

**University of Rhode Island, College of Pharmacy
Department of Biomedical and Pharmaceutical Sciences**

**ADVANCED PHARMACOKINETICS COURSE (BPS 670)
SPRING 2009**

GENERAL INFORMATION

Course coordinators	Fatemeh Akhlaghi, PhD
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Office Hours	Wednesday, 2-4 PM

CLASS SCHEDULE

Time Wednesday, 4-7
Place Pharmacy Practice Laboratory, Room 107, Fogarty Hall
Number of Credits 3 credits

GUEST LECTURERS

Rebecca Boyd PhD; Pfizer Groton
Diane Mould PhD; Projections Inc
Sara Rosenbaum PhD; Uni. of Rhode Island
Karthik Venkatarakrishnan PhD; Millennium: The Takeda Oncology Company
Li J. Yu PhD; Millennium: The Takeda Oncology Company

OBJECTIVES

The objective of the Advanced Pharmacokinetics course is to provide students an overall familiarity with various techniques pertinent to clinical pharmacokinetic studies carried out in drug development and an introduction to pharmacokinetic and pharmacodynamic modeling. Upon successful completion of this course the student will:

- Appreciate the analytical methods used to measure total and free drug concentration and biomarker levels.
- Appreciate the importance of plasma protein or red blood cell binding on the pharmacokinetics.
- Understand the linear and non-linear regression methods and how to select the best model.
- Be familiar with design of drug-drug interaction, first in man and mass balance studies as well as dose proportionality assessment.
- Be able to carry out non-compartmental pharmacokinetics analysis using WinNonlin.
- Be able to carryout one or two compartmental analysis using WinNonlin.
- Be able to use WinNonlin to analyze pharmacodynamic data either by non-linear regression or non-compartmental method.
- Have general familiarity with pre-clinical pharmacokinetic methods and the design and execution of pharmaco- or toxico-kinetic studies in animal models.
- To have introductory knowledge of pharmacokinetics and pharmacodynamic issues pertinent to proteins and peptides.
- To be introduced to population pharmacokinetic analysis using NONMEM and to appreciate the content of a population pharmacokinetics paper or report.

OTHERS

It is essential for the students to come to all classes and to participate in the discussions. Prior knowledge of pharmacokinetic and pharmacodynamic parameters including T_{max}, C_{max}, AUC, Clearance, V_d, E_{max} and EC₅₀ is assumed by all the instructors.

You must have functioning WinNonlin software installed at your computer to be able to participate in most classes. Also the class assignment will involve using this software.

Reference Books

Pharmacokinetic and Pharmacodynamic Data Analysis: Concepts and Applications, Fourth Edition by Johan Gabrielsson and Daniel Weiner; Swedish Pharmaceutical Society; 4th edition (July 4, 2007), ISBN-10: 9197651001

Pharmacokinetic-Pharmacodynamic Modeling and Simulation by Peter Bonate; Springer; 1st edition, ISBN-10: 038727197X

Pharmacokinetics in Drug Development: Clinical Study Design and Analysis (Volume 1); Eds: Peter Bonate and Danny Howard, American Association of Pharmaceutical Scientists; 1st edition (December 5, 2005), ISBN-10: 0971176744

WinNonlin version 5.2 manuals (as PDF within the software)

COURSE SCHEDULE

Date	Lecturer	Subject
21-Jan-09	FA	Principles of analytical techniques used for the measurement of total or free drug and methods used to study drug distribution
28-Jan-09	FA	Analytical method validation, kinetics of plasma and red blood cell binding and the measurement of biomarkers/pharmacodynamic markers
4-Feb-09	FA	Review of linear and non-linear regression methods and model discrimination in pharmacokinetics
11-Feb-09	KV ¹	Risk assessment and clinical pharmacologic evaluation of drug-drug interactions in drug development: principles, methods and case studies
18-Feb-09	Holiday	<i>No class</i>
25-Feb-09	FA	Non-compartmental analysis of pharmacokinetic data using WinNonlin, bioequivalence studies
4-Mar-09	FA	One and two compartmental analysis of data (IV and oral) using WinNonlin
11-Mar-09	FA	Pharmacokinetic and pharmacodynamic modeling and case study, non-compartmental analysis of pharmacodynamic data using WinNonlin
18-Mar-09	Spring break	<i>No class</i>

25-Mar-09	FA	Different pharmacodynamic models and analysis of urinary excretion data using WinNonlin
1-Apr-09	LY ²	Design and impact of preclinical pharmacokinetic studies in drug discovery and development
8-Apr-09	RB ³	Design of first-time-in-man studies, mass balance studies and dose proportionality assessment
15-Apr-09	DM ⁴	The pharmacokinetics and pharmacodynamics of biotech products-special considerations?
22-Apr-09	SR	Introduction to population pharmacokinetics; interpretation of a population pharmacokinetic paper
29-Apr-09	FA	Presentation of assignment by students

¹ This lecture will review the basic scientific principles and current methods (both in vitro and clinical) utilized to assess the risk for pharmacokinetic drug-drug interactions (DDI) and their clinical pharmacologic evaluation in drug development. The focus will be on metabolic drug-drug interactions at the level of cytochrome P450 inhibition and induction, both for the new molecular entity as a victim and as a perpetrator, with case studies from a drug development setting used to illustrate these concepts. The related topic of assessment of the impact of pharmacogenetic variation in molecular determinants of drug disposition will also be briefly covered using illustrative examples.

² 2-5 PM; this lecture will review preclinical pharmacokinetics methods and animal studies as well as dose projection methods in human by the means of allometric scaling etc. Design of toxicokinetic studies will be also discussed.

³ design and execution of first-time in man studies will be discussed and well as mass balance studies and how dose-linearity is verified in drug development.

⁴ Special considerations have to be given when evaluating the pharmacokinetic and pharmacodynamic behavior of biotech products. Proteins do not undergo the same sort of metabolic clearance that small molecules do, instead being cleared by binding, proteolytic degradation and sometimes by neutralizing antibodies. In situations where the clearance is at least partly via receptor mediated binding, the pharmacokinetic can appear nonlinear. Changes in receptor level or saturation can dramatically alter the pharmacokinetic behavior of these agents. The pharmacodynamic behavior of biotech products generally follows indirect type mechanisms but can be affected by changes in receptor density, and also other receptor changes subsequent to treatment. This lecture will cover some of the general considerations for evaluating these agents.

⁵ This lecture will provide an overview of population pharmacokinetics method and its application using NONMEM software. Students will be introduced to various ways that models can be presented in NONMEM and to the parameters for inter and intra-individual variability.