Clinical Pharmacokinetics and Pharmacodynamics

CONCEPTS AND APPLICATIONS

FOURTH EDITION

Clinical Pharmacokinetics and Pharmacodynamics

Concepts and Applications

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To Dawn and Margaret
for their continual love, patience, and tolerance.

ABOUT THE AUTHORS

MALCOLM ROWLAND

Malcolm Rowland is Professor Emeritus and former Dean (1998–2001), School of Pharmacy and Pharmaceutical Sciences, University of Manchester, and Adjunct Professor, School of Pharmacy, University of California, San Francisco. He was President of the European Federation of Pharmaceutical Sciences (1996–2000) and Vice-President, International Pharmaceutical Federation (FIP; 2001–2008), the organization that represents and serves pharmacy and pharmaceutical sciences around the globe. He received his pharmacy degree and PhD from the University of London, and was on faculty at the School of Pharmacy, University of California, San Francisco (1967–1975).

Dr. Rowland, together with Dr. Thomas Tozer, authored the introductory textbook, *Introduction to Pharmacokinetics and Pharmacodynamics: The Quantitative Basis of Drug Therapy*. He has authored over 300 scientific articles and chapters. His research interest is primarily in physiologically-based pharmacokinetics and its application to drug development and clinical use. In particular, he has pioneered the concept and application of clearance and developed approaches to the prediction of pharmacokinetics of drugs from a combination of physicochemical properties and in vitro information. He was an editor of the Journal of Pharmacokinetics and Pharmacodynamics (1973–2006), the premier journal dedicated to the subject, and has established workshops for teaching both basic- and advanced-level pharmacokinetics. He is an advisor to the pharmaceutical industry and sits on various scientific advisory boards.

Dr. Rowland has been awarded honorary doctorate degrees from the University of Poitiers (France) and Uppsala University (Sweden) as well as Honorary Membership of the Royal College of Physicians (London). He received various awards including the Distinguished Investigator Award of the American College of Clinical Pharmacology (ACCP, 2007) and the Millennial Pharmaceutical Scientist Award (FIP BPS, 2000). He has been made a fellow of the Academy of Medical Sciences, ACCP (Hon), American Association of Pharmaceutical Scientists, the Royal Pharmaceutical Society of Great Britain, and the Institute of Mathematics.

THOMAS N. TOZER

Dr. Tozer, Professor Emeritus of Biopharmaceutical Sciences and Pharmaceutical Chemistry, School of Pharmacy, University of California, San Francisco, received his BS, PharmD, and PhD degrees from the University of California, San Francisco. He is currently an Adjunct Professor of Pharmacology at the University of California, San Diego, where he teaches biopharmaceutics and clinical pharmacokinetics at the Skaggs School of Pharmacy and Pharmaceutical Sciences. After a 2-year postdoctoral fellowship in the laboratory of Dr. B. B. Brodie, National Institutes of Health,

Bethesda, Maryland, he joined the Faculty of the School of Pharmacy in San Francisco in 1965. Although now in emeritus status, he continues to teach courses and workshops in pharmacokinetics/pharmacodynamics and clinical pharmacokinetics at several institutions in the United States and Europe.

Dr. Tozer, together with Dr. Malcolm Rowland, authored *Clinical Pharmacokinetics: Concepts and Applications*, the title of the first three editions of this textbook. He has published more than 155 scientific papers on a variety of research topics with emphasis on the development and application of kinetic concepts in drug therapy. Dr. Tozer's research before retirement was focused in four areas: colon-specific drug delivery, toxicokinetics, kinetics of potential contrast agents for magnetic resonance imaging, and nonlinear pharmacokinetics. Other research included determination of drug disposition in disease states, particularly end-state renal disease. Emphasis here was placed on evaluating and predicting when and how drug administration to renal disease patients should be altered.

Dr. Tozer was a corecipient of the 2000 Meritorious Manuscript Award, American Association of Pharmaceutical Scientists, and was a Visiting Professor (1996–1999) at the University of Manchester, Manchester, England. He is a Fellow of the American Association of Pharmaceutical Scientists and has served as a consultant to the Food and Drug Administration and to many pharmaceutical companies.

PREFACE

Much has happened in the field of our textbook since the last edition was published in 1995. First, in recognition that there was a readership that sought a less in-depth textbook we wrote a companion, entitled *Introduction to Pharmacokinetics and Pharmacodynamics: The Quantitative Basis of Drug Therapy*; it was published in 2006. While emphasizing pharmacokinetics, the widening to include pharmacodynamics as an integral part of this introductory text reflected the increasing body of knowledge linking the two elements that explain the relationship between drug administration and response. We have continued this trend of integrating pharmacodynamics with pharmacokinetics in the current text, which is reflected in the title. Second, in addition to an expanding knowledge of pharmacodynamics, there has been an explosion in our understanding at the molecular and mechanistic levels of all the processes controlling the pharmacokinetics of drugs. The availability of the introductory text has therefore allowed us the opportunity to expand in this current edition on these new insights for those readers wishing to gain a greater in-depth understanding of the subject. This has required some enlargement over previous editions, but every attempt has been made to limit the size of the book.

As in our previous three editions, we are committed to developing and applying the concepts to explain and improve the therapeutic use of drugs. As such, we continue to have students and practitioners in pharmacy, medicine, pharmacology, and allied professions in mind as our readers. Accordingly, although the principles have wide application, emphasis continues to be at the clinical level. We recognize, however, that pharmacokinetics and pharmacodynamics are cornerstones in the industrial design, selection, and development of new drugs, and so believe that this textbook is of equal value to scientists engaged in all aspects of the pharmaceutical industry, as well as those working in regulatory agencies evaluating drug applications.

In addition to more detailed consideration of the basic principles compared to the introductory text, the current textbook expands greatly on why individuals vary in their response to drugs, which is central to personalizing drug therapy. Furthermore, there is an increase in the number of thought-provoking problems at the end of each chapter, with answers provided in the last appendix. While maintaining the overall structure and organization, there are also significant improvements over the third edition. In particular, we have incorporated advances in our understanding of the role of enzymes and transporters in pharmacokinetics, and of genetics in both pharmacokinetics and pharmacodynamics. As briefly mentioned above, we have greatly expanded on pharmacodynamics, which was a single chapter in the specialized topic section of the last edition, and have integrated it throughout the book. We have also incorporated Turnover Concepts and Dialysis, which were also previously specialized topics, into the body of the book, recognizing that these are fundamental to the subject. We have also added two new chapters. One deals with protein drugs, reflecting the rapid increase in recent years in the number of such medicines that have become a part of the armamentarium of modern therapeutics. The second concerns the prediction of human pharmacokinetics from in vitro and preclinical data, and subsequent simulation of likely kinetics in patients under a wide variety of clinical conditions and situations, which can improve the chances of selecting compounds that have desirable pharmacokinetic characteristics in planning clinical drug trials and in ensuring their subsequent optimal use.

We have also updated all chapters and replaced many of the examples and case histories with more modern ones, while providing many new problems with answers. To help approach these problems, we have provided at the end of each chapter a summary of key relationships. In addition, Drs. Hartmut Derendorf and Guenther Hochhaus, University of Florida, have prepared web-based simulations of many of the concepts presented throughout the book. The simulations allow the reader to explore the influence of changes in parameter values in both pharmacokinetics and pharmacodynamics on drug concentration and response with time following drug administration. Finally, to conform to the quality of all new figures, of which there are many, we have redrawn or improved the figures retained from previous editions.

ACKNOWLEDGMENTS

As with all previous editions, we wish to thank the many students, as well as participants of various workshops that we have taught, and colleagues for helping us shape the fourth edition. Their enthusiasm, commitment, and appreciation continue to be a source of immense satisfaction to us. We would also like to thank in particular Joe Balthasar for critiquing the protein drug chapter and Amin Rostami for assistance in the simulation of pharmacokinetic profiles in virtual patient populations.

It is now 30 years since the first edition of our textbook was published. Throughout this period, we have been enormously gratified by the wide and varied readership around the world, sometimes in the most unexpected of places. Our wish has always been to contribute to the improved design and more rational use of medicines. We hope that this fourth edition helps further this aspiration.

Malcolm Rowland, Manchester, UK
Thomas N. Tozer, San Francisco, California

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APPENDICES

NONPROPRIETARY AND BRAND NAMES OF DRUGS IN TEXT AND ILLUSTRATIONS

(For those drugs available only by brand name at time of manuscript submission, the brand name is provided.)

Abacavir	Ziagen	Asparaginase	Elspar
Abatacept		Aspirin	
Abciximab	ReoPro	Astemizole	
Acenocoumarol		Atenolol	
Acetaminophen		Atorvastatin	Lipitor
Acetazolamide		Azathioprine	
Acetylsalicylic acid		Azelastine	
Acyclovir		Azithromycin	
Adalimumab	Humira		
Adefovir		Bacitracin	
Agalsidase		Barbital	
Albendazole	Albenza	Basiliximab	Simulect
Albuterol		Benzylpenicillin	
Aldesleukin		Bethanechol Chloride	
Alefacept	Amevive		
Alemtuzumab	Campath	Bevacizumab	Avastin
Alendronate sodium	Fosamax	Bivalirudin	Angiomax
Alfentanil		Bosentan	Tracleer
Alglucosidase alfa	Myozyme	Budesonide	Pulmicort Respules® and Entocort EC
Allopurinol			
Alprazolam			
Alprenolol		Bufurolol	
Alteplase		Bumetanide	
Amikacin		Buprenorphine	
Amiloride		Bupropion	
Aminosalicylic acid		Buspirone	
Amiodarone		Busulfan	
Amitriptyline			
Amoxicillin		Caffeine	
Ampicillin		Calcitonin-salmon	Miacalcin
Amprenavir	Agenerase	Capromab pendetide	ProstaScint Kit
Amrinone		Captopril	
Anakinra	Kineret	Carbamazepine	
Anidulafungin		Carbenicillin	
Antipyrine		Carmustine	
Antihemophilic Factor (VIII)		Cefamandole	
		Cefazolin	
Antithrombin III		Cefepime	
Aprepitant	Emend	Cefonicid	
Aprotinin		Ceforanide	
Ascorbic acid		Cefotaxime	

Cefprozil	
Cefsulodin	
Ceftazidime	
Ceftizoxime	
Ceftriaxone	
Cefuroxime	
Celecoxib	Celebrex
Cephalexin	Keflex
Cephalothin	
Cephradine	
Cerivastatin	Baycol
Cetirizine	
Cetuximab	Erbitux
Chlordiazepoxide	
Chloroquine	Aralen
Chlorothiazide	
Chlorpheniramine	
Chlorpromazine	
Chlorzoxazone	
Cholestyramine	
Chorionic gonadotropin	
Cidofovir	
Cilastatin	Primaxin
Cimetidine	
Ciprofibrate	
Ciprofloxacin	
Cisapride	
Citalopram	Celexa
Cladribine	
Clarithromycin	
Clavulanate	
Clobazam	
Clofibric acid	
Clonazepam	
Clonidine	
Clopidogrel	Plavix
Clotting Factor VIIa	
Clotting Factor IX	
Cloxacillin	
Clozapine	
Cocaine	
Codeine	
Collagenase	
Cortisol	
Cosyntropin	
Crotalidae immune Fab	
Curare	
Cyclophosphamide	
Cyclosporine	
Cytarabine	DepoCyt Injection
Daclizumab	Zenapax
Dapsone	
Darifenacin	
Debrisoquine	
Delavirdine mesylate	Rescriptor
Denileukin diftitox	Ontak
Desflurane	Suprane
Desipramine	
Desirudin	Iprivask
Desloratadine	Clarinex
Desmopressin acetate	DDAVP
Dextroamphetamine	
Dextromethorphan	
Diazepam	
Diclofenac	
Dicloxacillin	
Dicumarol	
Didanosine	
Diethylcarbamazepine	
Diflunisal	
Digitoxin	
Digoxin	
Digoxin immune Fab	Digibind
Diltiazem	
Diphenhydramine	
Dipyridamole	
Disopyramide	
Dobutamine	
Dolasetron mesylate	Anzemet
Donepezil	Aricept
Dornase alfa	Pulmozyme
Doxepin	
Doxorubicin	
Doxycycline	
Draflazine	
Dronabinol	Marinol
Droperidol	
Dutasteride	Avodart
Efalizumab	Raptiva
Efavirenz	
Enalapril	
Encainide	
Enfuvirtide	Fuzeon
Enoxacin	
Epinephrine	
Epipodophyllotoxin	
Epoetin alfa	Epogen
Eptifibatide	Integrilin
Ergonovine	
Erythromycin	
Esmolol	
Estradiol	

Etanercept	Enbrel	Halothane	
Ethambutol		Heparin	
Ethchlorvynol		Hepatitis B immune globulin	
Ethinyl estradiol		Heptabarbital	
Etonogestrel	NuvaRing (combined with ethinyl estradiol)	Hirudin	
		Hydralazine	
		Hydrocortisone	
		Hydroxyzine	
Ezetimibe	Zetia (also combined with simvastatin [Vytorin®])	Ibandronate	
		Ibuprofen	
		Imiglucerase	Cerezyme
		Imipenem	Primaxin
		Imipramine	
Felbamate	Famvir	Imirestat	
Felodipine		Indinavir	Crixivan
Fenoldopam		Indocyanine green	
Fentanyl		Indomethacin	
Fexofenadine	Allegra	Infliximab	Remicade
Fibrinolysin		Insulin	
Filgrastim	Neupogen	Insulin glargine	Lantus
Flecainide		Interferon alfacon-1	Infergen
Flesinoxan			
Fluconazole		Interferon Alpha-2b (pegylated)	Pegintron
Flumazenil	Romazicon		
Fluorouracil		Interferon Beta-1a	Rebif
Fluoxetine		Interleukin-11 (Oprelvekin)	Neumega
Flurazepam			
Flurbiprofen		Intravenous gamma globulin	Gammagard
Fluvastatin			
Fluvoxamine		Irbesartan	Avalide, Avapro
Fosamprenavir	Lexiva	Irinotecan	Camptosar
Furosemide		Isoflurane	
		Isoniazid	
Gabapentin		Isosorbide dinitrate	
Ganciclovir	Cytovene	Itraconazole	
Gemcitabine	Gemzar		
Gemtuzumab ozogamicin	Mylotarg	Ketamine	
		Ketoconazole	
Gentamicin		Ketoprofen	
Gladase		Ketorolac	
Glibenclamide			
Glyburide		Labetalol	
Glipizide		Lansoprazole	
Glucagon		Laronidase	
Gonadotropin-releasing hormone		Leflunomide	Arava
		Lepirudin	Refludan
Goserelin	Zoladex	Leucovorin	
Griseofulvin		Leuprolide acetate	
Growth hormone		Levodopa	
		Levofloxacin	
Halazepam		Levonorgestrel	
Haloperidol		Lidocaine	

Lithium		Norelgestromin	Ortho Evra (combined with ethinyl estradiol)
Lomefloxacin			
Lomustine			
Loperamide			
Lopinavir	Kaletra (combined with ritonavir)	Norepinephrine	
		Norfloxacin	
		Normal immune globulin	
Lorazepam			
Losartan	Hyzaar	Nortriptyline	
Lovastatin			
Lymphocyte anti-thymocyte immune globulin		Octreotide	
		Olsalazine	
		Omalizumab	Xolair
		Omeprazole	
Maprotiline		Ondansetron	
Mefloquine	Arima	Orlistat	Xenical
Meloxicam		Otenzapad	
Memantine		Oxacillin	
Menotropins	Menopur	Oxaliplatin	
Meperidine		Oxazepam	
Mercaptopurine		Oxycodone	
Mesalamine		Oxytocin	
Metformin			
Methamphetamine		Paclitaxel	
Methotrexate		Palivizumab	Synagis
Methyldopa		Pamidronate	Aredia
Methylphenidate		Pancuronium	
Methylprednisolone		Panitumumab	Vectibix
Metoprolol tartrate		Para-aminohippuric acid	
Metronidazole			
Mibefradil		Pancrelipase	
Midazolam		Pantoprazole	
Minocycline		Papain	
Minoxidil		Paroxetine	
Misonidazole		Pegvisomant	
Misoprostol		Penciclovir	Denavir
Montelukast	Singulair	Penicillin G	
Morphine		Pentagastrin	
Moxalactam		Pentazocine	
Muromomab-CD3			Talwin® (combined with naloxone)
Naloxone			
Naproxen		Pentobarbital	
Nelfinavir mesylate	Viracept	Pentoxyphylline	
Neomycin		Pertussis immune globulin	
Nesiritide			
Niacin		Phenelzine	
Nicardipine		Phenobarbital	
Nicotine		Phenprocoumon	
Nicoumalone		Phenylbutazone	
Nifedipine		Phenytoin	
Nitrazepam		Pimozide	
Nitroglycerin		Piperacillin	

Piroxicam	
Pivampicillin	
Polymyxin B Sulfate	
Pravastatin	
Prazepam	
Prednisolone	
Prednisone	
Primaquine	
Primidone	
Probenecid	
Procainamide	
Procarbazine	
Progesterone	
Proguanil	
Promazine	
Propafenone	
Propantheline	
Propofol	
Propranolol	
Propylthiouracil	
Protriptyline	
Pyridostigmine	
Quinacrine	
Quinidine sulfate	
Rabies immune globulin	
Ranibizumab	Lucentis
Ranitidine	
Rasburicase	Elitek
Remifentanil	Ultiva
Rho(D) immune globulin	
Rifampin	
Ritonavir	Norvir
Rituximab	Rituxan, Mabthera
Rivastigmine	Exelon
Rolipram	
Rosiglitazone	Avandia
Rosuvastatin	Crestor
Salicylic acid	
Saquinavir mesylate	Invirase
Saruplase	
Scopolamine	
Sermorelin	
Sertraline	
Sevoflurane	Ultane
Sildenafil citrate	Viagra
Simvastatin	
Sirolimus	Rapamune
Somatropin	
Sparteine	
St. John's Wort	
Streptomycin	
Succinylcholine	
Sucralfate	
Sufentanil	
Sulfamethazine	
Sulfasalazine	
Sulfinpyrazone	
Sulindac	
Sumatriptan	
Tacrolimus	
Tamoxifen	
Tamsulosin	Flomax
Taxol	
Teicoplanin	
Telithromycin	Ketek
Tenecteplase	TNKase
Terazosin	
Terbutaline	
Terfenadine	
Teriparatide	Forteo
Testosterone	
Tetanus immune globulin	
Theophylline	
Thioguanine	
Thiopental	
Thyroxine	
Ticlopidine	Ticlid
Timolol maleate	
Tipranavir	
Tirofiban	Aggrastat
Tissue-type plasminogen activator (t-PA)	
Tobramycin	
Tolbutamide	
Tolmetin	
Tolterodine tartrate	Detrol
Tositumomab	Bexxar
Trandolapril	Mavik
Trastuzumab	Herceptin
Triazolam	
Trimipramine	Surmontil
Troleandomycin	
Tubocurarine	
Urokinase	

Vaccinia immune globulin		Vinblastine	
		Vincristine	
Valganciclovir	Valcyte	Viomycin	
Valproic acid		Vitamin C	
Valsartan	Diovan	Voriconazole	
Vancomycin			
Varicella-zoster immune globulin	Varivax	Warfarin	
Vasopressin		Zafirlukast	Accolate
Venlafaxine	Effexor	Zidovudine	
Verapamil hydrochloride		Zileuton	Zyflo
		Zoledronic acid	Reclast, Zometa

DEFINITIONS OF SYMBOLS

(Typical units are shown)

A	Amount of drug in body, mg or μmol.
Aa	Amount of drug at absorption site remaining to be absorbed, mg or μmol.
$A_{av,ss}$	Average amount of drug in body during a dosing interval at steady state, mg or μmol.
Ae	Cumulative amount of drug excreted in the urine, mg or μmol.
Ae_{∞}	Cumulative amount of drug excreted in the urine after a single dose to time infinity, mg or μmol.
A_{inf}	Amount of drug in body during a constant-rate infusion, mg or μmol.
$A(m)$	Amount of metabolite in the body, mg or μmol.
A_{min}	The minimum amount of drug in body required to obtain a predetermined level of response, mg or μmol.
$A_{max,N}$; $A_{min,N}$	Maximum and minimum amounts of drug in body after the Nth dose of fixed size and given at a fixed dosing interval, mg or μmol.
$A_{N,t}$	Amount of drug in body at time t after the Nth dose, mg or μmol.
A_{ss}	Amount of drug in body at steady state during constant-rate administration, mg or μmol.
$A_{max,ss}$; $A_{min,ss}$	Maximum and minimum amounts of drug in body during a dosing interval at steady state on administering a fixed dose at a fixed dosing interval, mg or μmol.
AUC	Area under the plasma drug concentration-time curve. Total area from time 0 to infinity is implied unless the local context indicates a specific time interval (e.g., a dosing interval), mg-hr/L or μM-hr.
AUC_b	Area under the blood concentration-time curve, mg-hr/L or μM-hr.
$AUC(m)$	Area under the plasma metabolite concentration-time curve, mg-hr/L or μM-hr.
AUC_{ss}	Area under the plasma concentration-time curve within a dosing interval at steady state, mg-hr/L or μM-hr.
$AUMC$	Total area under the first moment-time curve, mg-hr^2/L or μM-hr^2.
BMI	Body mass index, kg/m^2.
BSA	Body surface area, m^2.
C	Concentration of drug in plasma (or reservoir), mg/L or μM.
C_{50}	Concentration giving one-half the maximum effect, mg/L or μM.
$C(0)$	Initial plasma concentration obtained by extrapolation to time zero, after an intravenous bolus dose, mg/L or μM.
C_A	Drug concentration in arterial blood, mg/L or μM.

$C_{av,ss}$	Average drug concentration in plasma during a dosing interval at steady state on administering a fixed dose at equal dosing intervals, mg/L or μM.
C_{inf}	Concentration of drug in plasma during a constant-rate infusion, mg/L or mM.
C_b	Concentration of drug in blood, mg/L or μM.
CL	Total clearance of drug from plasma, L/hr or mL/min.
CL_b	Total clearance of drug from blood, L/hr or mL/min.
$CL_{b,H}$	Hepatic clearance of drug from blood, L/hr or mL/min.
CL_{cr}	Renal clearance of creatinine, mL/min or L/hr.
CL_D	Clearance by dialysis procedure, L/hr or mL/min.
CL_H	Hepatic clearance of drug from plasma, L/hr or mL/min.
CL_{int}	Intrinsic clearance of drug in organ of elimination (well-stirred model), L/hr or mL/min.
CL_R	Renal clearance of drug from plasma, L/hr or mL/min.
CLu	Clearance of unbound drug, L/hr or mL/min.
C_{lower}, C_{upper}	Lower and upper bounds of the therapeutic window of plasma concentrations, mg/L or μM.
C_{max}	Highest drug concentration observed in plasma after administration of an extravascular dose, mg/L or μM.
$C_{max,ss}$, $C_{min,ss}$	Maximum and minimum concentrations of drug in plasma at steady state on administering a fixed dose at equal dosing intervals, mg/L or μM.
$C(m)$	Concentration of a metabolite in plasma, mg/L or μM.
$C(m)_{ss}$	Concentration of a metabolite in plasma at steady state during a constant-rate infusion of a drug, mg/L or μM.
C_{min}	Concentration of drug in plasma required to give the minimum effect, mg/L or μM.
C_{out}	Concentration leaving the extractor in the reservoir model, mg/L or μM.
C_{ss}	Concentration of drug in plasma at steady state during constant-rate administration, mg/L or μM.
C_T	Average concentration of drug in tissues outside plasma, mg/L or μM.
Cu	Unbound drug concentration in plasma, mg/L or μM.
Cu_H	Unbound drug concentration within hepatocytes, mg/L or μM.
C_V	Concentration of drug in venous blood, mg/L or μM.
D_L	Loading (or priming) dose, mg.
D_M	Maintenance dose given every dosing interval, mg
$D_{M,max}$	Largest maintenance dose that will keep systemic exposure within the therapeutic window, mg.
E	Extraction ratio, no units. In pharmacodynamics, E means "effect," which may be either clinically desirable or adverse. Units are those of response measured.
E_H	Hepatic extraction ratio, no units.
E_{max}	Maximum effect, units of response measurement.
E_R	Renal extraction ratio, no units.

F	Bioavailability of drug, no units.
f_D	Fraction of total elimination occuring by dialysis, no units.
fe	Fraction of drug systemically available that is excreted unchanged in urine, no units.
F_{ev}	Bioavailability of drug after extravascular administration, no units.
FEV_1	Forced expiratory volume in one second, L.
F_F	Fraction of an oral dose that enters the gut wall, no units.
F_G	Fraction of drug entering the gut that passes on to the portal circulation, no units.
F_H	Fraction of drug entering the liver that escapes elimination on single passage through the organ, no units.
fm	Fraction of drug systemically available that is converted to a metabolite, no units.
Fm	Fraction of administered dose of drug that enters the general circulation as a metabolite, no units.
F_R	Fraction of filtered and secreted drug reabsorbed in the renal tubule, no units.
fu	Ratio of unbound and total drug concentrations in plasma, no units.
fu_b	Ratio of unbound and whole blood concentrations available for binding, no units.
fu_P	Ratio of unbound and total sites on a plasma protein, no units.
fu_R	Apparent fraction unbound in intracellular fluids, no units.
fu_T	Ratio of unbound and total drug concentrations in tissues (outside plasma), no units.
γ	Steepness of concentration–response relationship, no units.
GFR	Glomerular filtration rate, mL/min or L/hr.
k	Elimination rate constant, hr^{-1}.
ka	Absorption rate constant, hr^{-1}.
Ka	Association equilibrium constant, L/mol.
Kd	Dissociation constant for saturable binding, mg/L.
K_I	Inhibition equilibrium constant, mg/L or μM.
Km	Michaelis-Menten constant, mg/L or μM.
K_p	Equilibrium distribution ratio of drug between tissue and plasma, no units.
$K_{p,b}$	Equilibrium distribution ratio of drug between tissue and blood, no units.
K_T	Constant for saturable transport model, mg/L.
k_t	Fractional turnover rate, hr^{-1}.
k_T	Fractional rate at which drug leaves a tissue, hr^{-1}.
λ_1, λ_2	Exponential coefficients, hr^{-1}
m	Slope of the relationship between response and the log of the plasma concentration (between 20 and 80% of maximum response), units of the response.
MRT	Mean residence time of a drug molecule within the body, hr.
n	A unitless number.
N	Number of doses, no units.

P	Permeability coefficient, cm/sec.
P_T	Total concentration of binding protein in plasma, mM.
Q	Blood flow, L/min or L/hr.
Q_H	Hepatic blood flow (portal vein plus hepatic artery), L/min or L/hr.
Q_R	Renal blood flow, L/min or L/hr.
R_{ac}	Accumulation ratio (index), no units.
R_d	Ratio of unbound clearance of an individual patient with renal function impairment to that of a typical patient, no units.
RF	Renal function in an individual patient as a fraction of renal function in a typical patient, no units.
R_{inf}	Rate of constant intravenous infusion, mg/hr.
R_{syn}	Rate of synthesis or input of a substance into the body, mg/hr or μg/hr
R_t	Turnover rate, mg/hr.
SA	Surface area, m^2.
τ	Dosing interval, hr.
t_{max}	Maximum dosing interval to remain within the limits of C_{lower} and $C_{upper,}$ hr.
t	Time, hr.
t_D	Duration of response, hr
t_{inf}	Duration of a constant-rate infusion, hr.
Tm	Maximum rate of drug transport, mg/hr.
t_{max}	Time at which the highest drug concentration occurs after administration of an extravascular dose, min or hr.
t_t	Turnover time, hr.
$t_{1/2}$	Elimination half-life, hr.
$t_{1/2,a}$	Half-life of systemic absorption, hr.
V	Volume of distribution (apparent) based on drug concentration in plasma, L.
V_1	Initial dilution space or volume of central compartment in a two-compartment model, L.
V_b	Volume of distribution (apparent) based on drug concentration in whole blood, L.
V_B	Blood volume, L.
Vm	Maximum rate of metabolism by a given enzymatic reaction, mg/hr or μmol/hr.
$V(m)$	Volume of distribution (apparent) of a metabolite based on its plasma concentration, L.
V_P	Plasma volume, L.
V_R	Aqueous volume of intracellular fluids, L.
V_{ss}	Volume of distribution (apparent) under steady state conditions based on drug concentration in plasma, L.
V_T	Physiologic volume outside plasma into which drug appears to distribute, L.
Vu	Unbound volume of distribution, L.
W	Body weight, kg.