

# Time for Quantitative Clinical Pharmacology: A Proposal for a Pharmacometrics Curriculum

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**A formal training program in pharmacometrics is essential to train clinical pharmacology scientists. A proposal is made for a pharmacometrics curriculum. The curriculum has components at the undergraduate, graduate and postgraduate levels.**

## BACKGROUND

Ernest Rutherford is reputed to have said “Science is either stamp collecting or physics”.<sup>1</sup> Pharmacometrics provides a bridge between the stamp collecting (observations) and the physics (understanding) of medical science.

In 1990, a core curriculum for clinical pharmacology teaching of medical students was proposed by Nierenberg<sup>2–5</sup> and variations have been evaluated by other institutions. The common aim of these curricula is to train medical students to prescribe rationally when they became doctors. At the heart of a prescription is the selection of an appropriate drug, dose, and dosing regimen. The rational scientific basis for determining the correct dose for an individual patient rests on the disciplines of pharmacokinetics and pharmacodynamics, and quantitative evaluation of the dose–response relationship in clinical trials. These quantitative approaches embody the ideas and concepts of pharmacometrics.

In 1992, a group of scientists at Food and Drug Administration (FDA) and North American academic institutions pointed out the opportunities for using pharmacometric principles in drug development.<sup>6</sup> These ideas have been embraced widely and are a key component of the FDA Critical Path Initiative.<sup>7</sup>

Lewis Sheiner<sup>8–10</sup> has been a mentor to us and to many clinical pharmacologists who have explored quantitative clinical pharmacology. His contributions on pharmacometric topics have been numerous, but we highlight three because of the central role of applying pharmacokinetic–pharmacodynamic models to understand the pharmacological properties of drugs in clinical trials.

At a memorial symposium to Lewis Sheiner in 2006, a large number of clinical pharmacologists from academia,

health authorities, and industry gathered to pay tribute to his contributions to the science of clinical pharmacology. The final session of that meeting discussed the need for a core curriculum in pharmacometrics to maintain the momentum of his critical thinking and ideas.

On the basis of those discussions and our own experiences teaching pharmacometrics in an academic setting, we outline a proposal for a core curriculum to guide the training of clinicians and scientists involved in discovering and evaluating the properties of drugs.

## PROPOSAL

A central theme of our proposal relates to the need to consider *time*. Time is an essential component of almost all descriptions of drug actions in clinical trials. We explore how much time is needed to learn pharmacometrics, and at what times it could fit into the undergraduate, postgraduate, and postdoctoral training sequence. Finally, we propose that the time is upon us for renewed efforts in pharmacometric training.

Sheiner pointed out the need to recognize the separate goals of learning and confirming in drug development.<sup>10</sup> Pharmacometrics can be distinguished from biostatistics because its main aims are involved with the learning phases of clinical studies (quantitating drug properties), whereas biostatistics is concerned more with confirming processes (testing hypotheses).

## Aim of the curriculum

The aim of the curriculum is to train a pharmaceutical scientist to describe the time course of drug response in individual subjects, to identify individual factors (covariates), which predict differences in response, and to design clinical trials to elucidate drug properties.

## Students

Pharmacometricians will come mainly from three backgrounds – undergraduate training in medicine, pharmacy,

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**Table 1 Topics for an introductory pharmacometrics course**

Week	Lecture topic	Hands-on assignment
1	<i>Models and tools</i> Overview of PKPD modeling and pharmacometric tools	Log on to computer lab machine. Send an e-mail to the instructor to demonstrate basic computer competence
2	<i>User-defined models</i> Introduction to using Excel, ModelMaker and NONMEM	Code a simple PK model in Excel, ModelMaker, WinNonLin, and NONMEM
3	<i>Analysis of literature data</i> Discussion of how data is reported in the literature. Examples of literature reports with naïve or limited analysis	Find a clinical pharmacology data example in the literature. Propose a model and try to simulate it and estimate its parameters using Excel and WinNonLin
4	<i>Time course of effect</i> Immediate, delayed, and cumulative PKPD models	Simulate time course of effect in Excel. Estimate parameters using WinNonLin
5	<i>Absorption and disposition</i> First-order, zero-order, lag time absorption One and two compartment disposition	Simulate various absorption processes using Excel and estimate parameters using WinNonLin
6	<i>Lab discussion and presentation</i> Student presentation of literature analysis project. Discussion of results from previous weeks	—
7	<i>Ligand binding</i> One and two-site binding models with one and two ligands. Discussion of more complex ligand binding models and the need to properly account for measurement error	Use WinNonLin to estimate the parameters of a single binding site and a double binding site model with non-specific binding
8	<i>Error models and objective functions</i> Ordinary, weighted, and extended least-squares objective functions. The role of the residual error model in estimating parameters of a structural model	Use the Excel Solver Add-In to estimate parameters of simple PK and PD models with ordinary, weighted, and least-squares objective functions
9	<i>Two-compartment experiment</i> Description of a two-compartment model system built from two interconnected containers	Conduct an experiment with dye injected into the two-container system. Input is either a bolus, a constant rate infusion or a combination of a bolus, a constant rate, and a first-order decreasing infusion. Estimate the system parameters using WinNonLin
10	<i>Population Pd model</i> Description of mixed effect modeling and how to code simple models for NONMEM	NONMEM is used to analyze a pharmacodynamic data set taken from a real clinical trial. Students build their own models to search for covariates explaining the response to theophylline in asthma
11	<i>Population PK model</i> Further discussion of mixed effect models and the use of PREDPP for pharmacokinetic models with NONMEM	NONMEM is used to analyze a simulated pharmacokinetic data set. Students build their own models to describe the absorption and disposition and search for covariates explaining between subject differences
12	<i>Clinical trial design and simulation</i> Clinical trial simulation is explained as a means to design more informative trials	Students use the Pharsight Trial Simulator introduction to learn about trial simulation and how to use the program. They are asked to design a concentration-controlled trial similar to that used for the theophylline pharmacodynamic example studied previously

PKPD, pharmacokinetic-pharmacodynamic. An advanced pharmacometrics course of similar duration is illustrated in Table 2.

or pharmacology. These are the main sources of students because they are exposed to pharmacological concepts and become aware of the interesting challenges inherent in trying to describe drug action. Others will come from diverse non-biological backgrounds such as statistics and engineering. In particular, students with biostatistics or bioengineering background may have a suitable combination of skills, which with some physiology/pharmacology could provide a basis for pharmacometric studies.

### Undergraduate

A prerequisite for pharmacometrics is a sound understanding of general biology and pharmacology. The ability to interpret and describe clinical observations of drug action and its time course should be based firmly on sound pathophysiological and drug mechanism and disposition concepts. Basic concepts of statistics (properties of the normal distribution and linear regression analysis) and mathematics (elementary algebra and calculus) are necessary to apply pharmacometric methods. Familiarity with spreadsheet tables, formulae, and graphs (e.g., using Excel) provides a useful framework for subsequent computational tasks.

### Graduate

A systematic approach to the ideas and methods of pharmacometrics is best undertaken during the first graduate year, e.g., in a Masters or PhD program. Around 8 h per week might be expected from a student involved in an introductory one-semester course of lectures, tutorials, and hands-on computing assignments. Table 1 is an example of an introductory pharmacometrics course.<sup>11</sup>

An advanced pharmacometrics course of similar duration is illustrated in Table 2.

Students are expected to develop basic skills in a programming environment such as R, perl, Splus, or SAS. Database management skills are an essential part of pharmacometric data analysis projects. It also is essential to gain

**Table 2 Topics for an advanced pharmacometrics course**

Week	Lecture topic
1	Optimal design of PKPD studies
2	Model building strategies
3	Model diagnostics
4	Evaluation methods such as bootstrapping, predictive checks
5	Hypothesis testing based on randomization tests
6	Differential equation defined models
7	Non-continuous data analysis (binomial, categorical, frequency, time to event)
8	Bayesian estimation
9	Mixed effect methods
10	Disease Progression models
11	Advanced PKPD models
12	Simulation methods (deterministic and stochastic)

PKPD, pharmacokinetic-pharmacodynamic.

experience with the planning, conduct, and communication of results of pharmacometric projects.

### Postgraduate

Postgraduate training is a continuous process. Organizations, such as AAPS, offer specialized training as part of their annual meetings. PAGANZ (<http://www.paganz.org>) has a tradition of providing workshops for beginners and intermediate users in the use of mixed effect modeling methods.

### CONCLUSION

Central to the area of pharmacometrics is the concept of integrating multiple time courses—physiology, disease, drug intake, absorption, disposition, and action—and thus characterize (patho)physiological and pharmacological systems. A pharmacometric curriculum should provide the quantitative skills to students from a biological background. Likewise, students from a quantitative skills background could enter the area by learning physiology and pharmacology.

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### CONFLICT OF INTEREST

Dr Holford teaches pharmacometrics at the University of Auckland and at other institutions. Dr Karlsson is employed by Uppsala University, which is engaged in teaching pharmacometrics.

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