Extent in Bioequivalence Studies	Clinical PK	K5
Hongseok Chae	Comparing simulated responses to risperidone and extended release (ER) paliperidone	Clinical PK	M3
Satyendra Suryawanshi	Empirical Disease Progression Model for Ranibizumab in Age-Related Macular Degeneration	Disease Modeling	G5
James A. Rogers	Population Dose-Response Model for ADAS-cog Scores in Patients with Alzheimer's Disease by Meta-Analysis of a Mixture of Summary and Individual Data	Disease Modeling	L3
Nitin Mehrotra	Value of collecting PK in late phase clinical trials	Drug Development	F3
Paul Panorchan	Evaluation of the Dose-Response Relationship to Short-term Monotherapy with the HCV Protease Inhibitor, MK-7009	Exposure-Response	B5
Sriram Krishnaswami	PK/PD of Celecoxib in Pediatric Patients with Juvenile Rheumatoid Arthritis	Exposure-Response	C7

WEDNESDAY AFTERNOON			
Name	**Abstract Title**	**Topic**	**Location**
Sandeep Dutta	Population Pharmacokinetics and Exposure Response of Valproic Acid in Mania Associated with Bipolar Disorder-A Combined Analysis of Two Placebo-Controlled Phase 3 Trials	Exposure-Response	H3
Herbert Struemper	Estimation of the PK-Receptor Occupancy Relationship Based Upon PET Data with Large Test-Retest Variability.	Exposure-Response	N5
Immanuel Freedman	Bayesian Parametric Schild Analysis of Data from a Whole Blood Stimulation Assay.	Exposure-Response	P3
Tonya Quinlan	Pharmacokinetic/Pharmacodynamic Modeling of the Effects of Duloxetine on 3,4-dihydroxyphenylglycol (DHPG) in Plasma and Cerebrospinal Fluid in Healthy Subjects	Exposure-Response	Q3
Ahmed Salem	Pharmacodynamic Assessment of Vancomycin-Rifampin Combination against Methicillin-Resistant Staphylococcus aureus Biofilm	Exposure-Response	S3
Daniele Ouellet	Semi-Physiological Population PK/PD Modeling of Eltrombopag in Healthy Volunteers and Patients with Idiopathic Thrombocytopenic Purpura	Exposure-Response	V3
Michael Pelekis	Mechanistic Evaluation of the Population Systemic Exposure Related to the Use of Acetaminophen using GastroPlus™	Mechanistic Modeling/ Systems Biology	D5
John Harrold	Mechanistic Modeling of Combination Rituximab and rhApo2L Chemotherapy in Mice Bearing Ramos Lymphoma Xenografts	Mechanistic Modeling/ Systems Biology	J5
Mahesh N. Samtani	Simple Pharmacometric Tools for Oral Anti-Diabetic Drug Development: Competitive Landscape for Oral Non-Insulin Therapies in Type 2 Diabetes	Mechanistic Modeling/ Systems Biology	K3
Joerg Lippert	Multi-scale PK/PD modeling and simulation using PK-Sim® and MoBi®: A mechanistic whole-body pharmacogenomics model of tumor growth and cytostatic intervention	Mechanistic Modeling/ Systems Biology	L5
Cornelia Landersdorfer	Population PK/PD Modeling of the Effects of Vildagliptin on Active GLP-1, Glucose, and Insulin	Mechanistic Modeling/ Systems Biology	N3
Fahima Nekka	Evaluation of the Pharmacological Effect Induced by Patient Irregular Drug Intake	Mechanistic Modeling/ Systems Biology	T5
Dana Nickens	A Model-based Dose-response Meta-analysis of Single Agent Intraocular Pressure (IOP) Therapies Used to Evaluate Efficacy of a Potential New Therapy (PF-03187207) in Glaucoma Patients	Model-based meta analysis	U3
Ying Hong	Model-based Analysis to Propose Atazanavir Doses for HIV-Infected Pediatric Patients	Pediatrics	G3
James R. Bosley, Jr.	Pharmacokinetic Modeling, Simulation, and Scaling of Adult and Pediatric Data to Support International Regulatory Submissions	Pediatrics	R5

WEDNESDAY AFTERNOON			
Name	**Abstract Title**	**Topic**	**Location**
Kuenhi Tsai	Sensitivity Analysis on an IVIVC PK/PD Model	Sensitivity analysis	H5
Helen Kastrissios	A Population Pharmacokinetic Model for a Novel Oral Hypoglycemic Formed In Vivo: Comparing the Use of Active Metabolite Data Alone versus Using Data of Upstream and Downstream Metabolites	Special populations	U5
Thu Thuy Nguyen	Design evaluation and optimization in crossover pharmacokinetic studies analyzed by nonlinear mixed effects models. Application to bioequivalence or interaction trials.	Study Design/Conduct	B3
Joakim Nyberg	Optimal design on Time-To-Event models with an emphasis on dropouts in Disease Progression studies	Study Design/Conduct	P5
Partha Nandy	Evaluation of Exposure-response in Flexible Dose Clinical Trials: Comparison of Mixed Model Repeated Measures (MMRM) and Marginal Structural Models (MSM) via a Simulation Study	Tools and Techniques	A5
Mark Sale	Parallel Execution of NONMEM	Tools and Techniques	E5
Jonathan French	MSToolkit – An R library for simulating and evaluating clinical trial designs and scenarios	Tools and Techniques	M5
Holly Kimko	In Vitro – In Vivo Correlation of Extended Release Tablets to Support Proposed Bioequivalence Specifications	Tools and Techniques	Q5
Xiaoli S. Hou	D-optimal Design for PK Modeling	Tools and Techniques	R3
Charles Apelian	MODESIM – A high-performance computing environment for pharmacometrics and beyond	Tools and Techniques	T3

ACoP 2009 Exhibitors

The AEgis Technologies Group

acslX is used in a diverse range of applications in biological modeling including: classical compartmental PK/PD, physiologically-based PK, population PK/PD, disease modeling, systems biology, virtual tissues and organs, and IVIVC.

acslX is intuitive

- Models are constructed using either a simple equation-based language, or by composing models diagrammatically using "blocks" of pre-built model components
- Parameter estimation, sensitivity analysis, and Monte Carlo analysis studies are designed using a simple wizard-based user interface
- Scripts for controlling simulation runs and performing complex analyses can also be created using a Matlab-like scripting language
- Models can be constructed using the PBPK/PK/PD toolkit of pre-built simulation blocks, and an SBML import utility is provided for automatically generating acslX models from SBML

acslX is flexible

- acslX supports a wide range of robust algorithms for the numerical solution of ordinary differential equations, differential algebraic equations, delay differential equations, and discrete event behavior
- Analyses include a robust parameter estimation engine supporting maximum likelihood and nonlinear weighted least-squares techniques; global and local sensitivity analysis; conventional Monte Carlo analyses; and a statistical modeling language for user-defined Bayesian inference studies
- acslX models can be executed and analyzed in a variety of environments, including acslX itself, Microsoft Excel, Mathwork's Simulink/Matlab, and the freely available acslX Calc. Data import/export from Microsoft Access and Excel is easily performed

acslX is fast

- Models are compiled into executable binary code ensuring the fastest possible performance and support for extremely large or complex models
- Cluster computing extensions are provided to parallelize analyses in acslX, and cloud-hosted versions of acslX applications are available

acslX is open

- Models supplied with acslX are open and transparent, meaning the model code can be inspected and modified
- Many of the analyses used in acslX are implemented as M scripts, which can also be inspected and modified by end-users
- Open software interfaces are provided throughout the system for extending the capabilities of the acslX environment in a variety of ways

acslX is affordable

- Licenses for acslX start at $500
- The acslX Calc application for running and analyzing simulations created in acslX is freely downloadable and redistributable
- Corporate site licenses start at $7500
- acslX is completely free for educational use

For over 30 years, acslX and its predecessor ACSL have provided scientists and engineers with a powerful and flexible software environment for modeling, simulation and analysis of complex nonlinear biological systems and data.

More information about acslX is available at www.acslX.com, 800-647-ACSL or info@acslX.com.

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PK-SIM®

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- MoBi® The systems biology software tool for multiscale physiological modeling and simulation.
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Entelos (www.entelos.com) PhysioLab® platforms enable modelers to manage what is quantitatively known and unknown about disease processes, PK/PD, and patient responses to standard and novel treatment combinations, to better inform decision-makers through the robust prediction of clinical outcomes. Our cross-disciplinary teams of Ph.D. scientists and engineers use state-of-the-art PhysioLab technology to conduct in silico R&D in collaboration with our clients' clinical, pharmacometric, and preclinical experts.

Entelos has helped its pharmaceutical partners to:

- Save time and reduce patient requirements for clinical trials
- Determine the optimal dose for a clinical trial
- Compare efficacy of new compounds and combinations to standards of care
- Advance complex clinical strategies to meet efficacy, regulatory, and marketing requirements
- Identify compound/target advantages to support competitive differentiation claims
- Discover novel biomarker panels
- Translate results from preclinical experiments to clinical studies and results

Key features of the PhysioLab platforms and software tools include:

Virtual Patients and Populations are a key part of the PhysioLab technology, enabling the exploration of the full range of patient variability and alternate mechanistic hypotheses all layered on top of the core PhysioLab model. Virtual populations are designed to mirror real clinical populations and are then utilized for running simulated clinical trials and biomarker analyses.

Parameter and Simulation Management is optimized for efficiency in the software thus enabling high throughput and batch simulation runs for evaluation of variant PK, uncertainty in pharmacodynamics, and population variation. The results are stored in an Oracle® database and can be exported for analysis in other tools (e.g., Microsoft® Excel®, SAS®, Spotfire®) and an API enables interfacing with MATLAB and custom scripting.

Integrated Documentation allows data, modeling rationale, and parameter value sources to be annotated within the model and shared between users. This capability supports a corporate knowledge base by providing a knowledge management platform, as well as a learning tool for new users.

PhysioLab platforms are available in the following areas:

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- Respiratory – Asthma
- Autoimmune – Rheumatoid Arthritis, Type 1 Diabetes
- Hematopoiesis – Anemia
- Skin Sensitization

GVK Biosciences, Asia's leading Contract Research Organization, delivers customized innovative and value added services with speed and quality to leading Pharma, biotech and other companies in the area of Life Sciences.

In order to increase the success rate in Clinical Studies, a number of novel and innovative approaches such as PK/PD modeling of clinical data or the usage of Biomarkers are being followed in the recent past. GVK BIO has been offering customized services in both these areas. We have a unique Clinical Biomarker online database (www.gobiomdb.com). In PK/PD modeling and Simulation studies we offer manually curated Clinical Pharmacology databases for a number of Therapeutic areas/indications. These databases and associated custom curation process offer:

- Predictive modeling tools provide invaluable information to better streamline the drug development process
- Modeling approaches prove useful in determining relationships between biomarker responses, drug levels, and dosing regimens of new drugs faster and at a lower cost.
- We build and maintain indication specific clinical trial outcome databases to support simulation and modeling efforts

GVK BIO provides premier quality customized services that are regarded by our clients as highly effective.

Novartis accredits "The partnership with GVK Bio for data extraction and populating the spreadsheet has been established and has proved very effective" - Population Approach Group Europe (PAGE), June 23-26, 2009.

GVK BIO has also partnered with Quantitative Solutions, a modeling and simulation consultancy to the pharmaceutical and biotech industry, to market the existing QS clinical outcomes databases and to develop/market additional databases in high value disease areas.

- The databases capture summary level data for the clinical safety and efficacy outcomes from publicly available data sources. Models derived from them can be used to characterize the probability distribution of clinical efficacy and tolerability as a function of various treatment and patient factors.
- The databases can help companies conduct comparative efficacy and safety analysis, link/scale biomarkers to clinical outcomes, predict/improve trial outcome, and develop product differentiation strategies.
- The databases are supported by customization and M&S consulting services provided by GVK Bio and QS, respectively, to ensure maximum flexibility and benefits to our clients

In the future GVK BIO plans to expand its services from data curation to data analytics, providing modeling and simulation services to support drug development decision making.

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mangosolutions

Mango Solutions is a privately owned data analysis company producing tailored solutions for it's customers. Based in the UK but operating globally Mango have customers on several continents and work with some of the largest companies in the world such as KPMG and BP. Mango work with the biggest companies in the pharmaceutical sector such as Pfizer, Novartis and GSK among others.

Mango have a team of mathematicians, statisticians and IT programmers who provide a range of services including:-

- Customised training courses
- Application development services
- Data analysis consulting
- Support and validation of code

Mango have wide experience of technologies such as R, SAS, S-PLUS and Matlab and are able to integrate and develop these technologies to suit customer requirements. In all engagements Mango's methodology is to work closely with its customers to ensure complete satisfaction.

For more details of how we help our pharmaceutical customers please go to www.mango-solutions.com

MathWorks provides software tools for the entire PK/PD workflow, from modeling to analysis, within a single graphical environment. MathWorks PK/PD modeling environment, SimBiology®, provides point-and-click tools to make PK/PD modeling and analysis accessible, even for researchers with little to no programming experience. Built on MATLAB®, SimBiology provides direct access to an industry-tested simulation solver suite, and allows integration of PK/PD modeling with other functionality such as parallel computing, statistics, and optimization. SimBiology also allows modelers the ability to experiment with new cutting edge trends, such as integrating mechanistic and physiologically-based PK models.

Employing more than 2,000 people, The MathWorks was founded in 1984 and is headquartered in Natick, Massachusetts, with offices and representatives throughout the world. The company has been profitable every year since its inception and is privately held. Over 1,000,000 scientists and engineers in more than 100 countries, on all seven continents, use MathWorks products.

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Metrum Research Group provides contract services aimed at enhancing biomedical R&D through quantitative modeling and simulation. Our collaborations with the pharma/biotech industry are characterized by cutting-edge science, transfer of knowledge, quality deliverables and innovative, strategic application of modeling and simulation technologies. For more info visit: www.metrumrg.com

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Applications of Modeling over the Development Life Cycle of Biologics
Session Chairs: David D'Argenio and Don Mager

Predicting Human Pharmacokinetics-Pharmacodynamics of Biologics from Animal Data

Peiming Ma (1), Juan Jose Perez Ruixo (2)

(1) Amgen, Inc. Thousand Oaks, CA, USA; (2) Amgen, Puzol, Valencia, Spain

Over the years, the field of pharmacokinetic-pharmacodynamic (PK-PD) modeling and simulation (M&S) has clearly moved from using empirical functions to describe the data to developing mechanism-based PK-PD models that reflects the essential underlying physiology and allows for better quantification of the drug disposition and dynamics. Besides the physiology-based pharmacokinetic modeling, different methods have been used to scale the PK-PD properties of small molecules from animal to human. These methods normally are based on the allometry theory and use different approaches to deal with interspecies differences in protein binding and/or renal/liver elimination, which might not be relevant for biologics. In addition, these methods assume the amount of drug bound to the receptor is negligible compared with the dose administered, but the assumption is invalid for most of the biologics. Consequently, predicting human PK-PD of biologics from animal data presents unique challenges. Among them, the interspecies differences in the capacity and the affinity of the drug binding to the receptor, the receptor turnover rate and the immunogenicity are relevant factors to be considered in 1) selecting the relevant specie(s) to conduct adequate PK-PD studies, 2) developing appropriate models for integrating the animal PK-PD data, 3) predicting the human PK-PD properties from animal data, and 4) optimizing the design of first-time-in-man studies. Perhaps due to these complexities, there are only limited examples of interspecies PK-PD scaling successfully applied to biologics. In this talk, we will present examples that show the application of the population PK-PD M&S techniques to factor in these complexities, to successfully predict the human PK-PD of biologics from animal data, and to facilitate the early decision-making processes for planning clinical development strategies.

Modeling and simulations for assessment of pharmacokinetics and pharmacodynamics of a G-CSF biosimilar

Wojciech Krzyzanski (1), Pawel Wiczling (2), Phil Lowe (3), Etienne Pigeolet (3), Martin Fink (3); Alexander Berghout (4), Sigrid Balser (4)

(1) Department of Pharmaceutical Sciences, State University of New York at Buffalo, Buffalo, New York, USA; (2) Department of Biopharmaceutics and Pharmacodynamics, Medical University of Gdansk, Poland; (3) Novartis Pharma AG, Modeling & Simulation, Basel, Switzerland; (4) Sandoz Biopharmaceutical Development, Oberhaching, Germany.

Objectives: Zarzio® (EP2006) is a biosimilar of Neupogen® a recombinant human granulocyte colony stimulating factor (G-CSF). G-CSF is an endogenous protein also administered as a drug to stimulate production of neutrophils. The biological activity of rHuG-CSF is identical to the endogenous G-CSF. The disposition of rHuG-CSF is mostly determined by binding to its receptors that are expressed majorly on neutrophils. The objective of this analysis was to develop a pharmacokinetic (PK) and pharmacodynamic (PD) model that expands existing models of filgrastim to account for an increase in rHuG-CSF clearance upon multiple dosing due to an increase of the G-CSF receptor mediated endocytosis and apply it to describe PK/PD of Zarzio® in healthy volunteers. The model has been used to study the role of the dynamics of the G-CSF receptor pool on the change in C_{max}, AUC, and CL parameters upon multiple subcutaneous injections.

Methods: Healthy male (n=81) and female (n=63) volunteers were treated in four randomized crossover studies with two filgrastim products (Neupogen® and Zarzio®). We show results on modeling the Zarzio® data; to avoid possible period effects, only data from the first period were analyzed. Plasma concentration-time records were evaluated from rich sampling profiles. Filgrastim was administered as repeated s.c. daily administration for one week of 2.5, 5 and 10 μg/kg doses and as single i.v. (5 μg/kg) and s.c. (1 μg/kg) doses. Pharmacodynamic data (blood absolute neutrophil count, ANC) were available for the same time intervals. The PK model included first-order elimination from plasma, receptor binding, and internalization of drug receptors complexes. The PD model consisted of a series of transit compartments that represented the aging populations of neutrophil precursors in the bone marrow pool, and a neutrophil blood compartment. The rHuG-CSF effects were on the acceleration of the differentiation and maturation of the precursor cells and stimulation of the proliferation of the neutrophil progenitors in the bone marrow. The PD model was unable to identify a rHuG-CSF mobilizing effect on neutrophil precursors in the bone marrow and the rHuG-CSF effect of marginalization of circulating neutrophils that have been reported for single dose data. Consequently, these processes were excluded from the final model. All effects were described by the stimulatory Hill functions with a common SC_{50} and process specific S_{max} parameters. A feedback process from ANC controlling the total G-CSF receptor pool was included. Population nonlinear mixed-effect modeling was done using NONMEM VI. The first-order conditional estimation with interaction (FOCE) method was used.

Results: The estimate of the Zarzio® volume of distribution (V_D) was 3 L and the bioavailability of the drug from the subcutaneous site was about 70%. Due to model over parameterization, the PK model of target mediated disposition was reduced utilizing a quasi equilibrium assumption. The estimated typical value of the equilibrium dissociation constant (K_D) was 62 pM which is close to the K_D range 77-140 pM reported for rHuG-CSF. The model depicted the decaying trend in C_{max} values with repeated doses as well as an increase in ANC_{max} values consistently with an increase in the G-CSF receptor pool. Similarly, the calculated clearances after each dose exhibited an increasing pattern. The typical value of SC_{50} = 2 ng/mL was greater than the plasma concentration troughs for the highest SC dose. The estimates of S_{max} values were in the range 30-40 indicating a substantial increase in the neutrophil production upon exposure to the drug. The estimate of the blood neutrophil half-life was 9 h which is consistent with the values reported in the literature.

Conclusions: The presented model expanded previously published PK/PD models for filgrastim and pegfilgrastim by addition of the target mediated drug disposition. The increase in rHuG-CSF clearance upon multiple dosing was attributed to the increased ANCs paralleled by an increase in the total G-CSF receptor density. Simultaneous modeling of Zarzio® plasma concentrations and ANC was necessary to adequately describe PK data.

Population Pharmacokinetic-Pharmacodynamic Modeling of Biological Agents: When Modeling Meets Reality

Diane R Mould PhD, FCP and Bill Frame MS

Projections Research Inc 535 Springview Lane Phoenixville PA 19460 USA

Overview:
The pharmacokinetic and pharmacodynamic behaviors of many biological therapeutic agents have inherent complexities that require specialized modeling approaches in order to develop reliable, unbiased models. Several commonly encountered cases will be presented, including data that has a preponderance of zero values, subjects whose pharmacodynamic trajectories are not predictable based on a structural model, and evaluating models in adaptive dosing situations.

Preponderance of Zero values:
For engineered antibodies, it is not unusual to see high specificity and affinity for the target receptors. The concentration response relationship for these agents is very steep. Thus, many therapeutic monoclonal antibodies that are targeted against cell surface receptors can, at therapeutic doses, saturate these receptors. In this situation, free receptor levels fall to zero and may stay there for protracted periods of time, leading to a large number of zero values in the database. Owing to the assay methodology (usually FACS), the zero values are real observations and cannot be deleted from the database. The distribution of observations is heavy at, and near, the boundary and simple transformation (e.g. converting data to % saturation for instance) does not alleviate this problem. To model such data, a two part model (truncated delta lognormal distribution) may be utilized Zero observations are treated in an altered zero fashion and are modeled as discreet, so that the probability of a zero response is modeled. The natural logarithms of responses with values larger than or equal to 0.1 are modeled as if they arise from a truncated log normal distribution. This approach provides a distinct advantage because the output is a probability curve showing probability of saturation versus MAb concentration, which can be used to guide dose regimens that have optimal receptor saturation.

Models for Indescribable Subpopulations:
Most mixture models identify subpopulations based on bimodal or multimodal distributions of eta values. These subpopulations have an implied association with a missing covariate. In pharmacodynamic models, such subpopulations may arise due to subjects that are poor responders to a specific treatment. However, with biological agents, subject response may be completely compromised due to lack of receptors, or the measured pharmacodynamic marker may be affected due to other events resulting in large, erratic excursions of the marker. These subjects exhibit a large residue random walk around baseline or around a placebo trajectory. While on the average they are non-responders, locally in terms of time these subjects might be hyper-responders.

Eta distributions in this latter situation are often badly skewed but not modal, and transformation is not beneficial. Models are characterized by high residual variability. Stuart Beal proposed an alternative mixture model which he referred to as the "indescribable model". In this unique mixture model, the mixture is based on application of separate functions to a subpopulation where the indescribable population is allowed to progress as an untreated patient might. This latter mixture model also separates out subjects who are non responders, and can provide valuable diagnostic information into the pharmacological behavior of the drug.

Evaluation of models when adaptive dosing is used:
Many biological agents have adaptive dosing strategies which are based on a pharmacodynamic marker of interest. For example, alemtuzumab is targeted against CD52 which is present on lymphocytes, and acts to reduce their number. Dosage adjustments for this MAb are made based on absolute neutrophil count. When pharmacokinetic/dynamic models for agents that use adaptive dosing strategies are developed, the data used to develop the model includes the adaptive dosing. However when predictive checks are conducted with such agents, an adaptive dosing strategy must also be implemented. Failure to account for adaptive dosing in predictive checks can result in biased or inflated prediction intervals because subjects in the simulated data will have undergone dose adjustments for no viable reason. This impacts particularly for pharmacodynamic models, but also affects pharmacokinetic models for biological agents when the pharmacokinetics are affected by the pharmacodynamic response.

Model and Data Sharing Initiatives
Session Chairs: Klaus Romero and Brian Corrigan

TIPharma mechanism-based PKPD modeling platform

Meindert Danhof

Leiden University, Leiden-Amsterdam Center for Drug Research, P.O. Box 9502, 2300 RA Leiden, the Netherlands (www.lacdr.nl)

The "TIPharma mechanism-based PKPD modeling platform" is a public private partnership, sponsored by the Dutch Government through the Dutch Top Institute Pharma (TIPharma) (www.tipharma.com) with 7 industrial and 4 academic partners. The industrial partners in the platform are: Astellas, Eli Lilly, GlaxoSmithKline, Johnson & Johnson PRD, Nycomed, Pfizer and Schering-Plough. The academic partners are: Leiden University (coordinator), State University Groningen, Utrecht University and Erasmus University Rotterdam.

The objective of the platform is the development and implementation of a mechanism-based PKPD model library + a database of biological system specific information for use in drug discovery and development. The platform focuses on three key areas in drug research.

1. Translational pharmacology: the development of mechanism-based PKPD models for the prediction of efficacy-safety from non-clinical investigations. Current research projects focus on cardiovascular safety, neuropathic and schizophrenia.
2. Developmental pharmacology: modeling of the developmental changes in the expression and function of biotransformation enzymes, transporters and receptors in pediatrics. Current research projects focus on cytochrome P-450 isoenzymes, glucuronyl transferases, ABC transporters in renal excretion, opioid receptors, GABA receptors
3. Disease systems analysis: mechanism-based modeling of disease progression. Current research projects in this area focus on osteoporosis, COPD and schizophrenia.

A key feature of the platform is that, where possible, mechanism-based PKPD models are developed using existing data. To this end the partners have agreed to the sharing of data, models and biological system specific information. To enable this, a data management system is developed for semi-automated merging of data sets, data storage, with versioning of analyses, models and results.

The Coalition Against Major Diseases: Review of goals, accomplishments and future plans

Klaus Romero

Critical Path Institute (C-Path), Tucson, AZ

The goal of the Coalition Against Major Diseases (CAMD) is to bring together major pharmaceutical and biotech companies, the U.S. Food and Drug Administration (FDA), the European Medicines Agency (EMEA), the National Institute on Aging (NIA), the National Institute of Neurological Disorders and Stroke (NINDS), and Patient Groups in a collaboration to develop new knowledge that will enhance the industry's ability to develop innovative new therapies. CAMD will focus first on Alzheimer's and Parkinson's diseases and then expand to other areas.

This presentation describes the role and current status of the initial four workgroups that will generate new knowledge resulting in tools to improve the medical product development process. The major deliverables of the coalition are:

- To submit biomarkers to the FDA and EMEA for qualification to accurately diagnose disease, stratify patient populations, and predict patient outcomes.
- To submit quantitative models of disease progression to the FDA and EMEA for qualification that can be used to project the effects of potential diagnostics and treatments, as well as inform the design of clinical trials.
- To develop an integrated database from completed trials in a common Clinical Data Interchange Standards Consortium (CDISC) format usable for research by coalition members and others.

A workgroup has been created to work on each major deliverable. A fourth workgroup was formed to assist in the creation of the dossiers for submission to the FDA and EMEA.

It is not the intent of the coalition to duplicate current efforts already under way in these areas, but instead to leverage existing data and knowledge, create consensus on methods to advance product development, and make the methods available for broad applications. Where appropriate, the resulting applied data and new information will be submitted for FDA review, with the goal to have them qualified, and in all cases, to have them widely available for use in new medical product development.

The coalition is being founded and supported by the Critical Path Institute (C-Path) in collaboration with the Engelberg Center for Health Care Reform at the Brookings Institution. CAMD is a self-governing entity advised by scientists from the FDA, EMEA, and the National Institutes of Health (NIH) and directed by its members, who are pharmaceutical and biotech companies and patient groups committed to advancing the care of patients with neurodegenerative diseases.

OpenDiseaseModels.org: An Open Forum for Collaborative Model Building and Evaluation

William R. Gillespie, Marc R. Gastonguay, James A. Rogers, Matthew M. Riggs

Metrum Institute, Tariffville, CT, USA

Objectives: The objective of OpenDiseaseModels.org is to provide an open forum for collaborative model building and evaluation, driven by the following principles:

1. Development of disease/systems models is an extremely resource-intensive effort.

2. Pre-competitive insight and resources shared across companies/institutions will lead to better systems models than could be developed by a single institution.

3. Open models, which are transparently developed and publicly vetted, will be more widely accepted and will be better positioned to impact the entire scientific/biomedical/health community.

Methods: OpenDiseaseModels.org serves as a home for multiple disease/systems modeling projects. Each individual project is comprised of three participant groups:

The Core Model Development Team is made up of expert modeling and simulation scientists, with prior experience in disease progression or systems biology modeling for the particular biomedical domain of interest. This group serves as the primary developers and maintainers of the model source code and also reviews input from the Advisory Panel and the General Public regarding model revisions and improvements.

The Advisory Panel is comprised of scientists, clinicians, policy makers, and patient advocates with demonstrated expertise or interest in the disease(s) of interest. Their role is to provide guidance to the Core Model Development Team regarding clinical and therapeutic utility, biologic plausibility, and potentially, external research and funding opportunities.

The third group is comprised of contributors from the General Public, including other domain-relevant scientists, clinicians, policy makers, patient advocates, and anyone else with an interest in the modeling project. The role of this group is to impact the model development process by exploring, challenging, and motivating through contributed examples and open discussion.

All participants are allowed download and review model documentation, data and source code, participate in open discussion groups, and contribute new models or data via discussion group uploads.

Similar to open-source software development, the development of open systems/disease models is an iterative development cycle with delivery of key intermediate model milestones, or versions, throughout the course of development. Some important characteristics of OpenDiseaseModel.org development projects are: 1. Models are developed with readily accessible (preferably open-source) modeling tools with model code openly available. Ultimately these models may be translated to a common model language (e.g. an SBML-like language). 2. Full Bayesian modeling methods are emphasized in order to formally include prior information sources in the model development process, and also to facilitate exploration of sensitivity of model-based inferences to parameter (and model) uncertainty. 3. Models are developed using publicly available data, and those data sets are also be openly shared as part of the project. 4. Documentation of modeling efforts, features, improvements, and bug fixes is transparently available within each project. 5. All model code, data sets, and documentation is version-controlled using a modern software development versioning system. 6. Publication of modeling results in peer-reviewed literature must be allowed, and is encouraged, for all development projects. 7. Public review, discussion and extension of models is facilitated via a web-based discussion board. 8. All model code is distributed under the GNU General Public License.

Results: To date, three open model development projects have been initiated at OpenDiseaseModels.org. They include a systems biology model for calcium homeostatis and bone resorption, an Alzheimer's Disease progression model based on the ADAS-cog endpoint, and a schizophrenia disease progression model. Additional projects are in development.

Conclusions: The feasibility of an open, community-based, disease modeling collaboration has been prototyped with OpenDiseaseModels.org. This paradigm also provides an opportunity for integration with other model sharing initiatives, such as FDA's proprietary data based model-sharing efforts, in that ODM.org could provide a forum to host detailed summary level model evaluation data sets and public discussion forums related to assessing the performance of these models.

FDA Disease Models

Christoffer W Tornoe

U.S. Food and Drug Administration, Silver Spring, MD, USA

Objectives: One of the most important and unrecognized issues contributing to drug development and regulatory productivity and quality is the ability to employ prior knowledge to make the best informed decisions.

Initiatives to share clinical data have had little progress in the past and might be a too ambitious initial goal since the data is perceived to be the commercial advantage. At the other end of the spectrum is sharing model parameters which routinely are done through publications and at scientific meetings. However, it is hard to use this type of information since the detail level often is not sufficient to be able to reproduce the results or update it with new data.

Methods: As a potential solution that encompasses the above mentioned problems with sharing data and models, we propose that the Pharmacometrics community align and share knowledge through a system that enables acquiring, storing, analyzing, and reporting information through the development of data standards, tools and script libraries, and report templates to maximize the use of prior knowledge.

Results: Three examples will be presented to illustrate our experience in creating disease databases and templates, standardized scripts and tools for statistical and graphical analyses, and sharing disease models, i.e.

- **Antiviral Information Management System (AIMS):** Implementation of relational database structure, data templates and controlled terms to better leverage prior knowledge to better inform dose selection of new hepatitis C therapies [1].
- **Thorough QT (TQT) Data Analyses and Reporting Tool:** Standardization of TQT data analyses, archiving, and reporting in order to improve productivity, quality, and communication. The TQT tool can also be used as a platform to discuss strengths and limitations of the current methods and collaborate to improve the science [2].
- **Non-Small Cell Lung Cancer (NSCLC)**: Develop quantitative relationship between tumor size and overall survival which allow companies to plug in their drug-specific model components to improve oncology drug development through dose selection optimization and increased trial success [3].

Conclusion: The value of quantitative thinking in drug development and regulatory review is increasingly being appreciated. In order to utilize all available information and resources more efficiently,

The development of a disease databases, standardized scripts and tools, and disease model repositories will allow scientists to more efficiently and effectively use prior knowledge and available resources in the future thereby improving the quality and productivity of both drug development and regulatory review.

References:

[1] Neal, Lauren. *The Antiviral Information Management System (AIMS): Leveraging prior knowledge to inform dose selection of new hepatitis C therapies.* American Conference on Pharmacometrics, Podium Presentation, 2009.
[2] Tornoe *et al*. *Creation of an Automated Thorough QT Data Analyses, Repository, and Reporting Tool for Regulatory Review.* Manuscript in preparation.
[3] Wang *et al*. *Elucidation of Relationship Between Tumor Size and Survival in Non-Small-Cell Lung Cancer Patients Can Aid Early Decision Making in Clinical Drug Development.* CPT 2009 86(2) 167-174.

Dealing with Missing Data in Pharmacometrics
Session Chairs: Marc Gastonguay and Jonathan French

Introduction to missing data issues in pharmacometrics

Jonathan French

Pfizer, Inc., New London, CT, USA

Objectives: In this session we will define the standard statistical concepts underlying missing data research (e.g., missing completely at random, missing at random, missing not at random, ignorability) and discuss the missing data models commonly used in the statistics literature (likelihood-based MAR, and pattern-mixture, selection-, and shared parameter models). We will then relate these to models commonly reported in the Pharmacometrics literature, including those proposed by Hu and Sale [1] and Sheiner, Beal and Dunne [2]. Throughout the talk, we will use real-world examples as motivation.

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[1] C. Hu and M.E. Sale. A Joint Model for Nonlinear Longitudinal Data with Informative Dropout. *J. Pharmacokin. Pharmacodynam*. **30:** 83-103 (2003).

[2] L. B. Sheiner, S. L. Beal, and A. Dunne. Analysis of nonrandomly censored ordered categorical longitudinal data from analgesic trials. *J. Amer. Stats. Assn*. **92:**1235–1255 (1997).

When Should We Be Concerned About Nonignorably Missing Data?

Daniel F. Heitjan

University of Pennsylvania, Philadelphia, PA, USA

Objectives: Statisticians have come to recognize the potential biasing effects of nonignorable missing-data mechanisms. For example, if, say, larger observations are more likely to be missing or censored, then standard estimates such as the sample mean of the observed data (when some subjects are missing) or the Kaplan-Meier curve (when some subjects are censored) are invalid. Methods that attempt to estimate or test the degree of nonignorability are unsatisfactory thanks to conceptual and numerical difficulties associated with nonignorable models. If, however, we can determine that substantial nonignorability would be needed to affect estimates, then standard approaches should be safe to use. The effect of nonignorability would presumably depend on the amount and placement of the missing data. We seek therefore to construct measures of the sensitivity of inferences to the assumption of a nonignorable missing-data mechanism.

Methods: I propose to evaluate local sensitivity to nonignorability. [1] The method involves evaluating the effect on key parameter estimates of small departures from an ignorable model. The necessary computations are straightforward and do not involve the estimation of nonignorable models.

Results: An example from a cancer clinical trial that is subject to dropout illustrates the method's simplicity, flexibility and value in answering questions that can reasonably be answered. [2]

Conclusion: Sensitivity to nonignorability is a meaningful notion that one can readily quantity and compute directly even from complex data structures.

References:

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[2] Ma, Guoguang, Troxel, Andrea B. and Heitjan, Daniel F. (2005). An index of local sensitivity to nonignorable dropout in longitudinal modeling. *Statistics in Medicine* **24**, 2129–2150.

The Impact of Missing Data on Model Evaluation

Marc R. Gastonguay

Metrum Institute and Metrum Research Group LLC, Tariffville, CT, USA

Objectives:

Simulation-based model evaluation methods, such as the posterior predictive check and other related methods, have become a standard for assessing the performance of nonlinear-mixed effects models in pharmacometrics. The impact of missing data is, however, often ignored when interpreting model checking results. The objectives of this presentation are:

1. To identify situations in pharmacometrics where missing data may impact interpretation of model evaluation methods,
2. To suggest methodological solutions for the appropriate implementation of model evaluation under missing data conditions, and

3. To illustrate proposed solutions with real-world examples

Methods: Examples of simulation-based model evaluation methods in the pharmacometrics literature have been reviewed, with respect to their treatment of missing data. In the majority of cases, the impact of missing data has been ignored, and simulations conducted under complete data assumptions were compared with incomplete observed data. In a small number of cases, the impact of missing data has been acknowledged by either: 1) developing models for the missing data, assuming a missing-at-random (MAR) mechanism, incorporating the models for the missing data mechanism as part of the simulation for model evaluation purposes, and comparing the observed and simulation incomplete-data sets; or 2) implementing single or multiple imputation methods to augment the observed data records and create a complete observed data set, which is then compared with a complete-data simulation.

Results: Simulation-based model evaluation methods that did not incorporate the impact of missing data often provided a misleading assessment of model performance. Assuming MAR mechanisms, both the model-based and imputation-based solutions provided a more appropriate assessment of model performance.

Conclusions: Implementation of model evaluation methods, without considering the impact of missing data, results in misleading assessments of model performance. Solutions to this problem are relatively straightforward when the missing data mechanism is MAR, but none of the proposed model evaluation methods are valid if the missing data mechanism is MNAR. A formal sensitivity analysis should be conducted to explore the impact of missing data due to MNAR mechanisms.

References:

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4. Karlsson MO & Holford N. A Tutorial on Visual Predictive Checks. PAGE 17 (2008) Abstr 1434 [www.page-meeting.org/?abstract=1434]

Where will the pharmacometricians of the future come from?
Session Chairs: Bernd Meibohm and Hartmut Derendorf

Hartmut Derendorf(1), Bernd Meibohm(2), Sandra Allerheiligen(3), David Cadieu(4), Amita Joshi(5), Richard Lalonde(6)

(1) University of Florida, Gainesville, FL; (2) University of Tennessee Health Science Center, Memphis, TN; (3) Eli Lilly & Co., Indianapolis, IN; (4) KDC Group, Inc., Lawrenceville, NJ; (5) Genentech Inc., South San Francisco, CA; (6) Pfizer Inc., New London, CT

The discipline of pharmacometrics has evolved over decades from an often ad-hoc collection of straightforward analytical methods to a sophisticated, rigorous and multi-pronged approach for the descriptive and mechanistic interpretation of exposure-response relationships. Its impact has also increased in all facets of drug development, since the cluster of skills that define pharmacometrics provides powerful tools to maximize the information flow between for example preclinical and clinical development. However, the successful use of pharmacometrics requires considerable technical expertise, both with highly developed computational and algorithmic concepts (which include advanced statistical techniques and numerical simulations), and with the biological mechanisms of physiology, pathophysiology and action of drugs and biologics, which must be summarized in relatively simple mathematical-statistical expressions amenable to computer solution.

The pharmaceutical industry is currently facing a shortage of this kind of eclectic professional, caused at least in part by a “perfect storm” of circumstances in academic and industrial quarters. These include a reorientation of pharmaceutical sciences departments across the country’s universities during the last decade to a strong emphasis on molecular biological sciences and the consequent fading of the discipline of pharmacokinetics and clinical pharmacology. One of the main reasons for this reorientation on basic sciences is the limited availability of federal funding opportunities in pharmacokinetics and clinical pharmacology. Private and public institutions have started to look at nontraditional disciplines, such as biomedical engineering, to fill the gap.

The session will initiate a discussion about the discrepancy between the need for pharmacometricians in industry, research institutes and regulatory agencies and the number of scientists trained in this area by academic programs in the U.S. and beyond. The panel discussion will highlight the problem and its causes, and will discuss potential solutions to overcome this shortage of pharmacometricians in the mid- and long-term.

Development and utilization of disease models
Session Chairs: Mats Karlsson and Marc Pfister

Mechanism-based disease model for SGLT2 inhibitors in Type 2 Diabetes Mellitus (T2DM) Subjects

Chee Ng, Liping Zhang, Marc Pfister

Discovery Medicine and Clinical Pharmacology, Bristol-Myers Squibb, Princeton, NJ

Background/Aim: A novel approach to reducing serum glucose in T2DM is by inhibition of glucose reabsorption in the kidney via sodium-glucose co-transporter (SGLTs)-mediated pathway. Dapagliflozin (DAPA) is the first in a new class of selective oral SGLT2 inhibitors currently in development for the treatment of T2DM. The objective of this study is to develop a mechanism-based disease model that characterizes plasma-urine glucose relationships in placebo- and DAPA-treated T2DM patients in clinical studies.

Method: A two-compartment linear exposure model with Weibull reabsorption was used to describe DAPA concentration-time profiles. The proposed mechanism-based disease model consisted of (i) a two-compartment linear model with first-order absorption, endogenous production and elimination of serum glucose, (ii) a kidney compartment with glucose filtered by glomerulli and reabsorbed via SGLT-mediated pathway, (iii) a structural component to account for the circadian rhythm of endogenous glucose production, and (iv) an inhibitory Emax model to characterize the drug effect on SGLT-mediated glucose reabsorption. Hybrid iterative-two-stages (ITS) and Monte-Carlo Parametric Expectation Maximization (MCPEM) estimation methods implemented in a distributive/parallel computing platform were used to develop a final glucose plasma-urine model and obtain population parameter estimates.

Results/Conclusions: The final urine-plasma glucose model was able to describe serum and urine glucose profiles and showed good ability to simulate data. Such a mechanism-based disease model can be utilized (i) to better understand the role of SGLT-mediated reabsorption pathway in the regulation of serum glucose, (ii) to characterize the theoretical maximum effect of SLGT2 inhibitors in T2DM, and (iii) to estimate important physiological parameters (e.g., individual maximum glucose reabsorption capacity) using routine clinical data.

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Empirical Disease Progression Model for Ranibizumab in Age-Related Macular Degeneration

Satyendra Suryawanshi, PhD (1), Peter Kuebler, PharmD (2), Nitin Mehrotra, PhD (1), Bernd Meibohm, PhD, FCP (1)

(1) Departments of Pharmaceutical Sciences, University of Tennessee Health Science Center, Memphis, TN, USA; (2) Genentech Inc., South San Francisco, CA, USA.

Objectives: To develop an empirical disease progression model that describes the progressive loss of visual acuity in age-related macular degeneration (AMD) and to quantify the time course of its modulation by ranibizumab, a humanized antibody fragment against vascular endothelial growth factor-A (VEGF-A).

Methods: Time courses of visual acuity assessed with the Early Treatment Diabetic Retinopathy Study (ETDRS) charts at 2 m test distance were obtained from 716 subjects enrolled in MARINA and 184 subjects enrolled in PIER, two phase III multicenter, randomized, double-masked, sham-controlled clinical trials. Subjects were randomized at a 1:1:1 ratio to receive 0.5 mg ranibizumab, 0.3 mg ranibizumab or a sham injection. To allow for a combined analysis of the two studies, only data of observation periods with the same dosing frequency (once monthly) were considered, i.e. the first 3 months of the PIER data and the complete 2-year MARINA data. Decline in visual acuity in AMD was modeled as a negative monoexponential process that asymptotically approaches a stable value. The dose-dependent effect of ranibizumab on visual acuity was modeled as the combination of two components, a symptomatic effect (reversible gain in letters) and a protective effect (reduction in disease progression). The model was developed using NONMEM VI with FOCE.

Results: The model estimated visual acuity at baseline (~54 letters) decreased asymptotically with a first-order disease progression rate (K_{pro}) of 0.0014 day^{-1}. The model-estimated high between-subject variability of 179% for K_{pro} is supported by the observed data. The protective effect of ranibizumab after once monthly administration was comparable for the 0.5 mg and the 0.3 mg dose level (69.2% vs. 67.9% reduction in K_{pro} or 8.4 letters vs. 8.2 letters saving that has resulted from slowing the progression over a two-year period). Similarly, the symptomatic effect (12.7 (95%CI 9.85-19.77) letters for '0.5 mg once monthly' dose vs. 12.4 (95%CI 9.35-19.5) letters for '0.3 mg once monthly' dose) was indistinguishable between doses. A visual predictive check demonstrated agreement for central tendencies and 90% CI of observed data and 300 simulated data sets.

Conclusions: The empirical disease progression model characterized the change in visual acuity over time and allowed to determine the treatment effect of ranibizumab after once monthly doses. The results further support the symptomatic and protective benefit of ranibizumab in AMD and provide model-based evidence for a change in the rate of disease progression under ranibizumab therapy.

The Antiviral Information Management System (AIMS): Leveraging prior knowledge to inform dose selection of new hepatitis C therapies

Lauren Neal (1), Debbie Birnkrant (2), Ying Chen (1), Joga Gobburu (1), Peter Lee (1), Jules O'Rear (2), Jeff Murray (2), Kellie Reynolds (1), Guoxing Soon (3) and Pravin Jadhav (1)

(1) Office of Clinical Pharmacology, U.S. Food and Drug Administration; (2) Division of AntiViral Drug Products (DAVP), U.S. Food and Drug Administration; (3) Office of Biostatistics, U.S. Food and Drug Administration

Objectives: Dose selection and informative trial designs are key elements in the development of successful anti-Hepatitis C virus (HCV) treatments. With more than two dozen new HCV molecules in development, drug developers have the opportunity to achieve increased cure rates and improve tolerability. The Antiviral Information Management System (AIMS) proposes a framework to improve dose selection through (1) a structured database to archive HCV data in a queriable manner, and (2) an automated analysis tool to inform trial design elements. Successful implementation of the AIMS initiative will advance our understanding of viral RNA kinetics and provide quantitative solutions to trial design challenges. The initiative is well aligned with FDA's Critical Path Initiative in fulfilling our obligation to improve the health of the HCV patient population.

Methods: As a part of the AIMS initiative, industry and FDA scientists will work together to make crucial decisions about dose selection. Optimized dose finding for novel HCV agents will minimize the risks of toxicity due to too high a dose while limiting treatment failure and development of resistance due to too low a dose. With the increasingly rapid pace of development in this area, the use of prior knowledge and quantitative analysis are especially important for informing trial design. The AIMS initiative supports early discussion about dosing between industry and FDA, ideally no later than the End of Phase 2A. The AIMS tool will use a combination of pharmacokinetic and viral RNA dynamics modeling to estimate system and virus parameters and simulate clinical trials in order to answer specific trial design questions. For example, the tool will help identify an appropriate range of doses for testing in the proposed trial and provide quantitative support for dosing decisions. The tool will help FDA and industry choose doses to maximize virologic response rates while considering noncompliance, tolerability, dropouts etc.

Results: The main goal of AIMS is to improve the efficiency of the anti-HCV drug development process by using prior knowledge and quantitative methods for dose selection. Collaboration between industry and FDA scientists is essential for successful implementation and, therefore, efficient drug development. First, early communication will ensure earlier decisions about dosing. Second, the standardized data template will ensure efficient archival of the data submitted by industry sponsors in the AIMS database for meta-analyses of individual or classes of drugs. Third, the analysis tool will allow FDA and industry scientists to make dosing decisions through quantitative methods.

Conclusions: The AIMS initiative is the first FDA knowledge management initiative used to proactively archive disease data and apply trial simulations to inform dose selection. Although proprietary data will remain confidential, models and quantitative analysis techniques will be shared to encourage collaboration among FDA, industry and academic scientists to guide the HCV drug development process by addressing therapeutic challenges at each step. The implementation of AIMS will promote efficient and successful development and approval of emerging anti-HCV treatments to improve the health of the HCV patient population.

Acknowledgements: We would like to acknowledge important contributions of the scientists from Clinical Pharmacology (Shashi Amur, Vikram Arya, Stanley Au, John Lazor, Fang Li, Shirley Lu, Sarah Robertson, Jenny Zheng); Antiviral Drugs (Russ Fleisher, Linda Lewis, Lalji Mishra, Lisa Naeger, Scott Proestel, Kim Struble) and Biostatistics (Fraser Smith, Susan Zhou) divisions of the FDA.

A Modeling Framework to Simulate Motesanib Efficacy in Thyroid Cancer

Rene Bruno (1), Laurent Claret (1), Jian-Feng Lu (2), Yu-Nien Sun (2), Daniel E. Stepan (2),

(1) Pharsight Corporation, Marseille, France; (2) Amgen Inc., Thousand Oaks, CA, USA

Objectives: Motesanib is a highly selective, oral inhibitor of VEGF receptors 1, 2, and 3; PDGF receptor, and Kit that has antiangiogenic and direct antitumor activity. A modeling framework that simulates clinical endpoints, including objective response rate (ORR) per Response Evaluation Criteria in Solid Tumors (RECIST) and progression-free survival (PFS), was developed to support clinical development of motesanib. This study evaluated the framework using results from a study of motesanib in thyroid cancer.

Methods: Models for tumor growth inhibition [1] with drug effect driven by area under the motesanib concentration versus time curve (AUC) (as predicted by a population pharmacokinetic model), overall survival, and probability and duration of dose reductions were developed based on data from 93 patients with differentiated thyroid cancer (DTC) [2] and 91 patients with medullary thyroid cancer [3] enrolled in a phase 2 study who received motesanib monotherapy (125 mg once daily [QD]). The full simulation framework was assessed in predicting dose intensity (starting dose of 125 mg QD), tumor size over time, ORR, and PFS. Dose-response simulations were performed in DTC patients. The model for prediction of survival times followed a Weibull distribution with ECOG performance status, baseline tumor size, and change in tumor size from baseline at week 7 as predictors. An ordered categorical model combined with a Weibull model was used to describe the relationship between the probability and duration of dose reductions and AUC.

Results: Time to event Weibull models correctly predicted median daily exposure intensities up to week 24 with dose reductions and dose interruptions. The predicted ORR in DTC patients was 15.0% (95% prediction interval [PI], 7.5%–23.7%) compared with the observed ORR of 14.0%. Predicted median PFS was 40 weeks (95% PI, 32–49 weeks) compared with the observed median PFS of 40 weeks. Dose-response simulations confirmed the appropriateness of 125-mg QD dosing in DTC: the modeling framework predicted that no clinically relevant improvement in PFS would be obtained by dose intensification.

Conclusion: This modeling framework (dose reduction/tumor growth inhibition/survival) will be an important tool to simulate clinical response and support clinical development decisions. Further evaluation of the model using additional datasets will be required.

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[2] Sherman SI et al. N Engl J Med 2008;359:31-42.

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New Directions in Cardiovascular Modeling: From Biomarkers to Clinical Outcomes and Comparative Effectiveness
Session Chairs: Christine Garnett and Richard Lalonde

The RAAS Hypertension PhysioLab platform: A Systems Modeling Approach to Hypertension.

Ramprasad Ramakrishna (1), Anna Georgieva(1), Ramesh Sarangapani(1), Arthur Lo(2), Jennifer Beh(2), Sergey Ermakov(2), Saroja Ramanujan (2), Manoj Rodrigo(2), Stuart Friedman(2), Gabriel Helmlinger (1), Deborah Keefe (1), Alan Charney (1),William P. Dole (1), David Feldman (1), Hector De Leon(2).

(1) Novartis Pharmaceuticals, East Hanover, NJ, USA. (2) Entelos Inc., Foster City, CA, USA.

The RAAS Hypertension PhysioLab model presented here integrates biological, pathological, and therapeutic knowledge around the renin angiotensin aldosterone system (RAAS) and the effects of pharmacological intervention in this pathway on the progress of hypertension-related kidney disease. The general model comprises a series of modules including blood pressure (BP) regulation, renal function/dysfunction (glomerular filtration rate [GFR] and albuminuria), and systemic and intrarenal RAAS. Appropriate calibration and sensitivity analysis to refine the models in an iterative fashion will be discussed.

Virtual patients (VPs) and populations (Vpop) representing the range of physiology of specific phenotypes of interest are generated by constraining a set of response type (RT) criteria, a collection of feasible clinical measurements and values for a given phenotype. The mechanistic axes utilized to generate diversity of hypertensive VPs included: proximal and distal nephron sodium reabsorption, total peripheral resistance, preglomerular resistance, and hydrostatic glomerular conductance. A stepwise exploration of these mechanistic axes generated different combination sets, categorized as candidate VPs. These were further filtered to meet the criteria for phenotypic feasibility defined by the appropriate RTs. The effects of drugs, biologics or lifestyle modifications can then be tested (stimulus response tests, SRTs) in single VPs, cohorts and entire Vpops and examples of this approach will be presented.

The mechanistic basis of the RAAS Physiolab and the complementary VPs and Vpops approach provide a unique means of exploring the effect of RAAS and non-RAAS blockers on long-term hypertension progression.

Conceptual Framework for Evaluating the CV Risk Manifested By Drug induced Elevations in Systolic Blood Pressure

Rajanikanth Madabushi

U.S. Food and Drug Administration, Silver Spring, MD, USA

Objectives: Decades of research has established blood pressure as one of the strongest independent risk factors for cardiovascular morbidity and mortality. Subsequently, blood pressure reduction has become one of the most, if not the most, aggressively targeted goals in preventive medicine. Analyses of observational data have demonstrated that even small reductions in blood pressure, on a population level, could have a substantial public health impact on the prevalence of cardiovascular disease. Conversely, such data can also be used to estimate the effect that small increases in blood pressure may have on a population. Our goal is to leverage the quantitative relationship between blood pressure and the risk of cardiovascular disease for understanding the potential of drugs for chronic use to elevate the blood pressure and eventually the cardiovascular risk. We believe that this understanding will eventually lead to designing of trials that will allow for characterization of cardiovascular risk due to unintended elevation in blood pressure.

Methods: A survey of the literature was performed to summarize and identify the quantitative relationships characterizing the relationship between changes in systolic blood pressure and cardiovascular risk in epidemiological studies. Simulations were preformed utilizing this relationship to understand the effect of small unintended elevations in systolic blood pressure and the cardiovascular risk. The NHANES database and data from internal submission were used to create patient population. A bootstrap approach was utilized to calculate baseline cardiovascular disease (CVD) risk. Small elevations in systolic blood pressure in an additive fashion were simulated for three different scenarios (normal population, high risk population and a population from a regulatory submission) and the resulting CVD risk was calculated and plotted.

Results: A gender specific multivariable risk function that predicts risk of developing CVD and of its constituents (coronary heart disease, stroke, heart failure and intermittent claudication) developed by D'Agostino etal[1] was adopted to perform the simulations. The model was used to simulate the probability of 10-year survival which was predicted on risk factors such as age, total cholesterol, HDL, systolic blood pressure, treatment for hypertension, smoking status and diabetes. Increase in blood pressure resulted in increase in CVD risk in all the three scenarios. Elevations as small as 2 mm Hg result in 3 additional CVD events per every 1000 males over a 10 year period. The tolerability to the elevation in systolic blood pressure depends upon the expected benefit. Based on the simulations, a conceptual framework of a study design intended to capture small elevation in blood pressure and the corresponding CV risk was developed.

Conclusions: Small elevations in systolic blood pressure result in increased CVD risk. They should be clearly understood for chronically used drugs in order to better characterize the benefit-risk. The current work explores the utility of a quantitative relationship to understand the impact of small elevation in blood pressure. Future work will further evaluate other quantitative relationships with an ultimate aim to design focused trials for detecting drug effects on blood pressure and how they can be factored into the benefit-risk discussion.

References:

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Quantitative Approaches for Comparative Effectiveness and Pharmacoeconomics

Jens Grueger, PhD

Pfizer Inc. New York

Successfully developing and commercializing a new drug is increasingly difficult, lengthy and costly: in addition to concerns over safety, new customers (payers) are requesting additional information from manufacturers including comparative effectiveness and pharmacoeconomics. Particularly in disease areas where several classes of effective medicines have been available for many years and now often from multiple sources at generic prices, the criteria for market access for a new product are high. Not all of these criteria and expectations can be fulfilled in the traditional clinical development paradigm based on randomized double-blind clinical trials, optimized towards demonstrating efficacy in homogeneous well characterized patient populations. In this presentation I will discuss new quantitative approaches for addressing these issues, including the use of Bayesian methods, adaptive trial design and trial simulation for comparative effectiveness and pharmacoeconomics during clinical development. In addition, there is increasing recognition of the value of post-launch real world data collection to validate hypotheses that could not be investigated during clinical development.

Communication through Graphics: Looking at Data, Models, and Results
Session Chair: Andreas Krause

Exploratory Data Visualisation: Taming the Technology

Richard Pugh (1) and Niclas Jonsson (2)

(1) Mango Solutions, Chippenham, UK; (2) Exprimo, Upssala, Sweden

Objectives: The primary objective is to show a range of novel methods to visualise data in order to drive model selection, with particular emphasis on the necessary interactive nature of this process. Having presented a range of graphical methods, a secondary objective will be to show how these tools can be made available to all modellers, ensuring technology is not a barrier to advanced visual analysis.

Methods: Initially, the presenter will use the R language in order to generate the more common graphical methods for data evaluation. The presenter will then extend this to encompass more complex, innovative and interactive graphics that will lead to more effective model selection. This first section will establish that, with appropriate knowledge of such technologies, effective insights can be made that aid the modelling process.

The first section of the presentation will present interesting graphical methods using the advanced use of a technology. This, in itself, presents an issue: are these graphical tools therefore available only to those with sufficient skill in a particular software?

The second section will address an issue which is common to this type of presentation: how modellers who need the ability to create novel outputs can have quick, yet consistent, access to these tools. This will be illustrated by experienced gained from working with M&S groups who have, themselves, aimed to resolve this issue.

Results: Graphical methods will be presented to drive model selection, with a serious of suggested processes and technologies that can ensure these methods can be widely distributed within a M&S department.

Conclusions: Complex software can be readily embedded within a M&S groups processes and systems, in order to provide a platform for model selection using both standard and novel graphical tools.

Visualizing PK/PD Models using Berkeley Madonna

Andreas Krause

Actelion Pharmaceuticals, 4123 Allschwil, Switzerland.

Objectives: Present and discuss methods for effective visualization and communication of models and modeling results to technical and non-technical audiences. Assess the quantitative contributions of model components such as placebo effect, circadian rhythm, and tolerance as well as the individual covariates towards the change in pharmacokinetic and pharmacodynamic parameters.

Central aim: communicate an intuition for a model and its components to facilitate team discussions of modeling results.

Methods: Purely graphical methods, largely using Berkeley Madonna and its interactive techniques.

The presentation focuses on effective visualization and communication of PK/PD models to a wider audience that might include medical doctors, drug safety experts, pharmacologists, and managers.

Starting from a population PK model with covariates we illustrate graphically the relevance of covariates on the concentration-time course.

The PK model is extended to the PK/PD model that includes components such as a placebo effect, circadian rhythm, and tolerance. The model components are assessed graphically to help understanding of the relevance of the different components involved in the model.

In a next step, demographic and baseline covariates are analyzed for their relevance towards efficacy and safety parameters to arrive at dose-response profiles. The approach naturally leads to interactive exploration of alternative doses and dosing regimens using graphical tools.

Even simulations with particular setups can be conducted interactively. We will show an example of simulations that are run by moving a slider to select particular configurations.

We have been very successful in using Berkeley Madonna as the communication tool, and the presentation aims at highlighting the efficiency of interactive graphical methods to facilitate communication about models and thus compound characteristics. The clinical team

Alongside, we will show a few details of the underlying Berkeley Madonna code to enable the audience to start using the tool easily.

Results: The discussion of model and thus drug characteristics led to considerations of alternative drug administration. Studies are currently ongoing to substantiate the evidence of the model-predicted effects.

Conclusions: Using graphics enables the modeler to assess model characteristics easily, for example judgment about the adequacy of alternative structural models. Once the model is fully developed, graphics substantially facilitate the communication about the model to a non-technical audience, and it helps the modeler establish the relevance of the results with clinical teams. Interactive intuitive setups like the scripts created by Berkeley Madonna can even be given to clinical team members for their own explorations of the model. The approach leads to better questions by the clinical team members and appreciation of model-based approaches.

References:

[1] Berkeley Madonna home page: http://www.berkeleymadonna.com/

Simulation Graphics to Enable Model-Based Decision Making

Kevin Dykstra

Pharsight, Strategic Consulting Services, St. Louis, MO, USA

Objectives: Describe graphical presentation techniques that enhance decision making on the basis of MBDD simulation methods

Methods: Once a drug and disease model has been constructed and appropriately qualified, it is reasonable to ask "Well, so what?" While characterization of the data is frequently very useful in itself, drug development teams use models to best effect when they employ simulation to explore conditions (e.g., doses, population covariates, alternative formulations) that have not been directly studied, or to identify advantageous development scenarios. The impact of excellent simulation work can be greatly enhanced by well-executed visualization of the main results that clearly communicate findings, insights and clarify the inherent benefit-risk tradeoffs associated with drug development . A "killer graph" is the visual that displays the essence of the key insights and brings the development decisions impacted by the modeling into sharp focus for the entire clinical project team and other critical stakeholders, including senior management and regulatory authorities, who will review the work. We will discuss different types of simulations, visualizations for decisions based on clinical trial simulation vs. population simulations, graphics to aid decisions made on the basis of single vs. multiple endpoints, visual "decomposition" of disease progression-placebo effect-treatment effect, ways of enhancing the presentation of tables, and how complex decision criteria can be addressed in a compact and informative fashion.

Conclusions: Effective use of graphs and other visualization techniques and tools can significantly enhance the communication of complex modeling and simulation results for multi-disciplinary drug development experts. and decision-makers.

Event Driven/Non-continuous Data Models
Session Chairs: Raymond Miller and Celine Dartois Sarr

Exposure-Response Analysis for Spontaneously Reported Dizziness in Pregabalin Treated Patients with Generalized Anxiety Disorder.

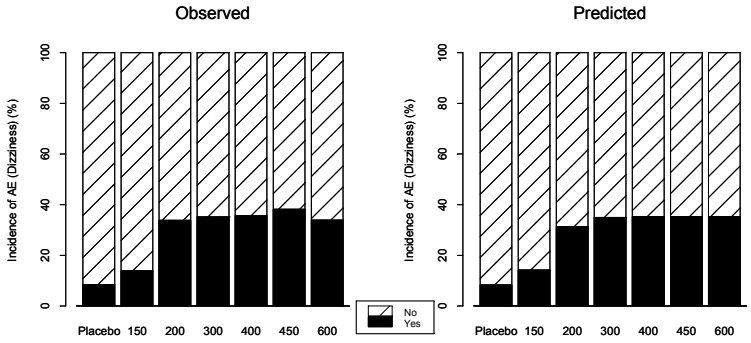
Kaori Ito, Matt Hutmacher, Jing Liu, Ruolun Qiu, Bill Frame, Raymond Miller

Pfizer Global Research and Development (New London, CT, Ann Arbor, MI)

Objectives: To describe the pregabalin exposure-adverse event (dizziness) relationship in patients with Generalized Anxiety Disorder (GAD).

Methods: Separate models were developed for the incidence of adverse event and for the conditional severity (0=none, 1=mild, 2=moderate, 3=severe) of adverse event given that an adverse event has occurred in 6 clinical studies in patients with GAD. The incidence component was modeled using a nonlinear logistic regression model. The conditional severity component was modeled as an ordered categorical variable with a proportional odds model. The exposure response relationship was evaluated as or linear or Emax relationship. To describe the time-course of severity, time-dependent effect (placebo effect, exposure effect, and tolerance effect) were also included. A Markov element was introduced to account for the correlation between adjacent observations.

Results: The dataset prepared for the 6 studies consisted of 47218 observations collected in 1630 patients. For the incidence model, a sigmoid Emax model best describes the dose-AE response relationship. Figure 1 shows the mean observed and predicted incidence by dose, including a summary of observed and predicted values with 95 % CI obtained from a non parametric bootstrap. For conditional severity, the model that best described the data was an Emax model with placebo time-course effect and a component that allows for an exponential attenuation of the AE severity. To account for the correlation between adjacent observations a Markov element was added to the model to obtain estimates of the cumulative probabilities of the AE's score given the preceding observation. Observed and predicted conditional probability plots with the Markov model are presented in Figure 2. These plots demonstrate that model fit is dramatically improved by incorporating the Markov element. To evaluate the predictive properties of the model, a posterior predictive check was performed. One hundred data sets were simulated from the final conditional severity model with and without the Markov element and the number of transitions between each possible transition were calculated. The numbers of observed transitions for all combinations were contained within the predictive check distributions from the Markov model, while the number of transitions were extremely overestimated or underestimated without the Markov element.



Daily Dose (mg/day)	Dizziness Incidence (%)	
	Observed	Predicted (Mean and 95%CI*)
Placebo	8.5	8.2 (5.8-10.9)
150	13.8	14.2 (9.6-19.1)
200	33.8	31.3 (22.7-37.3)
300	35.2	35.0 (31.7-38.2)
400	35.7	35.2 (32.9-38.5)
450	38.2	35.3 (32.9-38.7)
600	33.8	35.3 (33.0-38.7)

* obtained from non-parametric bootstrap (n=1000)

Figure 1. Mean Observed and Predicted Incidence of Dizziness

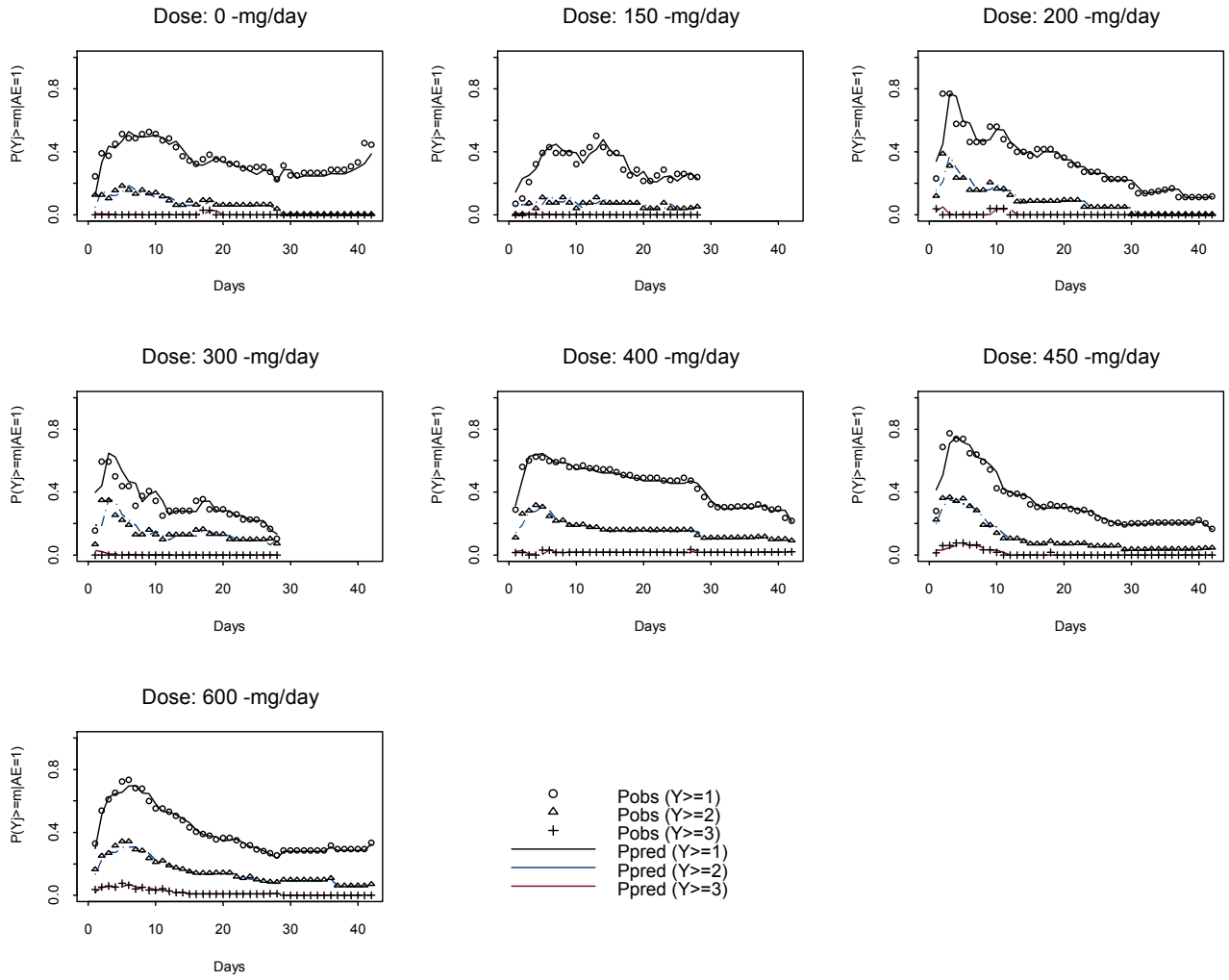


Figure 2. Observed and Predicted Conditional Probabilities for Dizziness by Dose (Markov)

Conclusions: The probability of experiencing dizziness during any day increases with pregabalin daily dose. The predicted mean incidence of dizziness was around 35 % at daily dose of 200 mg/day or greater, which was at least 2 fold higher compared to those at daily doses <150 mg/day. The most frequently reported severity was mild to moderate. The risk of mild or moderate dizziness increases up to 25 % within 1 week, but declines to around 7 % over 3 to 4 weeks. The proportional odds model including a time course of appearance and disappearance of adverse event could adequately describe the time-course of probability of dizziness. Incorporating a transition model including Markov elements improved the model fit and greatly improved the predictability of the time-course of probability of dizziness.

Impact of Dosing Regimens on Dropout Across Pregabalin Trials in the Treatment of Generalized Anxiety Disorder

Bojan Lalovic

Pfizer Global Research and Development (Groton, CT, Ann Arbor, MI)

Dropout represents an important clinical trial endpoint, which can be analyzed using time to event models which incorporate daily dosing (titrations) or other time varying information. Dropout has been historically mitigated based only on subjective and empirical clinical judgment. This presentation outlines a model-based strategy to predict prospective dropout based on a dose-adverse event-dropout model[1-2]. This dropout analysis is based on data from pregabalin clinical trials, which assessed the treatment of generalized anxiety disorder (GAD).

Dizziness was the predominant adverse events (AEs) reported representing a major determinant of study withdrawal (dropout) across the pregabalin GAD trials. Adverse-event incidence was modeled as a time-to event process, allowing incorporation of daily dosing (titrations) as a time-varying covariate. Conditional severity of adverse events was described as an ordered categorical variable with proportional odds accounting for both the time-course of effect and correlation between adjacent observations[3-4].

Subsequently, to model adverse event-based dropout, parametric, discrete-time, hazard models were fitted using dizziness severity as a time-varying covariate. A log-linear hazard model adequately described the decreasing dropout hazard over time for individuals with severe and moderate dizziness. Hazard was approximately constant for individuals reporting no or mild dizziness. Predictions of dropout were evaluated against the nonparametric (Kaplan Meier) estimates as a predictive check and data from an independent trial. Prospective simulations highlight the utility of this approach in examining dropout based on untested titration scenarios for future GAD trials.

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Apnea of prematurity: A mixed effects modeling approach to disease resolution and pharmacologic intervention modeling

CJ Godfrey

Anoixis Corporation, Natick, MA

The time course of resolution of apnea of prematurity and the pharmacodynamics (PD) of theophylline were investigated in a prospective and retrospective study of 97 premature neonates (postnatal age, 0-18.3 weeks; gestational age, 24-33 weeks; daily body weight, 0.4-3.5 kg). The data were analyzed with nonlinear mixed effects models.

The daily frequency of apneic episodes was modeled according to an overdispersed Poisson distribution with a log-normal distribution of interpatient means. The maturational course of daily episode counts was best described by a biexponential function of postnatal age and was influenced by gestational age and comorbidity of hyaline membrane disease. An inhibitory maximum effect model was used to describe the reduction of apneic episode frequency by theophylline. I_{max} and IC_{50} were 58% and 4.3 μg/mL, respectively.

Estimation of Mixed Hidden Markov Models with SAEM. Application to daily seizures data.

Marc Lavielle (1,5), Maud Delattre (1), Radojka Savic (2), Raymond Miller (3), Mats O. Karlsson (4)

(1) Department of Mathematics; University of Paris-Sud; Orsay; France; (2) INSERM U738 and University Denis Diderot – Paris 7, Paris, France; (3) Pfizer Global Research and Development, USA; (4) Department of Pharmaceutical Biosciences, Uppsala University, Uppsala, Sweden; (5) INRIA Saclay Ile-de-France; France

Background: Markov elements, which allow the likelihood of a given future state to be dependent on its present state, are often introduced in categorical and count data models to handle dependency of observations. However, the underlying state variable may not always been known. When there is no data available on a previous state, a hidden Markov model (HMM) can be utilized which still treats system as a Markov process, but the parameters of the model are assessed via some other observed variable influenced by this "hidden state". HMM has a finite set of states. Transitions among the states are governed by a set of probabilities called transition probabilities. In a particular state, an outcome can be generated, according to the associated probability distribution. The state is not directly visible.

This methodology has been utilized in other scientific areas; however it has never been extended to a mixed HMM, and therefore never applied within population analysis framework.

Objectives: To develop, evaluate and apply a new methodology for the estimation of Mixed Hidden Markov Models.

Methods: The Baum-Welch algorithm is a well-known EM-type algorithm [2]. It can compute maximum likelihood estimates for the parameters (transition and conditional probabilities) of an individual HMM, when given only emissions as training data. We propose the following methodology: i) the SAEM algorithm is combined with the Baum-Welch algorithm for estimating the population parameters of the model, ii) for each subject, the individual parameters are estimated using the Maximum A Posteriori (MAP) approach, iii) for each subject the most likely sequence of hidden states is computed with the Viterbi algorithm [2].

The performance of the HMM was evaluated using Monte Carlo studies. Further, the novel methodology was applied for modelling of epilepsy data, expressed as a daily seizure counts. The pronounced overdispersion phenomenon and a characteristic transition matrix of this data [1] were modelled using HMM where periods of low and high epileptic activity were treated as hidden states.

All analyses were performed using MONOLIX with additional Matlab scripts.

Results: The Mixed Hidden Markov Model methodology has successfully been developed using the SAEM algorithm. Monte Carlo studies indicated good performances of the proposed methodology (negligible bias, small RMSE, accurate estimation of parameter SE).

Daily seizures count data were successfully described using HMM. The model which consists of a mixture of two Poisson distributions dependent on underlying hidden state, described the overdispersion phenomenon, cumulative marginal distribution and a transition matrix of seizure counts well. Therefore, this novel approach offered further improvements compared to current state-of-the art methodologies [1].

Conclusions: The novel Mixed Hidden Markov Model methodology has successfully been developed combining the SAEM and the Baum-Welch algorithms. The SAEM appeared to be powerful and fast algorithm for estimating the parameters of a mixed HMM. The first results obtained with Monte Carlo simulations and using a real data example are extremely encouraging.

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Who Wants to Be the First to Dose this Drug in Children? Approaches to Use Knowledge to Inform Dosing Choices
Session Chair: Steven Kern

The Design and Analysis of Informative Pediatric Clinical Pharmacology Trials Based on Integrating Modeling and Simulation with Available Prior Knowledge

Jeffrey S. Barrett, PhD, FCP

(1) Division of Clinical Pharmacology & Therapeutics, The Children's Hospital of Philadelphia; Pediatrics Department, University of Pennsylvania Medical School, Philadelphia, PA, USA

Objectives: To review a process and procedures for incorporating prior knowledge into the design and subsequent analysis of pediatric clinical pharmacology trials with consideration for the disparity and uncertainty of the priors and variety of methodologies suited to the objectives of the trials.

Methods: A variety of pharmacometric methodologies including PBPK, Pop-PK, Monte Carlo simulation, etc and software solutions will be discussed in the context of available data. Data are hierarchical with respect to the drug development stage within which they are typically generated (e.g., structure → in vitro data → preclinical in vivo → adult → pediatric). Approaches involving allometric scaling, developmental and maturational functions on compartmental vs PBPK models are compared with prototypical examples including midazolam, esmolol and fluconazole. Design constructs for evaluation include PK scaling, PK/safety, dose finding based on exposure equivalence and dose finding based on PK/PD. Some considerations for efficacy trials are also discussed.

Results: The following results will be described and reviewed during the presentation:

- CYP-mediated, highly metabolized drugs (midazolam) can be accommodated with "bottom-up" approaches reliant on good in vitro data and well-defined ontologic relationships. This is more difficult for non-CYP (e.g., plasma esterase; esmolol) metabolism considerations
- PBPK and pop-PK models compare reasonably well when adult data is available to guide (scale) pediatric dose exposure relationships.
- Developmental and organ function considerations are also easily accommodated and compared well in both PBPK and compartmental, pop-PK approaches depending on the availability of physiologic, physiochemical and/or adult PK data.

Conclusions: Many methodologies are suitable to incorporate disparate prior knowledge into modeling and simulation paradigms that guide pediatric drug development. In most cases, the choice of methodology and approach is dictated by the type and quality of the prior knowledge but also the objectives of the project. The uncertainty of this guidance would seem to be improved by the data hierarchy with adult data offering additional guidance (and confidence) with respect to the therapeutic window. Bottom-up approaches would seem to be an obvious choice for high fidelity predictions when rigorous in vitro data are available and when the objectives are PK-centric.

No Experience, No Problem: First-in-Children Dosing Using Bottom-up Approaches

Andrea N. Edginton

School of Pharmacy, University of Waterloo, Waterloo, Ontario, Canada

North American and European regulators are requiring the pharmaceutical industry to consider the potential for pediatric use of their drug candidates early in clinical development. Based on the pediatric study decision tree used by the US Food & Drug Administration [1], pharmacokinetic study is always required. Growth and developmental changes that are inherent to this sub-population make prediction of the dose vs. exposure link difficult and, because there has been no prior experience in children for a new drug, planning this pharmacokinetic study is challenging. By leveraging information on the known pharmacokinetics from first-in-man studies, the physiological changes associated with age (e.g. body weight, organ blood flows, binding protein concentrations) and the drug related properties relevant to pharmacokinetics (e.g. metabolisation pathway(s) and kinetic(s), lipophilicity), an informed estimate of age-dependent pharmacokinetics is possible. Using this bottom-up approach, three areas of predictive modeling for pediatrics have been (are being) developed that evaluate drug distribution, drug elimination and bioavailability.

1. Distribution volume is a function of both the drug and the organism and the physiological changes associated with age may have a profound effect on this parameter. From a modeling perspective, incorporation of the age-related changes important for prediction of distribution volume (e.g. body fat content, total body water) into whole-body physiologically based pharmacokinetic (WB-PBPK) models [2,3] have the potential to guide us in estimating the likely change in distribution volume with age.

2. The age-related change in clearance has been the subject of much study and is the culmination of both changes in growth and in development. Growth-related changes are commonly scaled using allometry [4]. While this is generally sufficient for most drugs at an age where development is complete, for children under a certain age, this method alone will over predict clearance [5]. This is due to the reduced capacity of young children to eliminate some drugs due to immaturity in hepatic and renal function. Mechanistic approaches [6,7] to predicting clearance is possible through an examination of the numerous physiological (e.g. blood flow, enzyme concentration, protein binding) and drug-related (e.g. membrane permeability, protein binding affinity) properties that play a role in defining the extraction efficiency of an eliminating organ. These require knowledge of the pathways responsible for elimination and the importance of each to total clearance as well as an understanding of pathway ontogeny.

3. A method for the prediction of bioavailability of drug products in children is a work in progress. While we know that gastrointestinal properties (e.g. gastric emptying time, pH, surface area, bile acid concentration) are age-related, the prediction of how the rate and extent of drug absorption changes with age is largely undeveloped. A generalization that can be made for most interpretable clinical studies is that the rate of absorption increases with increasing age but the extent of absorption remains similar to that in adults. This is an area of predictive modeling that requires significant development.

These areas of predictive modeling for the guidance of the pediatric pharmacokinetic study are currently being employed by both industry and academia. Examples of these efforts will be presented.

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Evaluation of Performance of a Pediatric Pharmacokinetic Study Using a Simulation Based Design

Manisha Lamba, James Proulx, Rong Wang, Sriram Krishnaswami

Pfizer Inc., New London, CT, USA

Objectives: Pediatric development programs traditionally utilize a 2-stage approach: an initial pharmacokinetic (PK) study to identify doses followed by efficacy/safety trials. Yet, the efficiency of PK studies to select doses for efficacy/safety studies is often debatable. The purpose of this endeavor was to demonstrate a simulation-based framework using a single covariate of interest (body weight) to characterize the probability of making correct dosing-decisions (P(correct)).

Methods: The design optimization process involved: a) simulating individual clearance (CL) values for a trial design of interest, based on the assumed allometric weight-CL relationship (allometric model) and variability /uncertainty estimates; b) estimating CL and weight exponent for the simulated data using a weight-standardized power model; c) calculating predicted AUC for the weight range of interest using the typical CL for that weight range; and d) evaluating trial success by comparing the predicted AUC with that derived from the allometric model. P(correct) was calculated over 500 simulated trials. A prediction was considered correct if the predicted AUC fell within 66% to 150% (limits derived based on therapeutic index (TI) in adults) of those based on the allometric model. Weights were simulated for a given age by sampling from a distribution based on Center for Disease Control's growth-weight charts.

Results: Designs with 24 patients stratified into 3 age groups in the 2-18 year range (2-5; 6-11; and 12-18 years) with between-subject variability (BSV) in CL of 40% and an uncertainty in the typical value of 10%, provided approximately 81% probability of dosing correctly across a weight range of 8-70 kg (P(correct) range: 81% to 98%). Variations in allocation ratio within the target weight/age groups, BSV, and the therapeutic index significantly influenced the ability to select appropriate doses. Of note, decreasing the TI to 70-143% or increasing the BSV to 60%, reduced P(correct) for lower-weight subjects (8-14 kg) to 76% and 58% respectively. Interestingly, in the estimation model, if the weight exponent was fixed to 0.75 and an age effect was fitted, the P(Correct) for lower-weight subjects ranged from 70-80% at BSV of 40% and 42-50% at BSV of 60%.

Conclusions: A simulation-based framework, which accounts for all available information about the drug (e.g TI, variability/uncertainty, and other predictors of CL) to design PK studies in pediatric patients, should allow characterization of trial performance, resulting in better study design to select doses for pivotal trials. The findings are of particular importance to lower weight children who are susceptible to inaccurate dosing decisions even when there are no other covariates affecting PK.

PhRMA working group updates
Session Chairs: Julie Stone and Amit Roy

Adaptive Dose-Ranging Studies: An Update from the PhRMA Working Group

José Pinheiro

Novartis Pharmaceuticals, East Hanover, NJ, USA

Objectives: As part of its Pharmaceutical Innovation initiative, the Pharmaceutical Research and Manufactures of America (PhRMA) formed a working group on adaptive dose-ranging studies (ADRS) to explore the value of this innovative class of designs in improving dose selection in clinical drug development and, more broadly, understanding the dose response relationship.

Methods: The ADRS WG undertook extensive simulation studies comparing adaptive and non-adaptive dose-ranging methods, putting forward preliminary conclusions and recommendations on the use of these methods in drug development.

Results: This talk will present an overview of the second round of evaluations produced by the WG, focusing on additional adaptive dose-ranging methods, the use of exposure-response models in dose finding, and the impact of dose selection in Phase II on the probability of success of Phase III programs. Updated conclusions and recommendations will be presented and discussed.

Conclusions: Adaptive and model-based dose finding methods can lead to substantial gains in information efficiency and dose selection accuracy and should be routinely considered in clinical drug development. Their usefulness relative to alternative, more traditional designs and methods will depend on a number of factors, which should be careful considered at the planning stage of the trial.

Optimizing TQT Studies through PK-PD: An OQT Working Group

Larisa Reyderman

Eisai Medical Research, Woodcliff Lake, NJ, USA

Objectives: An Optimized QT (OQT) working group is a subteam of PhRMA Clinical Pharmacology Technical Group. The mission of the OQT working group is to optimize performance characteristics of thorough QT trials by applying PK/PD methodologies. The key goals include 1) building and sharing PK/PD models to reduce uncertainly in QT studies such that false positive results are decreased; 2) leveraging data to make better decisions about study designs and samples sizes and 3) to propose a scientific basis to reduce the number of placebo patients in QT studies.

Methods: The OQT working group evaluated current PK/PD computational methodologies and identified key issues that need to be addressed to allow concentration-QT analysis to be the primary analysis of the OQT trials.

Results: This talk will present an overview of the OQT scope and activities and proposed technical plan with an outline of recommended C-QT models, model diagnostics, hypothesis testing criteria and validation based on simulated and experimental data.

Conclusions: The OQT working group was created to serve as a vehicle to share data and expertise to advance the PK/PD science in support of TQT trials and to leverage repetitive modeling work across pharmaceutical companies. An optimized PK/PD analysis methodology will allow to assess QT prolongation in a more cost-efficient way.

Model-Based Drug Development PhRMA Initiative: Mapping the current status and future state for modeling and simulation in the pharmaceutical industry

Julie Stone (1), Dennis Grasela (2), Sandy Allerheiligen (3), Chris Banfield (4), Ih Chang (5), Rajesh Krishna (1), Chee Ng (2), Marc Pfister (2), Stacey Tannenbaum (5), and Jeff Wetherington (6)

PhRMA MBDD Committee: (1) Merck; (2) BMS; (3) Lilly; (4) Amgen; (5) Novartis; (6) GSK

Background: During the last decade, the pharmaceutical industry has increasingly applied modeling and simulation in drug development. This is consistent with the interest in model-based approaches by regulators and the directives outlined in documents such as FDA Critical Path Initiative and EU New Medicines Initiative. The full potential of incorporating model-based approaches in drug development and its impact on decision making has not been fully realized to date.

Objectives: A PhRMA initiative in model-based drug development (MBDD), sponsored by the Clinical Pharmacology Technical Group, was initiated with the aims: (1) to further understanding the current state of modeling and simulation in the pharmaceutical industry; (2) to assess future needs; and (3) to identify future directions necessary to realize the full potential of MBDD approaches in drug development.

Results: In this presentation, an overview of the ongoing activities to map the current state of MBDD (MBDD survey of PhRMA members, Strengths-Weaknesses-Opportunities-Threats [SWOT] analysis,) will be reviewed and results will be shared.

ACoP 2009 Participants

Abraham, Anson	University of Buffalo	ansonab@gmail.com
Abu-Raddad, Eyas	Eli Lilly and Company	eyas@lilly.com
Abutarif, Malaz	Bristol Myers Squibb	mabutarif@gmail.com
Adiwijaya, Bambang	Vertex Pharmaceuticals	Bambang_Adiwijaya@vrtx.com
Agarwal, Suresh	Rite Aid	suresh_suraj12002@yahoo.com
Agbo, Felix	AstraZeneca	felix.agbo@astrazeneca.com
Agersø, Henrik	Novo Nordisk A/S	hkag@novonordisk.com
Ahadieh, Sima	Pfizer	sima.ahadieh@pfizer.com
Ahamadi, Malidi	Simcyp Limited	m.ahamadi@simcyp.com
Ahn, Jae Eun	Pfizer	jaeeun.ahn@pfizer.com
Ait-Oudhia, Sihem	University at Buffalo	sihema@buffalo.edu
Ajavon, Antoinette	Long Island University	toniajavon@gmail.com
Akhlaghi, Fatemeh	University of Rhode Island	fatemeh@uri.edu
Aksenov, Sergey	Novartis	sergey.aksenov@novartis.com
Aldridge, Matthew	Mango Solutions	matt@mango-solutions.com
Allerheiligen, Sandra	Lilly Research Laboratories	srba@lilly.com
Al-Share, Qusai	University at Buffalo/ Novartis Pharmaceuticals	qalshare@yahoo.com
Alvey, Christine	Pfizer	christine.alvey@pfizer.com
Amantea, Michael	Pfizer	michael.amantea@pfizer.com
Andrew, Marilee	University of Washington	marilee@apl.washington.edu
Apelian, Charles	Novartis	charles.apelian@novartis.com
Arends, Roslin	Pfizer	rosalin.arends@pfizer.com
Bachman, William	ICON Development Solutions	william.bachman@iconplc.com
Baillie, Rebecca	Rosa & Co.	rbaillie@rosaandco.com
Balgi, Ganesh	Entelos, Inc.	balgi@entelos.com
Baron, Kyle	University of Minnesota	kbaron@gmail.com
Barton, Hugh	Pfizer	hugh.barton@pfizer.com
Barrett, Jeffrey	The Children's Hospital of Philadelphia	barrettj@email.chop.edu
Bauer, Robert	ICON Development Solutions	robert.bauer@iconplc.com
Baverel, Paul	Uppsala University	paul.baverel@farmbio.uu.se
Bazzoli, Caroline	INSERM U738	caroline.bazzoli@inserm.fr
Beaver, Ron	Rosa & Co.	rbeaver@rosaandco.com
Bender, Brendan	Genentech, Inc.	bbender@gene.com
Bennetts, Margherita	Pfizer	meg.bennetts@pfizer.com
Bergman, Arthur	Merck	arthur_bergman@merck.com
Bergsma, Tim	Metrum Research Group / Metrum Institute	timb@metrumrg.com
Bergstrand, Martin	Uppsala University	martin.bergstrand@farmbio.uu.se
Berry, Seth	Quintiles	seth.berry@quintiles.com
Betts, Alison	Pfizer	alison.betts@pfizer.com
Bhasi, Kavitha	Allergan	kbhasi@gmail.com
Bies, Robert	Indiana University	robertbies@yahoo.com
Bihorel, Sebastien	Cognigen Corporation	Sebastien.Bihorel@cognigencorp.com
Birnbaum, Angela	University of Minnesota	birnb002@umn.edu
Boni, Joseph	Wyeth Research	bonij@wyeth.com
Bosley, Jim	Rosa & Co.	jbosley@rosaandco.com
Boucher, Joseph	Pfizer	joseph.f.boucher@pfizer.com
Boyd, Jason		jasonlboydphd@gmail.com

Boyd, Rebecca	Pfizer	rebecca.boyd@pfizer.com
Brandquist, Christine	MDS Pharma Services	cbrandquist@yahoo.com
Brar, Satjit	FDA	satjit.brar@fda.hhs.gov
Brundage, Dianne	Methodist Hospital	brundd@parknicollet.com
Brundage, Dick	University of Minnesota	brund001@umn.edu
Bruno, Rene	Pharsight	rbruno@pharsight.com
Budha, Nageshwar	Genentech, Inc.	budha.nageshwar@gene.com
Bulitta, Jürgen	Ordway Research Institute	jbulitta@ordwayresearch.org
Bulychev, Alexey	Millennium Pharmaceuticals	bulychev@mpi.com
Byon, Wonkyung	Pfizer	wonkyung.byon@pfizer.com
Cadieu, Kent	KDC Group, Inc.	kdcgrp@placementgrp.com
Carrothers, TJ	Pharsight	tcarrothers@pharsight.com
Chae, Hongseok	Catholic university	kbilling@catholic.ac.kr
Chan, Hui Min	BMSR, University of Southern California	huichan@usc.edu
Chanu, Pascal	Pharsight	pchanu@pharsight.com
Chapel, Sunny	A2PG - Ann Arbor Pharmacometrics Group	sunny.chapel@a2pg.com
Chavan, Ajit	Cubist Pharmaceuticals	ajit.chavan@cubist.com
Checchio, Tina	Pfizer	tina.m.checchio@pfizer.com
Chen, Chunlin	Medimmune/University de Montreal	chench@medimmune.com
Chen, Danny	Pfizer	danny.chen@pfizer.com
Chew, Marci	Pfizer	marci.l.chew@pfizer.com
Chittenden, Jason	Pharsight	jchittenden@pharsight.com
Chiu, Joannellyn	GlaxoSmithKline	joannellyn.s.chiu@gsk.com
Chiu, Yu-Yuan	Dainippon Sumitomo Pharma America	ychiu@dsp-a.com
Chu, Hui-May	Anoixis Corporation	hui-may_chu@anoixiscorp.com
Cirincione, Brenda	Amylin Pharmaceuticals	brenda.cirincione@amylin.com
Claret, Laurent	Pharsight	lclaret@wanadoo.fr
Colucci, Philippe	University of Montreal	philippe.colucci@cetero.com
Comisar, Craig	Children's Hospital of Philadelphia	comisarc@email.chop.edu
Cook, Jack	Pfizer	jack.cook@pfizer.com
Corrigan, Brian	Pfizer	brian.corrigan@pfizer.com
Cronenberger, Carol	Pfizer	carol.cronenberger@pfizer.com
Danhof, Meindert	Leiden University	m.danhof@lacdr.leidenuniv.nl
D'Argenio, David	University of Southern California	dargenio@bmsr.usc.edu
Dartois, Celine	Novartis	celine.dartois@novartis.com
Deng, Rong	Genentech, Inc.	deng.rong@gene.com
Derendorf, Hartmut	University of Florida	hartmut@cop.ufl.edu
Diderichsen, Paul Matthias	Abbott GmbH & Co, KG	paulmatthias.diderichsen@abbott.com
Dirks, Nathaniel	Metrum Research Group / Metrum Institute	nated@metrumrg.com
Dontabhaktuni, Aruna	Imclone Systems	arunadonta@yahoo.com
Doshi, Sameer	Amgen Inc.	sdoshi@amgen.com
Drenth, Henk-Jan	LAP&P Consultants BV	h.drenth@lapp.nl
Dubois, Anne	INSERM U738	anne.dubois@inserm.fr
Dumond, Julie	University of North Carolina at Chapel Hill	jdumond@unc.edu
Dunlavey, Michael	Pharsight	mdunlavey@pharsight.com
Dunyak, James	Novartis	james.dunyak@novartis.com
Dutta, Sandeep	Abbott Laboratories	sandeep.dutta@abbott.com
Dykstra, Kevin	Pharsight	kdykstra@pharsight.com
Edginton, Andrea	School of Pharmacy, University of Waterloo	aedginto@uwaterloo.ca

El-Tahtawy, Ahmed	Pfizer	ahmed.el-tahtawy@pfizer.com
Estes, Kerry	PK-PDyne, Inc	pkpdyne@attglobal.net
Ette, Ene	Anoixis Corporation	ene_ette@anoixiscorp.com
Ezzet, Farkad	Pharsight	fezzet@pharsight.com
Facius, Axel	Nycomed	axel.facius@nycomed.com
Faessel, Helene	Pfizer	helene.m.faessel@pfizer.com
Fenneteau, Frédérique	Université de Montréal, Faculty of Pharmacy	frederique.fenneteau@polymtl.ca
Ferron, Geraldine	sanofi-aventis	geraldine.ferron@sanofi-aventis.com
Fetterly, Gerald	Roswell Park Cancer Institute	gerald.fetterly@roswellpark.org
Fiedler-Kelly, Jill	Cognigen Corporation	jill.fiedler-kelly@cognigencorp.com
Fisher, Dennis	P Less Than	fisher@plessthan.com
Fisher, Jeannine	Metrum Research Group, LLC	jeanninf@metrumrg.com
Flataos, Demiana	FDA	faltaosd@cder.fda.gov
Forrest, Alan	ICPD-Ordway Research Institute	aforrest-icpd@ordwayresearch.org
Freedman, Immanuel	GlaxoSmithKine	immanuel.q.freedman@gsk.com
Freiwald, Matthias	Boehringer Ingelheim	matthias.freiwald@boehringer-ingelheim.com
French, Jonathan	Pfizer	jonathan.l.french@pfizer.com
Freshwater, Ed	Long Island University	edfreshwater3636@aol.com
Freshwater, Tomoko	Schering-Plough	tomoko.freshwater@spcorp.com
Frevert, Uli	Bristol-Myers Squibb	uli.frevert@bms.com
Frey, Nicolas	F. Hoffmann-La Roche	nicolas.frey@roche.com
Friberg, Lena	Uppsala University	lena.friberg@farmbio.uu.se
Gao, Xiang	Pfizer	xiang.gao@pfizer.com
Garhyan, Parag	Eli Lilly and Company	pgarhyan@lilly.com
Garimella, Tushar	Abbott Laboratories	tushar.garimella@abbott.com
Garnett, Christine	FDA	christine.garnett@fda.hhs.gov
Gastonguay, Marc	Metrum Research Group / Metrum Institute	marcg@metrumrg.com
Gaudreault, Francois	Université de Montréal, Faculty of Pharmacy	francois.gaudreault@umontreal.ca
Ghahramani, Parviz	Forest Research Institute	parvizghahramani@hotmail.com
Ghobrial, Oliver	Eli Lilly and Company	oliver1@ufl.edu
Gibiansky, Ekaterina	QuantPharm LLC	EGibiansky@quantpharm.com
Gibiansky, Leonid	QuantPharm LLC	lgibiansky@quantpharm.com
Gillespie, Bill	Metrum Research Group / Metrum Institute	billg@metrumrg.com
Girgis, Ihab	Johnson and Johnson PRD	igirgis@its.jnj.com
Godfrey, CJ	Anoixis Corporation	cj_godfrey@anoixiscorp.com
Goel, Varun	University of Minnesota	goel0032@umn.edu
Goggin, Timothy	F. Hoffmann-La Roche	timothy.goggin@roche.com
Gomeni, Roberto	GlaxoSmithKine	roberto.a.gomeni@gsk.com
Grasela, Thaddeus	Cognigen Corporation	ted.grasela@cognigencorp.com
Green, Michelle	Pharsight	mgreen@pharsight.com
Grover, Anita	UCSF	anita.grover@ucsf.edu
Grueger, Jens	Pfizer	jens.grueger@pfizer.com
Gupta, Manish	Genentech, Inc.	manishg@gene.com
Gupta, Neeraj	Abbott Laboratories	neeraj.gupta@abbott.com
Gupta, Pankaj	Pfizer	pankaj.gupta@pfizer.com
Haddish-Berhane, Nahor	Pfizer	nahor.haddish-berhane@pfizer.com
Hall, Jeff	Metrum Research Group / Metrum Institute	jeffhall@metrumrg.com
Han, Seunghoon	Catholic Medical Center	waystolove@catholic.ac.kr

Hane, Jeff	Metrum Research Group / Metrum Institute	jeffh@metrumrg.com
Hang, Yaming	Merck	yaming_hang@merck.com
Hansson, Emma	Uppsala University	emma.hansson@farmbio.uu.se
Harnisch, Lutz	Pfizer	lutz.o.harnisch@pfizer.com
Harrold, John	SUNY at Buffalo	jharrold@buffalo.edu
Hazra-Raybon, Anasuya	Pfizer	anasuya.hazra@pfizer.com
Heathman, Michael	Lilly Research Laboratories	heathman@lilly.com
Heilig, Joseph	Amylin Pharmaceuticals	joseph.heilig@amylin.com
Heitjan, Daniel	University of Pennsylvania	dheitjan@upenn.edu
Helmlinger, Gabriel	Novartis	gabriel.helmlinger@novartis.com
Henin, Emilie	Uppsala University	emilie.henin@farmbio.uu.se
Henry, Ana	Pharsight	ahenry@pharsight.com
Hermann, David	Great Lakes Drug Development, Inc	dhermann@gldrugdev.com
Ho, Richard	Entelos	ho@entelos.com
Hoke, Frank	GlaxoSmithKline	frank.j.hoke@gsk.com
Hooker, Andrew	Uppsala University	andrew.hooker@farmbio.uu.se
Hou, Xiaoli Shirley	Merck	xiaoli_hou@merck.com
Housand, Conrad	The AEgis Technologies Group	lhousand@aegistg.com
Hovde, Mark	Pharsight	mhovde@pharsight.com
Hsu, Chyi-Hung	Novartis	chyihung.hsu@novartis.com
Hsu, Joy	F. Hoffmann-La Roche	joy.hsu@roche.com
Huang, Jiayin	Vertex Pharmaceuticals	jiayin_huang@vrtx.com
Hutmacher, Matthew	A2PG - Ann Arbor Pharmacometrics Group	matt.hutmacher@a2pg.com
Ingwersen, Steen	NovoNordisk/Biomodelling	si@novonordisk.com
Ito, Kaori	Pfizer	kaori.ito@pfizer.com
Ivaturi, Vijay Deep	University of Minnesota	ivatu001@umn.edu
Jadhav, Pravin	FDA	pravin.jadhav@fda.hhs.gov
James, David	Novartis	davida.james@novartis.com
James, John	Mango Solutions	jjames@mango-solutions.com
Jang, In-Jin	Seoul National University	ijjang@snu.ac.kr
Jang, Seong Bok	Yonsei University College of Medicine	sbjang83@yuhs.ac
Jansen, Mendel	Eisai Medical Research Inc.	mendel_jansen@eisai.net
Jaworowicz, David	Cognigen Corporation	David.Jaworowicz@cognigencorp.com
Jen, Frank	Pfizer	frank_jen@hotmail.com
Jennings, Donald	Eli Lilly and Company	donald.jennings@lilly.com
Jin, Jin	Genentech, Inc.	jinj@gene.com
Jonsson, Niclas	Exprimo nv	niclas.jonsson@exprimo.com
Joshi, Amita	Genentech, Inc.	amita@gene.com
Kahn, Joseph	Novartis	joseph.kahn@novartis.com
Kaibara, Astunori	Astellas Pharma Global Development, Inc	atsunori.kaibara@us.astellas.com
Kaila, Nitin	Novartis	nitin.kaila@novartis.com
Kamal, Mohamed	Roche	mohamed.kamal@roche.com
Karlsson, Kristin	Uppsala University	kristin.karlsson@farmbio.uu.se
Karlsson, Mats	Uppsala University	mats.karlsson@farmbio.uu.se
Kastrissios, Helen	Pharsight	hkastrissios@pharsight.com
Kerbusch, Thomas	Schering-Plough	thomas.kerbusch@spcorp.com
Kern, Steven	University of Utah	steven.kern@utah.edu
Khariton, Tatiana	Forest Research Institute	tatiana.khariton@frx.com
Khatri, Amit	University of Minnesota	khat0025@umn.edu
Khurana, Manoj	US Food and Drug Administation	manoj.khurana@fda.hhs.gov

Kim, Hyewon	University of Minnesota	kimxx987@umn.edu
Kim, Tae Eun	University of North Carolina at Chapel Hill	taeeun.grace@gmail.com
Kim, Yoon	Dankook University	kyg90@dankook.ac.kr
Kimberlin, Oliver	Mango Solutions	okimberlin@mango-solutions.com
Kimko, Hui	Johnson and Johnson PRD	hkimko@its.jnj.com
King, Jennifer	University of Alabama at Birmingham	jennifer.king@ccc.uab.edu
Kitchen, Valerie	Bristol Myers Squibb	valerie.kitchen@bms.com
Knebel, Bill	Metrum Research Group / Metrum Institute	billk@metrumrg.com
Korth-Bradley, Joan	Wyeth Research	korthbj@wyeth.com
Kowalski, Kenneth	A2PG - Ann Arbor Pharmacometrics Group	ken.kowalski@a2pg.com
Krause, Andreas	Actelion Pharmaceuticals	andreas.krause@actelion.com
Krishnaswami, Sriram	Pfizer	sriram.krishnaswami@pfizer.com
Krudys, Kevin	FDA	kevin.krudys@fda.hhs.gov
Krzyzanski, Wojciech	University at Buffalo	wk@buffalo.edu
Kumar, Vikas	Pfizer	vikas.kumar@pfizer.com
Lala, Mallika	FDA	mallika.lala@fda.hhs.gov
Lalonde, Richard	Pfizer	richard.lalonde@pfizer.com
Lalovic, Bojan	Pfizer	bojan.lalovic@pfizer.com
Lamba, Manisha	Pfizer	manisha.lamba@pfizer.com
Landersdorfer, Cornelia	Institute for Clinical Pharmacodynamics	CLandersdorfer-icpd@ordwayresearch.org
Langdon, Grant	Pfizer	grant.m.langdon@gmail.com
Lavielle, Marc	INRIA	marc.lavielle@math.u-psud.fr
Lavigne, Jean	MDS Pharma Services	jean.lavigne@mdsinc.com
Le, Kha	Millennium Pharmaceuticals	kha.le@mpi.com
Leary, Robert	Pharsight	bleary@pharsight.com
Lee, Joo-Yeon	FDA	jooyeon2.lee@fda.hhs.gov
Lee, Yoon Jung	Yonsei University College of Medicine	yjlee@yuhs.ac
Leggas, Markos	University of Kentucky	mark.leggas@uky.edu
Leil, Tarek	Bristol-Myers Squibb	tarek.leil@bms.com
Levi, Micha	F. Hoffmann-La Roche	micha.levi@roche.com
Li, Fang	FDA	fang.li@fda.hhs.gov
Li, Hanbin	Quantitative Solutions	hli@wequantify.com
Li, Jianguo	AstraZeneca	jianguo.li@astrazeneca.com
Li, Jun	Université de Montréal	li@crm.umontreal.ca
Li, Xiujiang	Merck Research Labs	xiujiang_li@merck.com
Lim, Lay Ahyoung	Yonsei University College of Medicine	MADPINK@yuhs.ac
Lindbom, Lars	Pharsight	llindbom@pharsight.com
Lippert, Joerg	Bayer Technology Services GmbH	joerg.lippert@bayertechnology.com
Liu, Feng	University of Sheffield / GSK	fenglpku2000@gmail.com
Liu, Jiang	FDA	jiang.liu@fda.hhs.gov
Liu, Jing	Pfizer	jing.liu@pfizer.com
Liu, Wei	Abbott Laboratories	wei.liu@abbott.com
Lo, Arthur	Entelos	lo@entelos.com
Lockwood, Peter	Pfizer	peter.lockwood@pfizer.com
Lopez-Anaya, Arturo	Eisai Medical Research Inc.	arturo_lopez-anaya@eisai.com
Lovern, Mark	GlaxoSmithKine	mark.r.lovern@gsk.com
Lu, Dan	Genentech, Inc.	danlu@gene.com
Lu, Jianfeng	Amgen Inc.	jianfeng@amgen.com
Lu, Tong	BMSR, University of Southern California	tonglu@usc.edu
Lu, Yasong	Pfizer	yasong.lu@pfizer.com

Lu, Zheng	Millennium Pharmaceuticals	zheng.lu@mpi.com
Lubin, Rachelle	University at Buffalo/Novartis Pharmaceuticals	rachelle.lubin@novartis.com
Ludden, Thomas	ICON Development Solutions	thomas.ludden@iconplc.com
Ludwig, Elizabeth	Cognigen Corporation	Elizabeth.Ludwig@cognigencorp.com
Luu, Kenneth	Pfizer	kenneth.luu@pfizer.com
Ma, Peiming	Amgen Inc.	peimingm@amgen.com
Madabushi, Rajanikanth	FDA	rajnikanth.madabushi@fda.hhs.gov
Mager, Donald	University at Buffalo, SUNY	dmager@buffalo.edu
Mandema, Jacob	Quantitative Solutions	jmandema@wequantify.com
Marathe, Anshu	FDA	anshu.marathe@fda.hhs.gov
Marsan, Jim	Metrum Research Group / Metrum Institute	jimm@metrumrg.com
Marsteller, Douglas	The Children's Hospital of Philadelphia	marstellerd@email.chop.edu
Marston, Sarah	Otsuka Pharmaceutical Dev. & Comm	sarah.marston@otsuka-us.com
Mattison, Donald	NICHD, NIH	mattisod@mail.nih.gov
Mayersohn, Michael	University of Arizona	mayersohn@pharmacy.arizona.edu
McDougall, Robin	The AEgis Technologies Group	rmcdougall@acslx.com
Mehrotra, Nitin	FDA	nitin.mehrotra@fda.hhs.gov
Meibohm, Bernd	University of Tennessee	bmeibohm@utmem.edu
Meng, Zhaoyu	the Chinese University of Hong Kong	zhaoyumeng@cuhk.edu.hk
Menon, Sujatha	Pfizer	suja.menon@pfizer.com
Mentre, France	INSERM U738	france.mentre@inserm.fr
Miller, Raymond	Pfizer	raymond.miller@pfizer.com
Milligan, Peter	Pfizer	peter.a.milligan@pfizer.com
Mondick, John	Metrum Research Group / Metrum Institute	johnm@metrumrg.com
Moore, Helen	Pharsight	hmoore@pharsight.com
Mouksassi, Samer	Pharsight	smouksassi@pharsight.com
Mould, Diane	Projections Research Inc	drmould@attglobal.net
Moy, Fred	New York Medical College	moy@nymc.edu
Mu, Song	F. Hoffmann-La Roche	song.mu@roche.com
Naganuma, Hideo	Daiichi-Sankyo Co., Ltd.	naganuma.hideo.eb@daiichisankyo.co.jp
Nakade, Susumu	Ono Pharma USA, Inc.	s.nakade@ono.co.jp
Nandy, Partha	Johnson and Johnson PRD	pnandy@its.jnj.com
Narwal, Rajesh	MedImmune	narwalr@medimmune.com
Neal, Lauren	FDA	lauren.neal@fda.hhs.gov
Nebot, Noelia	University of North Carolina/GSK	noelia_nebot@unc.edu
Neelakantan, Srividya	Pfizer	srividya.neelakantan@pfizer.com
Nekka, Fahima	Université de Montréal	fahima.nekka@umontreal.ca
Nestorov, Ivan	Biogen IDEC	ivan.nestorov@biogenidec.com
Ng, Chee	Bristol-myers Squibb	chee.ng@bms.com
Nguyen, Anne Q.N.	Université de Montréal	qna.nguyen@umontreal.ca
Nguyen, Thu-Thuy	INSERM U738	thu-thuy.nguyen@inserm.fr
Nicholas, Tim	Pfizer	timothy.nicholas@pfizer.com
Nichols, Alice	Wyeth Research	nichola2@wyeth.com
Nickens, Dana	Pfizer	dana.j.nickens@pfizer.com
Nieforth, Keith	Roche	keith.neiforth@roche.com
Nucci, Gianluca	Pfizer	gianluca.nucci@pfizer.com
Nyberg, Joakim	Uppsala University	joakim.nyberg@farmbio.uu.se
O'Connell, Michael	TIBCO Software, Inc. - Spotfire Division	moconnel@tibco.com
OGorman, Melissa	Pfizer	melissa.t.ogorman@pfizer.com
Okudaira, Noriko	Daiichi Sankyo Co., Ltd.	okudaira.noriko.ra@daiichisankyo.co.jp

Okusanya, Olanrewaju	Institute for Clinical Pharmacodynamics	Ookusanya-icpd@ordwayresearch.org
Ouellet, Daniele	GlaxoSmithKine	daniele.x.ouellet@gsk.com
Pagano, Sharon	Entelos	pagano@entelos.com
Panetta, Carl	St. Jude Children's Research Hospital	carl.panetta@stjude.org
Panorchan, Porntula	Merck	porntula_panorchan@merck.com
Papasouliotis, Orestis	Merck Serono S.A.	orestis.papasouliotis@merckserono.net
Park, Kyungsoo	Yonsei University College of Medicine	kspark@yuhs.ac
Pelekis, Michael	Simulations Plus, Inc.	michael@simulations-plus.com
Pereira, Luis	CHB/HMS	luis.pereira@childrens.harvard.edu
Peterson, Mark	Biogen IDEC	mark.peterson@biogenidec.com
Petersson, Klas	Uppsala University	klas.petersson@farmbio.uu.se
Pfister, Marc	Bristol Myers Squibb	marc.pfister@bms.com
Phillips, Luann	Cognigen Corporation	Luann.Phillips@cognigencorp.com
Plan, Elodie	Uppsala University	elodie.plan@farmbio.uu.se
Ploeger, Bart	LAP&P Consultants BV	b.ploeger@lapp.nl
Plowchalk, David	Pfizer	david.r.plowchalk@pfizer.com
Poland, William	Pharsight	bpoland@pharsight.com
Polepally, Akshanth	University of Minnesota	polep002@umn.edu
Poola, Nagaraju	Dainippon Sumitomo Pharma America	npoola@dsp-a.com
Pugh, Richard	Mango Solutions	rich@mango-solutions.com
Purohit, Vivek	Pfizer	vivek.s.purohit@pfizer.com
Qiu, Ruolun	Pfizer	ruolun.qiu@pfizer.com
Quartino, Angelica	Uppsala University	angelica.quartino@farmbio.uu.se
Quinlan, Tonya	Eli Lilly and Company	quinlan_tonya@lilly.com
Rajagopalan, Prabhu	Bayer HealthCare Pharmaceuticals	prabhu.rajagopalan@bayer.com
Raje, Sangeeta	Wyeth Research	rajes@wyeth.com
Ramakrishna, Ramprasad	Novartis	ramprasad.ramakrishna@novartis.com
Ravva, Patanjali	Pfizer	patanjali.ravva@pfizer.com
Raybon, Joseph	Bristol-Myers-Squibb	joseph.raybon@bms.com
Reyderman, Larisa	Eisai Medical Research Inc.	larisa_reyderman@eisai.com
Ribbing, Jakob	Pfizer	jakob.ribbing@pfizer.com
Riggs, Matthew	Metrum Research Group / Metrum Institute	mattr@metrumrg.com
Riley, Steve	Pfizer	steve.riley@pfizer.com
Ring, Arne	Boehringer Ingelheim Pharma	arne.ring@boehringer-ingelheim.com
Risch, Nancy	Pharsight	nrisch@pharsight.com
Rizwan, Ahsan	University of North Carolina	ahsan.rizwan@unc.edu
Robbie, Gabriel	MedImmune	robbieg@medimmune.com
Roberts, John	AstraZeneca	john.roberts@astrazeneca.com
Rogers, Jim	Metrum Research Group / Metrum Institute	jimr@metrumrg.com
Romero, Klaus	The Critical Path Institute	kromero@c-path.org
Roy, Amit	Bristol Myers Squibb	amit.roy@bms.com
Roy, Mike	Astellas Pharma Global Development, Inc	mike.roy@us.astellas.com
Rubino, Christopher	Institute for Clinical Pharmacodynamics	Crubino-icpd@ordwayresearch.org
Rutkin, Adam	Pharsight	arutkin@pharsight.com
Sabarinath, Sreedharan Nair	University of Florida	sabarinath@ufl.edu
Sale, Mark	Next Level Solutions	mark@nextlevelsolns.com
Salem, Ahmed	University of Minnesota	sale0074@umn.edu
Salinger, David	Amgen, Inc.	salinger@amgen.com
Sallas, William	Novartis	william.sallas@novartis.com
Sam, Wai Johnn	National Institutes of Health	samw@cc.nih.gov

Samtani, Mahesh	Johnson and Johnson PRD	msamtani@its.jnj.com
Sanduja, Sachin	Rudraya Corporation	sachin@rudraya.com
Savant, Ishani	Celgene Corporation	isavant@celgene.com
Sawamoto, Taiji	Astellas Pharma Global Development, Inc	taiji.sawamoto@us.astellas.com
Seng Yue, Corinne	University of Montreal	corinne.seng.yue@umontreal.ca
Shaik, Naveed	Pfizer	naveed.shaik@pfizer.com
Sharma, Manish	University of Chicago	manish.sharma@uchospitals.edu
Shi, Jun	Metrum Research Group / Metrum Institute	juns@metrumrg.com
Shoji, Satoshi	Pfizer	satoshi.shoji@pfizer.com
Simonsson, Ulrika	Uppsala University	ulrika.simonsson@farmbio.uu.se
Singh, Pratap	Pfizer	pratap.singh.charan@gmail.com
Singh, Rajendra	University of Florida	rpsingh@ufl.edu
Song, Xiaoou	Cephalon, Inc.	ssong@cephalon.com
Staab, Alexander	Boehringer Ingelheim	alexander.staab@boehringer-ingelheim.com
Standing, Joseph	Uppsala University	joseph.standing@farmbio.uu.se
Statkevich, Paul	Schering Plough	paul.statkevich@spcorp.com
Stein, Andrew	Novartis	andrew.stein@novartis.com
Stone, Julie	Merck Research Labs	julie_stone@merck.com
Struemper, Herbert	GlaxoSmithKline	herbert.struemper@yahoo.com
Subramoney, Vishak	Roche	vishak.subramoney@roche.com
Sullivan, Don	TIBCO Software, Inc. - Spotfire Division	dsulliva@tibco.com
Sun, Xiaoyong	Iowa State University	sunx1@iastate.edu
Suryawanshi, Satyendra	University of Tennessee	satyendra.suryawanshi@gmail.com
Sweeney, Kevin	Pfizer	kevin.sweeney@pfizer.com
Tagami, Sanae	CTC Laboratory Systems	sanae.fujita@ctc-g.co.jp
Tagen, Michael	St. Jude Children's Research Hospital	michael.tagen@stjude.org
Tan, Beesan	The University of Iowa	beesan-tan@uiowa.edu
Tannenbaum, Sandra	ACoP Staff	sandie@go-acop.org
Tannenbaum, Stacey	Novartis	stacey.tannenbaum@novartis.com
Taylor, Timothy	Shenandoah University/Projections Research Inc.	ttaylor@pri-home.net
Tensfeldt, Thomas	Pfizer	thomas.g.tensfeldt@pfizer.com
Teuscher, Nathan	Alcon Labs	nathan.teuscher@alconlabs.com
Thanneer, Neelima	Bristol-Myers Squibb	neelima.thanneer@bms.com
Thatavarthi, Rajsekhar	GVK Biosciences Pvt Ltd	rajsekhar@gvkbio.com
Thomas, Greg	Hoffmann-La Roche	greg_j.thomas@roche.com
Tian, Xianbin	Archemix	xtian@archemix.com
Tibbitts, Jay	Genentech, Inc.	tibbitts@gene.com
Tornoe, Christoffer	FDA	christoffer.tornoe@fda.hhs.gov
Tortorici, Michael	Pfizer	michael.tortorici@pfizer.com
Troy, Steven	Shire Pharmaceuticals	stroy@shire.com
Tsai, Alice	Vertex Pharmaceuticals	alice_tsai@vrtx.com
Tsai, Kuenhi	Merck	kuenhi_tsai@merck.com
Tsai, Max	Takeda	mtsai@tgrd.com
Uchizono, James	University of the Pacific	juchizono@pacific.edu
Udata, Chandrasekhar	Wyeth	udatac@wyeth.com
Upton, Richard	Projections Research Inc	richard.upton@adelaide.edu.au
Urquhart, John	UCSF Center for Drug Development Science	urquhart@ix.netcom.com
Vaddady, Pavan Kumar	University of Tennessee	pvaddady@utmem.edu

Vage, Chandra	Pfizer	Chandra.Vage@pfizer.com
Van, Linh	Bristol Myers Squibb	linh.van@bms.com
VanWart, Scott	Institute for Clinical Pharmacodynamics	Svanwart-icpd@ordwayresearch.org
Varin, France	Université de Montréal	france.varin@umontreal.ca
Wada, Russ	Quantitative Solutions	rwada@wequantify.com
Wald, Jeffrey	GlaxoSmithKine	jeffrey.a.wald@gsk.com
Wang, Diane	Pfizer	diane.wang@pfizer.com
Wang, Xiaoli	Sigma	zyzwxl@gmail.com
Wang, Xiaoning	Bristol-Myers Squibb	xiaoningw@gmail.com
Wang, Yaning	FDA	yaning.wang@fda.hhs.gov
Waterhouse, Tim	Eli Lilly and Company	waterhouseth@lilly.com
Wattanavijitkul, Thitima	The University of Iowa	thitima-wattanavijitkul@uiowa.edu
Wei, Xiaohui	sanofi-aventis	xiaohui.wei@sanofi-aventis.com
Weiner, Daniel	Pharsight	dlweiner@gmail.com
Weiss, Wolfgang	Bayer Technology Services GmbH	wolfgang.weiss@bayertechnology.com
Willavize, Susan	Cognigen Corporation	sawandjmp@cs.com
Williams, Jason	The Children's Hospital of Philadelphia	williamsj2@email.chop.edu
Willmann, Stefan	Bayer Technology Services GmbH	stefan.willmann@bayertechnology.com
Wu, Benjamin	University of Florida	wube@ufl.edu
Wu, Di	Children's Hospital of Philadelphia	wudi@email.chop.edu
Xiao, Alan	AstraZeneca	alan.xiao@astrazeneca.com
Xie, Rujia	Pfizer	rujia.xie@pfizer.com
Xin, Yan	Genentech, Inc.	xin.yan@gene.com
Xu, Huiping	Pfizer	huiping.xu@pfizer.com
Xu, Jian	Pfizer	jian.xu@pfizer.com
Xu, Lu	Genentech, Inc.	lxu@gene.com
Xuan, Dawei	Pfizer	dawei.xuan@pfizer.com
Yim, Dong-Seok	The Catholic Univ of Korea	yimds@catholic.ac.kr
Yin, Yin	GlaxoSmithKine	yin.a.yin@gsk.com
Yu, Li	Millennium Pharmaceuticals	li.yu@mpi.com
Yu, Zhiling	Allergan	yu_steve@allergan.com
Zandvliet, Anthe	Schering-Plough	anthe.zandvliet@spcorp.com
Zannella, Kristen	The MathWorks	kristen.zannella@mathworks.com
Zha, Jiuhong	Vertex Pharmaceuticals	jiuhong_zha@vrtx.com
Zhang, Liping	Bristol-Myers Squibb	liping.zhang3@bms.com
Zhang, Xiaoping	F. Hoffmann-La Roche	amy.zhang@roche.com
Zhang, Yi	Genentech, Inc.	zhang.yi@gene.com
Zhao, Liang	MedImmune	liangzhao2000@hotmail.com
Zhao, Ping	OCP/FDA	ping.zhao@fda.hhs.gov
Zhao, Qinying	Pfizer	qinying.zhao@pfizer.com
Zhou, Huafeng	Merck	huafeng_zhou@merck.com
Zhou, Susan	Bristol-Myers Squibb	susan.zhou@bms.com
Zhu, Hao	FDA	hao.zhu@fda.hhs.gov
Zhu, Rui	BMSR, University of Southern California	rzhu@usc.edu
Zhu, Yali	Schering-Plough	yali.zhu@spcorp.com
Zuo, Peiying	GlaxoSmithKline	peiying.q.zuo@gsk.com

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