New Advances in Model-Based, Goal-Oriented Optimal Individualized Drug Therapy: Relationship to Population PK/PD Modelling and to Multiple Model Methods for Optimal Tracking of Drug Behavior andOptimal Dosage Design

Friday & Saturday, Sep 12-13, 2003

This course is intended for physicians, pharmacists, clinical toxicologists and biomedical scientists with an interest in population pharmacokinetic and pharmacodynamic modelling and in therapeutic drug monitoring and optimal individualization of drug therapy for patient care. Prior experience in clinical pharmacokinetics will be an advantage. Participants will be introduced to the USC*PACK and NONMEM software programs which can be used both for therapeutic drug monitoring as well as for parametric and nonparametric population PK/PD and physiological modelling.

Objectives and Expectations:

After this conference, the participant should:

1. Understand the strengths and weaknesses of both parametric and nonparametric population modeling methods.
2. Be able to incorporate population PK/PD models into the general approach of Goal-Oriented, Model-based therapy, using Bayesian adaptive control, including the planning, therapeutic drug monitoring, and subsequent adjusting of drug dosage regimens for patient care.
3. Be able to begin both parametric and nonparametric population PK/PD modeling, using web-based resources.
4. Understand the contribution of the Multiple Model approach to optimize drug therapy.
5. Apply these concepts to optimize practical therapy with Aminoglycosides, Vancomycin, Digoxin, and Cyclosporine, and other drugs.

Faculty:
Dr. Nils Hoem, University of Oslo, Norway
Dr. Roger Jelliffe, USC Laboratory of Applied Pharmacokinetics, Los Angeles CA
Dr. Alison Thomson, University of Glasgow, UK
Dr. Sander Vinks, University of Cincinnati, Ohio

Day 1 - Introduction and Review of Basic Pharmacokinetics, related responses, and Clinical Applications

8:30 AM - Registration
9:00 AM - Welcome - Dr. Jelliffe
9:15 AM – Review of basic concepts in pharmacokinetics, including
Basic Pharmacokinetic behavior, Models, Elimination, and Renal Function - Dr. Vinks
9:30 AM – Evaluating Creatinine Clearance Dr. Jelliffe
9:45 AM - Bayes' Theorem – its use with parametric and nonparametric PK/PD models - the Bayesian scenario of planning, monitoring, and adjusting drug dosage regimens for patients. - Dr. Jelliffe
10:00 AM - Introduction to the Win - USC*PACK Parametric Bayesian Clinical Program - Using PK software to optimize drug dosage - Dr. Jelliffe

Demo – One compartment model Planning the Initial regimen –
Gentamicin - entering past doses and levels, analyzing the data, planning the new regimen.
An difficult patient on Tobramycin.

10:20 AM – Introduction to the new MM-USC*PACK Nonparametric Bayesian Clinical Program for Optimally Precise Tracking of Drug Behavior and Optimally Precise Dosage.
The difficult patient on Tobramycin.

10:40 AM BREAK

10:55 AM - Modeling diffusion into endocardial vegetations, and the postantibiotic effect - Dr. Jelliffe

11:10 AM - Modeling bacterial growth and kill - Dr. Vinks.
The interesting patient on Tobramycin.

11:30 AM - Demo Vancomycin - Setting the initial goals, planning the initial regimen - Dr. Jelliffe. Continuous versus intermittent IV regimens.

11:45 AM - 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

12:15 PM - Lunch

1:30 PM – A New Unified Approach to Parametric and Nonparametric Population Modelling - Dr. Jelliffe

1:45 PM - Determining the Assay Error Polynomial - Dr. Jelliffe

2:00 PM - Parametric Population Models - Dr. Jelliffe
Iterative 2 stage Bayesian

2:30 PM Introduction to NONMEM - Dr. Thomson

3:15 PM Break

3:30 PM - Nonparametric Population models - Dr. Jelliffe
NPEM, NPML, NPAG

4:00 PM - Optimal procedures for population modelling - Dr. Jelliffe
First, determine the assay error pattern polynomial, to weight each data point properly
Second, use a parametric population model, get gamma, ranges
Third, use an NP population model, use gamma, ranges, get the entire parameter distribution. Why?

4:30 PM Multiple Model Dosage Design for maximally precise goal oriented, model based drug dosage regimens. - Dr. Jelliffe

5:00 PM – Adjourn

Day 2 - Intermediate and Advanced Population Modeling

8:30 AM - General Guidelines for making, validating, and comparing population PK/PD Models – Dr. Jelliffe
Weighting the data appropriately. Fitting the data – comparing methods.
Validating models – what does this involve?

Comparing patient populations – how to do this. Likelihoods, correlations.
9:00 AM – Optimal Times to get Serum concentrations – Dr. Vinks

9:20 AM - Demonstration - The NONMEM Parametric Population Modeling Program - Dr. Thomson

10:00 AM - Break

10:15 AM - Demonstration The IT2B Parametric Population Modeling Program. - Dr. Jelliffe
Modeling Amikacin. A typical patient data file
Running the program. Getting gamma, ranges, evaluating the results
10:30 AM - Demonstration The NPEM Nonparametric Population Modeling Program - Dr. Jelliffe
The new NPAG: NPEM with an Adaptive Grid
Modelling Amikacin further. Using gamma, ranges. Evaluating the results: the log-likelihood function, and descriptors of dispersion :
The 2 and 3-D plots of the marginal and joint marginal PDF's
Linking Nonparametric Models to Multiple Model Adaptive Control
Deriving individual Bayesian posterior patient parameter joint densities
Relationships between parameters and covariates
11:00 AM - Cost Effectiveness of Goal-Oriented, Model-Based Drug Regimens - Dr. Vinks.
11:40 AM – Converting Parametric Models to Nonparametric ones: The Maximum Entropy Approach. Dr. Jelliffe

12:00 Noon Lunch

1:15 PM - Making Large and Nonlinear Population Models - Dr. Jelliffe
1:30 PM - Demo The IT2B program. - Dr. Vinks
Demo - Using BOXES making a Michaelis-Menten model of Piperacillin
2:15 PM - Demo NONMEM and large models - Dr. Thomson

3:00 PM - Break

3:15 PM - Demo Big NPEM: Modelling Piperacillin - Dr. Vinks
Using gamma, ranges
3:45 PM - Big NPEM: Modeling Cyclosporine. Setting up the model, the data, the instructions, sending it over the web, analyzing it, evaluating the results - Dr. Hoem
4:30 PM - Clinical Application: Multiple Model Dosage Design - Dr. Jelliffe
5:00 PM - Group discussion session - all participants
5:30 PM - Adjourn