Notice

Medicine is an ever-changing science. As new research and clinical experience broaden our knowledge, changes in treatment and drug therapy are required. The authors and the publisher of this work have checked with sources believed to be reliable in their efforts to provide information that is complete and generally in accord with the standards accepted at the time of publication. However, in view of the possibility of human error or changes in medical sciences, neither the authors nor the publisher nor any other party who has been involved in the preparation or publication of this work warrants that the information contained herein is in every respect accurate or complete, and they disclaim all responsibility for any errors or omissions or for the results obtained from use of the information contained in this work. Readers are encouraged to confirm the information contained herein with other sources. For example and in particular, readers are advised to check the product information sheet included in the package of each drug they plan to administer to be certain that the information contained in this work is accurate and that changes have not been made in the recommended dose or in the contraindications for administration. This recommendation is of particular importance in connection with new or infrequently used drugs.
About the Authors

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Preface

The publication of this sixth edition of *Applied Biopharmaceutics and Pharmacokinetics* represents over 30 years in print. We are grateful to our readers for their loyalty and helpful suggestions throughout the years. As with the previous editions, we want to continue to maintain our original scope and objectives.

This text integrates basic scientific principles with drug product development and clinical pharmacy practice.

The major objective is to provide the reader with a basic and practical understanding of the principles of biopharmaceutics and pharmacokinetics that can be applied to drug product development and to drug therapy. This revised and updated edition of the text remains unique in teaching basic concepts that may be applied to understanding complex issues associated with *in vivo* drug delivery that are essential for safe and efficacious drug therapy.

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. Secondary audiences for this textbook are research and development scientists in pharmacuetics, biopharmaceutics, and pharmacokinetics.

**There are many improvements in this edition.**

- **Chapter Objectives** are added at the beginning of each chapter
- **Chapter Summary** at the end of each chapter.
- **Frequently Asked Questions** are seeded within each chapter to help the student focus on key concepts.
- Most chapters are revised to reflect our current understanding of drug disposition, pharmacodynamics, and drug therapy.
- The growing importance of drug transporters, CYP enzymes, and influence of pharmacogenetics on long-term drug response and other relevant topics have been updated to reflect current knowledge and application of pharmacokinetic/pharmacodynamics to drug therapy.
- **Chapter 15 is expanded and re-titled, Drug Product Performance, In Vivo: Bioavailability and Bioequivalence**, to reflect the consideration of bioequivalence as an *in vivo* measure of drug product performance and that bioequivalence is important in both brand and generic drug product development.
- **Chapter 16 is now titled, Impact of Drug Product Quality and Biopharmaceutics on Clinical Efficacy.** This chapter describes the types of safety and efficacy risks and various means for preventing them including the roles of drug product quality and drug product performance.
- In addition, the concept of quality-by-design (QbD) may be applied to improve critical quality attributes essential for drug product safety and efficacy
- **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.**

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

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## Glossary

<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Definition</th>
</tr>
</thead>
<tbody>
<tr>
<td>A, B, C</td>
<td>Preexponential constants for three-compartment model equation</td>
</tr>
<tr>
<td>a, b, c</td>
<td>Exponents for three-compartment model equation</td>
</tr>
<tr>
<td>( \alpha, \beta, \gamma )</td>
<td>Exponents for three-compartment model equation (equivalent to ( a, b, c ) above)</td>
</tr>
<tr>
<td>( \lambda_1, \lambda_2, \lambda_3 )</td>
<td>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)</td>
</tr>
<tr>
<td>Ab</td>
<td>Amount of drug in the body of time ( t ); see also ( D_B )</td>
</tr>
<tr>
<td>( \text{Ab}^\infty )</td>
<td>Total amount of drug in the body</td>
</tr>
<tr>
<td>ABC</td>
<td>ABC transport protein</td>
</tr>
<tr>
<td>AE</td>
<td>Adverse event</td>
</tr>
<tr>
<td>ANDA</td>
<td>Abbreviated New Drug Application; see also NDA</td>
</tr>
<tr>
<td>ANOVA</td>
<td>Analysis of variance</td>
</tr>
<tr>
<td>API</td>
<td>Active pharmaceutical ingredient</td>
</tr>
<tr>
<td>AUC</td>
<td>Area under the plasma level–time curve</td>
</tr>
<tr>
<td>([\text{AUC}]_0)</td>
<td>Area under the plasma level–time curve extrapolated to infinite time</td>
</tr>
<tr>
<td>([\text{AUC}]_0^{t} )</td>
<td>Area under the plasma level–time curve from ( t = 0 ) to last measurable plasma drug concentration at time ( t )</td>
</tr>
<tr>
<td>AUMC</td>
<td>Area under the (first) moment–time curve</td>
</tr>
<tr>
<td>BA</td>
<td>Bioavailability</td>
</tr>
<tr>
<td>BCS</td>
<td>Biopharmaceutics classification system</td>
</tr>
<tr>
<td>BDDCS</td>
<td>Drug disposition classification system</td>
</tr>
<tr>
<td>BE</td>
<td>Bioequivalence</td>
</tr>
<tr>
<td>BLA</td>
<td>Biologic license application</td>
</tr>
<tr>
<td>BM</td>
<td>Biomarker</td>
</tr>
<tr>
<td>BMI</td>
<td>Body mass index</td>
</tr>
<tr>
<td>BRCP</td>
<td>Breast cancer-resistance protein (an ABC transporter)</td>
</tr>
<tr>
<td>BUN</td>
<td>Blood urea nitrogen</td>
</tr>
<tr>
<td>C</td>
<td>Concentration (mass/volume)</td>
</tr>
<tr>
<td>( C_a )</td>
<td>Drug concentration in arterial plasma</td>
</tr>
<tr>
<td>( C_{av} )</td>
<td>Average steady-state plasma drug concentration; see also</td>
</tr>
<tr>
<td>( C_c ) or ( C_p )</td>
<td>Concentration of drug in the central compartment or in plasma</td>
</tr>
<tr>
<td>( C_{Cr} )</td>
<td>Serum creatinine concentration, usually expressed as mg%</td>
</tr>
<tr>
<td>CE</td>
<td>Clinical endpoint</td>
</tr>
<tr>
<td>( C_{eff} )</td>
<td>Minimum effective drug concentration</td>
</tr>
<tr>
<td>( C_{GI} )</td>
<td>Concentration of drug in gastrointestinal tract</td>
</tr>
<tr>
<td>CI</td>
<td>Confidence interval</td>
</tr>
<tr>
<td>( C_m )</td>
<td>Metabolite plasma concentration</td>
</tr>
<tr>
<td>( C_{\text{max}} )</td>
<td>Maximum concentration of drug</td>
</tr>
<tr>
<td>Symbol</td>
<td>Definition</td>
</tr>
<tr>
<td>---------</td>
<td>---------------------------------------------------------------------------</td>
</tr>
<tr>
<td>$C_{max}$</td>
<td>Maximum steady-state drug concentration; see also $C_{ssmax}$</td>
</tr>
<tr>
<td>$C_{min}$</td>
<td>Minimum concentration of drug</td>
</tr>
<tr>
<td>$C_{min}$</td>
<td>Minimum steady-state drug concentration; see also $C_{ssmin}$</td>
</tr>
<tr>
<td>$C_p$</td>
<td>Concentration of drug in plasma</td>
</tr>
<tr>
<td>$C_p^0$</td>
<td>Concentration of drug in plasma at zero time ($t = 0$) (equivalent to $C_0$)</td>
</tr>
<tr>
<td>$C_p'$</td>
<td>Steady-state plasma drug concentration (equivalent to $C_{ss}$)</td>
</tr>
<tr>
<td>$C_{p,u}$</td>
<td>Last measured plasma drug concentration</td>
</tr>
<tr>
<td>$C_{ss}$</td>
<td>Concentration of drug at steady state</td>
</tr>
<tr>
<td>$C_{ssav}$</td>
<td>Average concentration at steady state</td>
</tr>
<tr>
<td>$C_{ssmax}$</td>
<td>Maximum concentration at steady state</td>
</tr>
<tr>
<td>$C_{ssmin}$</td>
<td>Minimum concentration at steady state</td>
</tr>
<tr>
<td>$C_t$</td>
<td>Concentration of drug in tissue</td>
</tr>
<tr>
<td>cGMP</td>
<td>Current good manufacturing practices</td>
</tr>
<tr>
<td>CKD</td>
<td>Chronic kidney disease</td>
</tr>
<tr>
<td>$Cl_{Cr}$</td>
<td>Creatinine clearance</td>
</tr>
<tr>
<td>$Cl_{D}$</td>
<td>Dialysis clearance</td>
</tr>
<tr>
<td>$Cl_h$</td>
<td>Hepatic clearance</td>
</tr>
<tr>
<td>$Cl_{int}$</td>
<td>Intrinsic clearance</td>
</tr>
<tr>
<td>$Cl_{int}^u$</td>
<td>Intrinsic clearance (unbound or free drug)</td>
</tr>
<tr>
<td>$Cl_{nr}$</td>
<td>Nonrenal clearance</td>
</tr>
<tr>
<td>$Cl_{R}$</td>
<td>Renal clearance</td>
</tr>
<tr>
<td>$Cl_{R}^u$</td>
<td>Renal clearance of uremic patient</td>
</tr>
<tr>
<td>$Cl_t$</td>
<td>Total body clearance</td>
</tr>
<tr>
<td>COX-1</td>
<td>Cyclo-oxygenase-1</td>
</tr>
<tr>
<td>CRF</td>
<td>Case report form</td>
</tr>
<tr>
<td>CRFA</td>
<td>Cumulative relative fraction absorbed</td>
</tr>
<tr>
<td>$C_v$</td>
<td>Drug concentration in venous plasma</td>
</tr>
<tr>
<td>%CV</td>
<td>Percent coefficient of variation</td>
</tr>
<tr>
<td>CYP</td>
<td>Cytochrome P-450</td>
</tr>
<tr>
<td>$D$</td>
<td>Amount of drug (mass, eg, mg)</td>
</tr>
<tr>
<td>$D_A$</td>
<td>Amount of drug absorbed</td>
</tr>
<tr>
<td>$D_B$</td>
<td>Amount of drug in body</td>
</tr>
<tr>
<td>$D_{L}$</td>
<td>Loading (initial) dose</td>
</tr>
<tr>
<td>$D_{m}$</td>
<td>Maintenance dose</td>
</tr>
<tr>
<td>$D_{GI}$</td>
<td>Amount of drug in gastrointestinal tract</td>
</tr>
<tr>
<td>$D_{N}$</td>
<td>Normal dose</td>
</tr>
<tr>
<td>$D_{P}$</td>
<td>Drug in central compartment</td>
</tr>
<tr>
<td>$D_{u}$</td>
<td>Amount of drug in tissue</td>
</tr>
<tr>
<td>$D_{0}$</td>
<td>Dose of drug</td>
</tr>
<tr>
<td>$D_0$</td>
<td>Amount of drug at zero time ($t = 0$)</td>
</tr>
<tr>
<td>$E$</td>
<td>Pharmacologic effect</td>
</tr>
<tr>
<td>$e$</td>
<td>Intercept on y axis of graph relating pharmacologic response to log drug concentration</td>
</tr>
<tr>
<td>eGFR</td>
<td>Estimate of GFR based on an MDRD equation</td>
</tr>
<tr>
<td>$E_{max}$</td>
<td>Maximum pharmacologic effect</td>
</tr>
<tr>
<td>$E_0$</td>
<td>Pharmacologic effect at zero drug concentration</td>
</tr>
<tr>
<td>$EC_{50}$</td>
<td>Drug concentration that produces 50% maximum pharmacologic effect</td>
</tr>
<tr>
<td>ELS</td>
<td>Extended least square</td>
</tr>
<tr>
<td>ER</td>
<td>Extraction constant (equivalent to $E_h$); extraction ratio</td>
</tr>
<tr>
<td>$F$</td>
<td>Fraction of dose absorbed (bioavailability factor)</td>
</tr>
<tr>
<td>$f$</td>
<td>Fraction of dose remaining in the body</td>
</tr>
<tr>
<td>$f_e$</td>
<td>Fraction of unchanged drug excreted unchanged in urine</td>
</tr>
<tr>
<td>$f_{u}$</td>
<td>Unbound fraction of drug</td>
</tr>
<tr>
<td>$f(t)$</td>
<td>Function representing drug elimination over time (time is the independent variable)</td>
</tr>
<tr>
<td>$f'(t)$</td>
<td>Derivative of $f(t)$</td>
</tr>
<tr>
<td>GI</td>
<td>Gastrointestinal tract</td>
</tr>
<tr>
<td>GFR</td>
<td>Glomerular filtration rate</td>
</tr>
<tr>
<td>GI</td>
<td>Gastrointestinal tract</td>
</tr>
<tr>
<td>GMP</td>
<td>Good Manufacturing Practice</td>
</tr>
<tr>
<td>[I]</td>
<td>Inhibitor concentration in an enzymatic reaction</td>
</tr>
</tbody>
</table>
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 \(k_{el}\)
\(K_a\)  Association binding constant
\(k_a\)  First-order absorption rate constant
\(K_d\)  Dissociation binding constant
\(k_e\)  Excretion rate constant (first order)
\(k_{el}\)  Excretion rate constant (first order)
\(k_{e0}\)  Transfer rate constant out of the effect compartment
\(k_i\)  Inhibition constant: \(= k_f/k_p\)
\(K_M\)  Michaelis–Menten constant
\(k_m\)  Metabolism rate constant (first order)
\(k_N\)  Normal elimination rate constant (first order)
\(k_{NR}\)  Nonrenal elimination constant of normal patient
\(k_{NR}^U\)  Renal elimination constant of uremic patient
\(k_u\)  Uremic elimination rate constant (first order)
\(k_{on}\)  First-order association rate constant
\(k_{off}\)  First-order dissociation constant
\(k_0\)  Zero-order absorption rate constant
\(k_{le}\)  Transfer rate constant from the central to the effect compartment
\(k_{21}\)  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
mAbs  Monoclonal antibodies
MAT  Mean absorption time
MDR1  p-Glycoprotein, ABCB1
MDRD  MDRD equation used to estimate of GFR
MDT  Mean dissolution time
MEC  Minimum effective concentration
miRNA  MicroRNA
MLP  Maximum life-span potential
MRP  Multidrug resistance-associated proteins
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
NTI  Narrow therapeutic index; see also critical dose drug
OTC  Over-the-counter drugs
OATP  Organic anion transporting polypeptide
OAT  Organic anion transporter
\(P\)  Amount of protein
PD  Pharmacodynamics
PEG  Polyethylene glycol
P-gp  p-Glycoprotein, MDR1, ABCB1
PGt  Pharmacogenetics
PK  Pharmacokinetics
PPI  Patient package insert
\(Q\)  Blood flow
QA  Quality assurance
QBd  Quality by design
QC  Quality control
<table>
<thead>
<tr>
<th>Symbol</th>
<th>Definition</th>
</tr>
</thead>
<tbody>
<tr>
<td>$R$</td>
<td>Infusion rate; ratio of $C_{\text{max}}$ after $n$ dose to $C_{\text{max}}$ after one dose (see Chapter 8) (accumulation ratio); pharmacologic response (see Chapter 19)</td>
</tr>
<tr>
<td>$r$</td>
<td>Ratio of mole of drug bound to total moles of protein</td>
</tr>
<tr>
<td>$R_{\text{max}}$</td>
<td>Maximum pharmacologic response</td>
</tr>
<tr>
<td>RLD</td>
<td>Reference-listed drug</td>
</tr>
<tr>
<td>RNA</td>
<td>Ribonucleic acid</td>
</tr>
<tr>
<td>RNAi</td>
<td>RNA interference</td>
</tr>
<tr>
<td>SD</td>
<td>Standard deviation</td>
</tr>
<tr>
<td>siRNA</td>
<td>Small inhibitory RNA</td>
</tr>
<tr>
<td>SNP</td>
<td>Single-nucleotide polymorphism</td>
</tr>
<tr>
<td>$t$</td>
<td>Time (hours or minutes); denotes tissue when used as a subscript</td>
</tr>
<tr>
<td>$t_{\text{eff}}$</td>
<td>Duration of pharmacologic response to drug</td>
</tr>
<tr>
<td>$t_{\text{inf}}$</td>
<td>Infusion period</td>
</tr>
<tr>
<td>$t_{\text{lag}}$</td>
<td>Lag time</td>
</tr>
<tr>
<td>$t_{\text{max}}$</td>
<td>Time of occurrence for maximum (peak) drug concentration</td>
</tr>
<tr>
<td>$t_0$</td>
<td>Initial or zero time</td>
</tr>
<tr>
<td>$t_{1/2}$</td>
<td>Half-life</td>
</tr>
<tr>
<td>$\tau$</td>
<td>Time interval between doses</td>
</tr>
<tr>
<td>USP</td>
<td><em>United States Pharmacopeia</em></td>
</tr>
<tr>
<td>$V$</td>
<td>Volume (L or mL)</td>
</tr>
<tr>
<td>$v$</td>
<td>Velocity</td>
</tr>
<tr>
<td>$V_{\text{app}}$</td>
<td>Apparent volume of distribution (binding)</td>
</tr>
<tr>
<td>$V_C$</td>
<td>Volume of central compartment</td>
</tr>
<tr>
<td>$V_D$</td>
<td>Volume of distribution</td>
</tr>
<tr>
<td>$V_e$</td>
<td>Volume of the effect compartment</td>
</tr>
<tr>
<td>$V_i$</td>
<td>$V_i$ and $V$ are the reaction velocity with and without inhibitor, respectively</td>
</tr>
<tr>
<td>$V_{\text{max}}$</td>
<td>Maximum metabolic rate</td>
</tr>
<tr>
<td>$V_p$</td>
<td>Volume of plasma (central compartment)</td>
</tr>
<tr>
<td>$V_t$</td>
<td>Volume of tissue compartment</td>
</tr>
<tr>
<td>$(V_D)_{\text{exp}}$</td>
<td>Extrapolated volume of distribution</td>
</tr>
<tr>
<td>$(V_D)<em>{\text{SS}}$ or $V</em>{\text{DSS}}$</td>
<td>Steady-state volume of distribution</td>
</tr>
</tbody>
</table>