



**APPLIED**

**BIOPHARMACEUTICS  
& PHARMACOKINETICS**

**FIFTH EDITION**

**LEON SHARGEL  
SUSANNA WU-PONG  
ANDREW B.C. YU**

APPLIED

BIOPHARMACEUTICS

& PHARMACOKINETICS

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5<sup>th</sup> Edition

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## Preface

The fifth edition of *Applied Biopharmaceutics and Pharmacokinetics* continues to maintain the scope and objectives of the previous editions. The major objective is to provide the reader with a basic understanding of the principles of biopharmaceutics and pharmacokinetics that can be applied to drug product development and drug therapy. This revised and updated edition of the popular text remains unique in teaching the student the basic concepts that may be applied to understanding the complex issues associated with the processes of drug delivery and the essentials of safe and effective drug therapy.

This text integrates basic scientific principles with clinical pharmacy practice and drug product development. Practical examples and questions are included to encourage students to apply the principles in patient care and drug consultation situations. Active learning and outcome-based objectives are highlighted.

The primary audience is pharmacy students enrolled in pharmaceutical science courses in pharmacokinetics and biopharmaceutics. This text fulfills course work offered in separate or combined courses in these subjects. A secondary audience for this textbook is research and development scientists in the pharmaceutical industry, particularly those in pharmaceutics, biopharmaceutics, and pharmacokinetics.

Some of the improvements in this edition include the re-ordering of the chapters and content to reflect the current curriculum in pharmaceutical sciences and the addition of two new chapters including *Pharmacogenetics* and *Impact of Drug Product Quality and Biopharmaceutics on Clinical Efficacy*. Each chapter has been revised to include the latest concepts in biopharmaceutics and pharmacokinetics with new practice problems and clinical examples that can be applied to pharmacy practice and research.

Susanna Wu-Pong, PhD, RPh, Associate Professor, Department of Pharmaceutics, Virginia Commonwealth University, Richmond, Virginia, has collaborated with the original authors. Her expertise adds to the quality of this edition.

*Leon Shargel  
Susanna Wu-Pong  
Andrew B.C. Yu  
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## **Applied Biopharmaceutics & Pharmacokinetics, 5th Edition**

Leon Shargel, Susanna Wu-Pong, Andrew B.C. Yu

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**GLOSSARY**

$A, B, C$ : Preexponential constants for three-compartment model equation

$a, b, c$ : Exponents for three-compartment model equation

$\alpha, \beta, \gamma$ : Exponents for three-compartment model equation (equivalent to  $a, b, c$  above)

$\lambda_1, \lambda_2, \lambda_3$ : Exponents for three-compartment-type exponential equation (equivalent to  $a, b, c$  above; more terms may be added and indexed numerically with  $\lambda$  subscripts for multiexponential models)

$A_b$ : Amount of drug in the body of time  $t$ ; *see also*  $D_b$

$A_b^{\infty}$ : Total amount of drug in the body

ANDA: Abbreviated New Drug Application; *see also* NDA

ANOVA: Analysis of variance

AUC: Area under the plasma level–time curve

$[AUC]^{\infty}_0$ : Area under the plasma level–time curve extrapolated to infinite time

$[AUC]^t_0$ : Area under the plasma level–time curve from  $t = 0$  to last measurable plasma drug concentration at time  $t$

AUMC: Area under the (first) moment–time curve

BA: Bioavailability

BCS: Biopharmaceutics classification system

BE: Bioequivalence

BMI: Body mass index

$C$ : Concentration (mass/volume)

$C_a$ : Drug concentration in arterial plasma

$C_{av}^{\infty}$ : Average steady-state plasma drug concentration

$C_c$  or  $C_p$ : Concentration of drug in the central compartment or in plasma

$C_{Cr}$ : Serum creatinine concentration, usually expressed as mg%

$C_{eff}$ : Minimum effective drug concentration

$C_{GI}$ : Concentration of drug in gastrointestinal tract

CI: Confidence interval

$C_m$ : Metabolite plasma concentration

$C_{max}$ : Maximum concentration of drug

$C_{max}^{\infty}$ : Maximum steady-state drug concentration

$C_{min}$ : Minimum concentration of drug

$C_{min}^{\infty}$ : Minimum steady-state drug concentration

$C_p$ : Concentration of drug in plasma

$C_p^0$ : Concentration of drug in plasma at zero time ( $t = 0$ )

$C_p^{\infty}$ : Steady-state plasma drug concentration (equivalent to  $C_{SS}$ )

$C_{p_n}$ : Last measured plasma drug concentration

$C_{SS}$ : Concentration of drug at steady state

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$C_t$ : Concentration of drug in tissue

$Cl_{Cr}$ : Creatinine clearance

$Cl_D$ : Dialysis clearance

$Cl_h$ : Hepatic clearance

$Cl_{int}$ : Intrinsic clearance

$Cl_{int}^f$ : Intrinsic clearance (unbound or free drug)

$Cl_{nr}$ : Nonrenal clearance

$Cl_R$ : Renal clearance

$Cl^u_R$ : Renal clearance of uremic patient

$Cl_T$ : Total body clearance

CRFA Cumulative relative fraction absorbed

$C_v$ : Drug concentration in venous plasma

$D$ : Amount of drug (mass, eg, mg)

$D_A$ : Amount of drug absorbed

$D_B$ : Amount of drug in body

$D_E$ : Drug eliminated

$D_{GI}$ : Amount of drug in gastrointestinal tract

$D_L$ : Loading (initial) dose

$D_m$ : Maintenance dose

$D_U$ : Total amount of metabolite excreted in the urine

$D_N$  Normal dose

$D_p$ : Drug in central compartment

$D_t$ : Amount of drug in tissue

$D_u$ : Amount of drug in urine

$D_0$ : Dose of drug

$D^0$ : Amount of drug at zero time ( $t = 0$ )

$E$ : Pharmacologic effect

$e$ : Intercept on  $y$  axis of graph relating pharmacologic response to log drug concentration

$E_{max}$ : Maximum pharmacologic effect

$E_0$ : Pharmacologic effect at zero drug concentration

$EC_{50}$ : Drug concentration that produces 50% maximum pharmacologic effect

ELS: Extended least square

ER: Extraction constant (equivalent to  $E_h$ ); extraction ratio

$F$ : Fraction of dose absorbed (bioavailability factor)

$f$ : Fraction of dose remaining in body

$f_e$ : Fraction of unchanged drug excreted unchanged in urine

$f_u$ : Unbound fraction of drug

FDA: U.S. Food and Drug Administration

$f(t)$ : Function representing drug elimination over time (time is the independent variable)

$f'(t)$ : Derivative of  $f(t)$

GFR: Glomerular filtration rate

GI: Gastrointestinal tract

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GMP: Good Manufacturing Practice

IBW: Ideal body weight

IVIVC: *In-vitro* ↔ *in-vivo* correlation

$k$ : Overall drug elimination rate constant ( $k = k_e + k_m$ ); first-order rate constant, similar to  $k_{e1}$

$K_a$ : Association binding constant

$k_a$ : First-order absorption rate constant

$K_d$ : Dissociation binding constant

$k_e$ : Excretion rate constant (first order)

$k_{e0}$ : Transfer rate constant out of the effect compartment

$K_M$ : Michaelis-Menten constant

$k_m$ : Metabolism rate constant (first order)

$k_N$ : Normal elimination rate constant (first order)

$k_{NR}^N$ : Nonrenal elimination constant of normal patient

$k_{NR}^U$ : Renal elimination constant of uremic patient

$k_U$ : Uremic elimination rate constant (first order)

$k_0$ : Zero-order absorption rate constant

$k_{1e}$ : Transfer rate constant from the central to the effect compartment

$k_{12}$ : Transfer rate constant (from the central to the tissue compartment); first-order transfer rate constant from compartment 1 to compartment 2

$k_{21}$ : Transfer rate constant (from the tissue to the central compartment); first-order transfer rate constant from compartment 2 to compartment 1

LBW: Lean body weight

$m$ : Slope (also slope of  $E$  versus  $\log C$ )

$M_U$ : Amount of metabolite excreted in urine

MAT: Mean absorption time

MDT: Mean dissolution time

MEC: Minimum effective concentration

MLP: Maximum life-span potential

MRT: Mean residence time

$MRT_c$ : Mean residence time from the central compartment

$MRT_p$ : Mean residence time from the peripheral compartment

$MRT_t$ : Mean residence time from the tissue compartment (same as  $MRT_p$ )

MTC: Minimum toxic concentration

$\mu_0$ : Area under the zero moment curve (same as AUC)

$\mu_1$ : Area under the first moment curve (same as AUMC)

NDA: New Drug Application

NONMEN: Nonlinear mixed effect model

$P$ : Amount of protein

PD: Pharmacodynamics

PK: Pharmacokinetics

$Q$ : Blood flow

$R$ : Infusion rate; ratio of  $C_{max}$  after  $N$  dose to  $C_{max}$  after one dose ( $\rho$ ) (accumulation ratio); pharmacologic response ( $\rho$ )

$r$ : Ratio of mole of drug bound to total moles of protein

$R_{max}$ : Maximum pharmacologic response

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SD: Standard deviation

$t$ : Time (hours or minutes); denotes tissue when used as a subscript

$t_{\text{eff}}$ : Duration of pharmacologic response to drug

$t_{\text{inf}}$ : Infusion period

$t_{\text{lag}}$ : Lag time

$t_{\text{max}}$ : Time of occurrence for maximum (peak) drug concentration

$t_0$ : Initial or zero time

$t_{1/2}$ : Half-life

$\tau$ : Time interval between doses

USP: *United States Pharmacopeia*

$V$ : Volume (L or mL)

$v$ : Velocity

$V_{\text{app}}$ : Apparent volume of distribution (binding)

$V_C$ : Volume of central compartment

$V_D$ : Volume of distribution

$V_e$ : Volume of the effect compartment

$V_{\text{max}}$ : Maximum metabolic rate

$V_p$ : Volume of plasma (central compartment)

$V_t$ : Volume of tissue compartment

$(V_D)_{\text{exp}}$ : Extrapolated volume of distribution

$(V_D)_{\text{SS}}$  or  $V_{\text{DSS}}$ : Steady-state volume of distribution

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