

CONTENTS

Preface	xv
Contributors	xix
1 Introduction	1
<i>Corinne Kay</i>	
1.1 Introduction	1
1.2 Voyage Through The Digestive System	2
1.2.1 The Mouth	3
1.2.2 The Stomach	4
1.2.3 The Small Intestine: Duodenum	7
1.2.4 The Small and Large Intestine: Jejunum, Ileum, Colon	9
1.2.5 Hepatic-Portal Vein	13
1.3 The Liver Metabolism	15
1.3.1 CYP450 (CYPs)	17
1.4 The Kidneys	21
1.4.1 Active Tubular Secretion	23
1.4.2 Passive Tubular Reabsorption	24
1.5 Conclusions	25
References	25

2	<i>In Silico</i> ADME/Tox Predictions	29
	<i>David Lagorce, Christelle Reynes, Anne-Claude Camproux, Maria A. Miteva, Olivier Sperandio, and Bruno O. Villoutreix</i>	
2.1	Introduction	29
2.2	Key Computer Methods for ADME/Tox Predictions	30
2.2.1	Drug Discovery	30
2.2.2	Applying or Not ADME/Tox Predictions, Divided Opinions	35
2.2.3	<i>In Silico</i> ADME/Tox Methods and Modeling Approaches	39
2.2.4	Physicochemistry, Pharmacokinetics, Drug-Like and Lead-Like Concepts	46
2.2.5	Lipophilicity	51
2.2.6	p <i>K</i> _a	53
2.2.7	Transport Proteins	61
2.2.8	Plasma Protein Binding	62
2.2.9	Metabolism	65
2.2.10	Elimination	67
2.2.11	Toxicity	67
2.3	Preparation of Compound Collections and Computer Programs, Challenging ADME/Tox Predictions and Statistical Methods	73
2.3.1	Preparation of Compound Collections and Computer Programs	73
2.3.2	Preparing a Compound Collection: Materials and Methods	75
2.3.3	Cleaning and Designing the Compound Collection	83
2.3.4	Searching for Similarity	85
2.3.5	Generating 3D Structures	86
2.4	ADME/Tox Predictions within Pharmaceutics Companies	86
2.4.1	Actelion Pharmaceuticals Ltd.	86
2.4.2	Bayer	86
2.4.3	Bristol-Myers Squibb	87
2.4.4	Hoffmann-La Roche Ltd.	87
2.4.5	Neurogen Corporation	87
2.4.6	Novartis	88
2.4.7	Schering AG	88
2.4.8	Vertex Pharmaceuticals	88
2.5	Challenging ADME/Tox Predictions	88
2.5.1	Tolcapone	89
2.5.2	Factor V Inhibitors	89
2.5.3	CRF-1 Receptor Antagonists	90
2.6	Statistical Methods	90
2.6.1	Principal Component Analysis	90
2.6.2	Partial Least Square	93
2.6.3	Support Vector Machine	96

2.6.4	Decision Trees	98
2.6.5	Neural Networks	101
2.7	Conclusions	104
	References	105
3	Absorption and Physicochemical Properties of the NCE	125
	<i>Jon Selbo and Po-Chang Chiang</i>	
3.1.	Introduction	125
3.2.	Physicochemical Properties	126
3.3.	Stability	127
3.4.	Dissolution and Solubility	128
3.4.1.	Dissolution Rate, Particle Size, and Solubility	128
3.4.2.	pH and Salts	130
3.4.3.	<i>In Vivo</i> Solubilization	133
3.5.	Solid State	134
	References	139
4	ADME	145
	<i>Martin E. Dowty, Dean M. Messing, Yurong Lai, and Leonid (Leo) Kirkovsky</i>	
4.1	Introduction	145
4.2	Absorption	146
4.2.1	Route of Administration	146
4.2.2	Factors Determining Oral Bioavailability	149
4.3	Distribution	157
4.3.1	Drug Distribution	157
4.3.2	Volume of Distribution	158
4.3.3	Free Drug Concentration	160
4.3.4	CNS Penetration	162
4.4	Elimination	165
4.4.1	Elimination Versus Clearance	165
4.4.2	Metabolism Versus Excretion	165
4.4.3	Drug-Free Fraction and Clearance	166
4.4.4	Lipophilicity and Clearance	166
4.4.5	Transporters and Clearance	166
4.4.6	Metabolism	167
4.4.7	Excretion	171
4.5	Drug Interactions	174
4.5.1	Absorption-Driven DDI	174
4.5.2	Distribution-Driven DDI	174
4.5.3	Excretion-Driven DDI	174
4.5.4	Metabolism-Driven DDI	175
4.5.5	Tools for Studying Drug Metabolism	177
4.5.6	Applications of Drug Metabolism Tools	180

4.5.7	Tools for Studying Drug Excretion	184
4.6	Strategies for Assessing ADME Properties	186
4.6.1	Assessing ADME Attributes at Different Stages of Discovery Projects	186
4.7	Tool Summary for Assessing ADME Properties	190
	References	190

5 Pharmacokinetics for Medicinal Chemists 201

Leonid (Leo) Kirkovsky and Anup Zutshi

5.1	Introduction	201
5.1.1	History of Pharmacokinetics as Science	201
5.2	ADME	202
5.2.1	Absorption	202
5.2.2	Distribution	204
5.2.3	Metabolism	207
5.2.4	Excretion	207
5.3	The Mathematics of Pharmacokinetics	211
5.3.1	Compartmental Versus Noncompartmental Analysis	212
5.4	Drug Administration and PK Observations	212
5.4.1	Analysis of Intravenous PK Data	213
5.4.2	Analysis of Extravascular PK Data	227
5.4.3	Analysis of Intravenous Infusion Data	230
5.4.4	Analysis of PK Data after Multiple Dose Administrations	231
5.4.5	Analysis of PK Data after Escalating Dose Administrations	233
5.5	Human PK Projection	235
5.5.1	Allometric Scaling	235
5.5.2	Scaling by Physiologically Based Pharmacokinetic Modeling	237
5.5.3	<i>In Vitro–In Vivo</i> Correlations	239
5.6	PK Practices	239
5.6.1	PK Studies for Different Stages of Discovery Projects	240
5.6.2	Key Parameters of PK Studies	241
5.7	Engineering Molecules with Desired ADME Profile	269
5.A	Appendices	269
5.A.1	General Morphometric Data for Different Species	269
5.A.2	Organ Weights in Different Species	270
5.A.3	Organ, Tissue, and Fluid Volumes in Different Species	271
5.A.4	Blood Content in Different Rat Organs	271
5.A.5	Biofluid Flow through the Organs in Different Species	272
5.A.6	Anatomical Characteristics of GI Tract in Different Species	273
5.A.7	The pH and Motility of GI Tract in Different Species	274
5.A.8	Phase I and Phase II Metabolism in Different Species	274
	Acknowledgments	277
	References	277

6	Cardiac Toxicity	287
	<i>Ralf Kettenhofen and Silke Schwengberg</i>	
6.1	Introduction	287
6.2	Ion Channel-Related Cardiac Toxicity	287
6.2.1	Cardiac Electrophysiology	288
6.2.2	Delayed Repolarization: Mechanisms and Models	290
6.2.3	Shortened Ventricular Repolarization	294
6.2.4	Alterations in Intracellular Ca ²⁺ Handling	296
6.2.5	Preclinical Models for Assessment of Ion Channel-Related Cardiotoxicity	297
6.3	Nonarrhythmic Cardiac Toxicity	299
6.3.1	Definition of Drug-Induced Cardiac Toxicity	300
6.3.2	Assays for Detection of Nonarrhythmic Cardiac Toxicity	300
6.3.3	Biochemical and Molecular Basis of Drug-Induced Cardiac Toxicity—Impairment of Mitochondrial Function	304
	References	306
7	Genetic Toxicity: <i>In Vitro</i> Approaches for Medicinal Chemists	315
	<i>Richard M. Walmsley and David Elder</i>	
7.1	Introduction	315
7.1.1	Scope of this Chapter	315
7.1.2	Definitions	316
7.1.3	Positive Genotoxicity Data is not Uncommon and Very Costly	316
7.1.4	Why Genome Damage is Undesirable	317
7.1.5	The Inherent Integrity of the Genome and its Inevitable Corruption	317
7.1.6	Many Chemicals can Cause Cancer, but do not Pose a Significant Risk to Humans	318
7.1.7	The False Positives: Many Chemicals Produce Positive Genotoxicity Data that are neither Carcinogens nor <i>In Vivo</i> Genotoxins	318
7.1.8	Defense Against Genotoxic Damage	319
7.1.9	Mechanisms of Genotoxic Damage	320
7.1.10	Genotoxicity Assessment Occurs after Medicinal Chemistry Optimization	321
7.2	Limitations in the Regulatory <i>In Vitro</i> Genotoxicity Tests	322
7.2.1	Biology Limitations of <i>In Vitro</i> Tests	322
7.2.2	Hazard and Safety Assessment have Different Requirements	323
7.2.3	The Data from Genetic Toxicologists	323
7.3	Practical Issues for Genotoxicity Profiling	324
7.3.1	Vehicle	324

7.3.2	Dilution Range	324
7.3.3	Purity	324
7.4	Computational Approaches to Genotoxicity Assessment: The <i>In Silico</i> Methods	325
7.4.1	General Considerations	325
7.4.2	The Chemistry of Genotoxins	328
7.5	Genotoxicity Assays for Screening	335
7.5.1	Bacterial Gene Mutation Assays	337
7.5.2	Mammalian Cell Mutation Assays	338
7.5.4	Chromosome Damage and Aberration Assays	339
7.5.5	The “Comet” Assay	340
7.5.6	DNA Adduct Assessment	341
7.5.7	Gene Expression Assays	341
7.6	The “Omics”	343
7.7	Using Data from <i>In Vitro</i> Profiling: Confirmatory Tests, Follow-Up Tests, and the Link to Safety Assessment and <i>In Vivo</i> Models	343
7.7.1	Annotations from Screening Data	344
7.7.2	Can a Genetic Toxicity Profile Assist with <i>In Vivo</i> Testing Strategies?	344
7.8	What to Test, When, and How	345
7.9	Changes to Regulatory Guidelines Can Influence Screening Strategy	346
7.10	Summary	347
	Acknowledgment	347
	References	348
8	Hepatic Toxicity	353
	<i>Jinghai James Xu and Keith Hoffmaster</i>	
8.1	Introduction	353
8.2	Mechanisms of DILI	354
8.2.1	Reactive Metabolite Formation	355
8.2.2	Mitochondrial Dysfunction and Oxidative Stress	357
8.2.3	Bile Flow, Drug-Induced Cholestasis, and Inhibition of Biliary Efflux Transporters	359
8.3	Assays and Test Systems to Measure Various Types of DILI	360
8.4	Medicinal Chemistry Strategies to Minimize DILI	365
8.5	Future Outlooks	370
	Acknowledgment	370
	References	370
9	<i>In Vivo</i> Toxicological Considerations	379
	<i>John P. Devine, Jr.</i>	
9.1	Introduction	379
9.2	Route of Administration	379

9.2.1	Oral Route	380
9.2.2	Intravenous Route	381
9.2.3	Dermal Route	382
9.3	Formulation Issues	383
9.4	Compound Requirements	384
9.5	Animal Models	385
9.5.1	Mouse	385
9.5.2	Rat	386
9.5.3	Dog	386
9.5.4	Swine	386
9.5.5	Nonhuman Primates	387
9.6	IND-Supporting Toxicology Studies	387
9.6.1	Single-Dose Studies	387
9.6.2	Repeat-Dose Studies	388
9.7	Study Result Interpretation	392
9.7.1	Clinical Observations	392
9.7.2	Body Weight/Feed Consumption	393
9.7.3	Clinical Pathology	393
9.7.4	Clinical Chemistry	393
9.7.5	Electrocardiograms	394
9.7.6	Organ Weights	394
9.7.7	Pathology	395
9.8	Genetic Toxicology Studies	395
9.8.1	Gene Mutation	395
9.8.2	Chromosomal Aberration	396
9.8.3	<i>In Vivo</i> Mouse Micronucleus	396
9.9	Conclusion	396
	References	397
10	Preclinical Candidate Nomination and Development	399
	<i>Nils Berghem</i>	
10.1	Introduction	399
10.2	Investigational New Drug Application and Clinical Development	400
10.2.1	Chemistry, Manufacturing, and Control Information	401
10.2.2	Animal Pharmacology and Toxicology Studies	401
10.2.3	Clinical Protocols and Investigator Information	401
10.3	Strategic Goals for the Preclinical Development	402
10.4	Selection of Preclinical Development Candidate	403
10.4.1	Efficacy	403
10.4.2	Safety/Tolerance	405
10.4.3	PK	407
10.4.4	Non-GLP Toxicological Study	407

10.5	CMC	408
10.5.1	Solubility	408
10.5.2	Solutions Stability	408
10.5.3	Synthetic Feasibility, Solid-State Stability, and Hygroscopicity	408
10.5.4	Patent Position	408
10.6	Preclinical Studies	409
10.6.1	Example 1: IND Enabling Data Package to Support 1 Month Dosing in Man	410
10.6.2	Example 2: Peroxisome Proliferator-Activated Receptor Agonist for Type-2 Diabetes	410
10.6.3	Mass Balance	410
10.6.4	Animal Pharmacology and Toxicology Studies	410
10.6.5	Regulatory	414
10.7	Conclusions	415
	References	415
11	Fragment-Based Drug Design: Considerations for Good ADME Properties	417
	<i>Haitao Ji</i>	
11.1	Introduction	417
11.2	Fragment-Based Screening	418
11.2.1	Fragment Library Design	419
11.2.2	Detection and Characterization of Weakly Binding Ligands	420
11.2.3	Approaches from Fragment to Lead Structures	427
11.3	Case Studies of Fragment-Based Screening for Better Bioavailability	431
11.3.1	Adenosine Kinase	431
11.3.2	Leukocyte Function-Associated Antigen-1	432
11.3.3	Matrix Metalloproteinase 3 (Stromelysins)	432
11.3.4	Protein Tyrosine Phosphatase 1B	433
11.3.5	β -Secretase (BACE-1)	436
11.3.6	SH2 Domain of pp60Src [62, 129]	439
11.3.7	Thrombin	439
11.3.8	Urokinase	441
11.3.9	Cathepsin S	442
11.3.10	Caspase-3	442
11.3.11	HIV-1 Protease	444
11.4	<i>De Novo</i> Design	445
11.4.1	<i>In Silico</i> Fragment Screening	447
11.4.2	Scaffold Hopping	448

11.5	Case Studies of <i>De Novo</i> Design for Better Bioavailability	450
11.5.1	DNA Gyrase	450
11.5.2	Factor Xa	450
11.5.3	X-Linked Inhibitor of Apoptosis Protein	451
11.5.4	Activator Protein-1 [196b]	451
11.6	Minimal Pharmacophoric Elements and Fragment Hopping	452
11.6.1	Minimal Pharmacophoric Elements	452
11.6.2	Fragment Hopping	453
11.6.3	Case Study: Nitric Oxide Synthase	457
11.7	Conclusions and Future Perspectives	459
	Acknowledgments	460
	References	460
Index		487

