

**Hands-on Workshop  
Principles of Pharmacokinetics - Parametric and Nonparametric  
Population PK and PD Modeling and its Applications to  
Therapeutic Drug Monitoring: WIN-USC\*PACK**

**March 20-22, 2002**

**Official Language:** English

**Admission to the Workshop:** free – The number of the participants is limited to 30. The place is assigned on a first-come, first served basis.

**Registration to the Workshop:** please send an e-mail or a Fax to the Organizing Secretary

**Chairmen:**

Roger Jelliffe, M.D., Professor of Medicine, USC School of Medicine, Director, USC Laboratory of Applied Pharmacokinetics

Mario Eandi, M.D., Professor of Clinical Pharmacology, Medical School University of Torino

**Organizing Secretary**

Roberto Passera, PharmD [roberto.passera@tin.it](mailto:roberto.passera@tin.it)  
Gian Paolo Zara MD [gianpaolo.zara@unito.it](mailto:gianpaolo.zara@unito.it)  
Phone: +39 011 6707803  
Fax: +39 011 6707788

**Housing Information:** Please contact

Miss Silvia Pasquini  
CO.AL.PI  
Phone: +39 011 5613760  
Fax : +39011 5621738 E-Mail: [hotelres@hotelres.it](mailto:hotelres@hotelres.it)

**Department of Anatomy,  
Pharmacology, and Forensic Sciences  
Medical School - University of Torino  
Italian Society of Pharmacology**

**POPULATION PHARMACOKINETIC  
WEEK  
AT THE UNIVERSITY OF TORINO**

**March 19-22 2002**

**Hands-on Workshop  
Principles of Pharmacokinetics - Parametric  
and Non-Parametric Population PK and PD  
Modelling and its Application to Therapeutic  
Drug Monitoring: WIN-USC\*PACK**

**March 20-22, 2002**

**Computer Classroom - School of Medicine  
Via Michelangelo 32 – 10125 Torino - Italy**

## **Hands-on Workshop**

### **Principles of Pharmacokinetics - Parametric and Nonparametric Population PK and PD Modeling and its Applications to Therapeutic Drug Monitoring: WIN-USC\*PACK**

**March 20-22, 2002**

**Main Teacher:** Prof. R Jelliffe

#### **Faculty:**

Nathalie Bleyzac, Pharm.D, Hospital Debrousse, Lyon, France

Nils Ove Hoem, Ph.D, School of Pharmacy, University of Oslo, Norway

Roger Jelliffe, M.D., USC School of Medicine, Los Angeles, USA

Irina Bondareva, Ph.D., Institute of Physical and Chemical Medicine, Moscow Russia

#### **Computer Classroom**

**School of Medicine**

**Via Michelangelo 32 – 10125 Torino - Italy**

3:00 PM BREAK

3:15 PM Optimal Times to Sample Serum Concentrations and other Responses - Dr. Jelliffe.

4:15 PM Making Discrete "Nonparametric" Population Models from Literature Data - Dr. Jelliffe.

4:45 PM Population PK/PD Modeling over the web - Dr. Jelliffe

### **Day 3 Advanced Population Modeling - Large and Nonlinear Models**

9:00 AM Modeling Cyclosporine - Dr. Hoem

9:30 AM Making large and nonlinear population models - Dr. Jelliffe  
Demo - Using BOXES making a model of Cyclosporine

10:15 AM Hands on session - Using BOXES making a model of Cyclosporine - Dr. Jelliffe

10:45 AM BREAK

11:00 AM Demo setting up Big IT2B Modelling Cyclosporine - Dr. Jelliffe

A typical subject data file. Setting up the model, the data, the instructions, sending it, analyzing it. Evaluating the results

11:30 AM Hands-on session - setting up big IT2B - Modelling Cyclosporine.

Setting up the model, the data, sending it, analysing it, Evaluating the results

12:30 PM LUNCH

1:30 PM Demo Big NPEM Modelling Cyclosporine - Dr. Jelliffe  
Setting up the model, the data, sending it, analyzing it, Evaluating the results

2:00 PM Hands-on session - Big NPEM Modelling Cyclosporine  
Setting up the model, the data, sending it, analyzing it, Evaluating the results

## Day 2 Intermediate Population Modeling

- 9:00 AM Optimizing drugs in neuropsychiatry - dr. Bondareva
- 9:30 AM Individualization of Busulfan Therapy in Children for Bone Marrow Transplantation - Dr. Bleyzac
- 10:00 AM Optimal procedures for population modeling - Dr. Jelliffe  
1) determine the assay error pattern polynomial, to weight each data point properly  
2) use a parametric population model, get gamma, ranges  
3) use an NP population model, use gamma, ranges, get the entire parameter distribution.
- 10:30 AM Demo - getting the assay error polynomial - Dr. Jelliffe
- 10:45 AM Hands - on session - getting the assay error polynomial
- 11:00 AM BREAK
- 11:15 AM Demo - The IT2B program. Modelling Amikacin  
Dr. Jelliffe  
A typical patient data file: Running the program.  
Getting gamma, ranges, evaluating the results
- 11:45 AM Hands-on session Modeling Amikacin.  
Running the program. Getting gamma, ranges, evaluating the results
- 12:30 LUNCH
- 1:30 PM Demo NPEM: Modeling Amikacin further. Using gamma, ranges results - Dr. Jelliffe  
Evaluating the results - The log-likelihood function  
Descriptors of dispersion : The DF50 and DF95  
The 2 and 3-D plots of the marginal and joint marginal PDF's
- 2:15 PM Hands-on session - NPEM: Amikacin. Using gamma, ranges - Dr. Jelliffe  
Linking Nonparametric Models to the Multiple Model  
Adaptive Control Software  
Deriving individual Bayesian posterior patient parameter joint densities  
Evaluating relationships between parameters and covariates

This course is intended for physicians, pharmacists and biomedical scientists with an interest in population pk/pd modeling, and also for those interested in therapeutic drug monitoring and optimally precise individualization of drug therapy for patient care.

Prior experience in clinical pharmacokinetics will be an advantage. Participants will be introduced to the USC\*PACK software, which can be used both for therapeutic drug monitoring and optimal individualization of drug dosage regimens, as well as for parametric and nonparametric population PK/PD and physiological modeling.

This course will also introduce the new Win\*USC\*PACK software for "Multiple Model" design of dosage regimens that hit target goals with maximal precision.

This method is based first on nonparametric population models. It also obtains a patient's Bayesian posterior nonparametric individual model, and, if needed, to detect and quantify the interoccasional variability in each patient's individual model, thus permitting detection of unsuspected changes in parameter values such as take place with the volume of distribution (and other parameters), in aminoglycoside antibiotics, for example, with changes in the patient's status.

This sequential Bayesian "Interacting Multiple Model" Bayesian approach to interoccasional intra-individual variability comes from the aerospace community, where it is used to track evasive targets.

It is new, to our knowledge, in the pharmacokinetic community. It is designed to track the behavior of drugs, especially in unstable patients, with maximum precision, to detect unsuspected changes in a patient's parameter values during the period of the data analysis, and to permit achievement of target therapeutic goals with maximum precision.

**Day 1 Basic Pharmacokinetics, Introduction to Population Modelling, and Clinical Applications**

		2:30 PM	Getting MM Bayesian Posterior Individual Parameter Distributions. The Interacting MM (IMM) Approach - Dr. Jelliffe.
9:00 AM	Welcome - Prof. M. Eandi		
9:15 AM	Introduction to basic concepts in pharmacokinetics, including Review of Basic Pharmacokinetic Behavior. Drug Elimination and Renal Function - Prof. R. Jelliffe	3:00 PM	Introduction to the new Windows USC*PACK MM and IMM Clinical Program to Achieve Target Goals with Maximum Precision - Dr. Jelliffe Demo - 1 compartment model Planning the Initial regimen - Gentamicin: CCr = 100, 50, 5.
9:30 AM	Evaluating Renal Function – Prof R. Jelliffe		
9:45 AM	Bayes' Theorem and the Bayesian Scenario of Planning, Monitoring, and Adjusting Drug Dosage for patients - Dr. Jelliffe		
10:00 AM	Introduction to Population Modeling - Dr. Jelliffe Why model? For description? For action? Traditional Data Fitting Methods Linear regression, NLLS, Bayesian	3:15 PM	BREAK
10:30 AM	BREAK	3:30 PM	Entering past doses and levels, analysing the data. A patient on Gentamicin. An interesting patient on Tobramycin. - Dr. Jelliffe
10:45 AM	Parametric Population Models (Iterative 2 stage Bayesian, NONMEM )- Dr. Jelliffe	4:00 PM	Hands on session - Dr. Jelliffe The patient on Gentamicin. The interesting patient on Tobramycin.
11:15 AM	Nonparametric Population models (NPML, NPEM) - Dr. Jelliffe	4:30 PM	Demo - 2 compartment model Digoxin - Dr. Jelliffe Setting the initial goals, planning the initial regimen A simple patient with atrial fibrillation. Another interesting patient with atrial fib
11:45 AM	Nonparametric Adaptive Grid (NPAG) Modeling - Dr. Jelliffe	5:00 PM	Hands on session - Setting the initial goals, planning the initial regimen. The simpler patient with atrial fib
12:30 PM	LUNCH	5:30 PM	Demo Vancomycin - Setting the initial goals, planning the initial regimen. - Dr. Jelliffe
1:30 PM	Comparing Parametric and Nonparametric Approaches (IT2B, NPEM, NPAG) - Dr. Jelliffe	5:45 PM	Hands on session - Setting the initial goals, planning the initial regimen.
2:00 PM	Multiple Model (MM) Dosage Design for maximum precision regimens - Dr. Jelliffe		