CONTENTS

Contributors xv
Preface xvii
Acknowledgement xxi

1 Translational Concept and Determination of Drug Absorption 1

1.1 Drug Absorption, Mechanism, and its Impact on Drug Bioavailability, Drug Disposition, and Drug Safety, 1
1.1.1 Drug Absorption and Oral Bioavailability, 2
1.1.2 Contribution of Intestinal Drug Transporters and Drug-Metabolizing Enzymes on Extent of Absorption and Mechanism, 4
1.1.2.1 Intestinal Transporters, 4
1.1.2.2 The Impact of Intestinal Metabolism on Drug Absorption, 8

1.2 Effect of Physiochemical Property–Related Factors on Drug Absorption, 9
1.2.1 Lipophilicity, Solubility and Dissolution, and Permeability, 9
1.2.1.1 Lipophilicity, 9
1.2.1.2 Solubility, 11
1.2.1.3 Permeability, 12
1.3 Effect of GI-Physiological Factors and Patient Condition on Drug Absorption, 14
  1.3.1 Effect of pH, Intestinal Surface Area, Gastric Emptying, Transient Time, and Bile Acid, 14
    1.3.1.1 Effect of pH and Surface Area, 14
    1.3.1.2 Effect of Gastric Emptying and Intestinal Transit Time, 17
    1.3.1.3 Effect of Bile and Bile Salts, 17
  1.3.2 Impact of Age and Disease State on Drug Absorption, 18
    1.3.2.1 Drug Absorption in Pediatric Populations, 18
    1.3.2.2 Drug Absorption in Disease State, 19
  1.4 Effect of Food and Formulation on Drug Absorption, 20
    1.4.1 Effect of Food, 20
    1.4.2 Formulation Effect, 21
    1.4.3 The BCS in Relation to Intestinal Absorption, 22
  1.5 Translational Approaches to Determine Drug Absorption in Clinical Studies, 24
    1.5.1 Cellular Intestinal Model, 24
    1.5.2 In Vitro Artificial Membrane, 24
    1.5.3 Non–In Vitro Models: In Situ and In Vivo, 25
  References, 27

2 Distribution: Principle, Methods, and Applications 37

  2.1 Introduction: Drug Distribution in Relation to Drug Disposition in Humans, 37
  2.2 Influence of Drug-Related Physiochemical Factors on Drug Distribution, 39
  2.3 Influence of Physiological Factors on Drug Distribution, 42
    2.3.1 Effect of Body Water Content, Perfusion, and Diffusion on Drug Distribution, 43
      2.3.1.1 Effect of Body Water, 43
      2.3.1.2 Effect of Perfusion and Diffusion on Drug Distribution, 44
  2.4 Plasma Protein Binding, 45
    2.4.1 Effect of Biomedical Conditions: Disease State and Pregnancy, 45
    2.4.2 Protein Binding as a Function of Age, 46
  2.5 Role of Drug Transporters in Drug Distribution, 47
    2.5.1 Drug Distribution as a Function of Efflux Drug Transporters, 48
  2.6 Translational Methods and Approaches in Determining Drug Distribution, 49
    2.6.1 In Vitro Methods for Determination of Protein Binding, 49
    2.6.2 In Vivo Protein Binding Studies in Preclinical Animals and Humans, 51
2.6.2.1 Using Radiolabeled Drugs, 51
2.6.2.2 Applying Advanced Translational Tools for Determining Drug Distribution in Humans, 52

2.6.3 Assess Drug Distribution from Transporter Studies, 53
2.6.3.1 Use of Membrane Vesicles, 53
2.6.3.2 Use Cultured-Cell Based Assay, 53

2.7 Impact of Drug Distribution in Drug Disposition DDI in Clinic, 55
References, 58

3 Metabolism: Principle, Methods, and Applications 63

3.1 Introduction: An Overview on Drug Metabolism in Relation to Clearance—Mediated by Phase I, Phase II, and Phase III Drug-Metabolizing Enzymes, 63

3.2 Common Phase I, II, and III Drug Metabolism Reactions, 69
3.2.1 Phase I Drug Metabolism, 69
3.2.1.1 Oxidation Reaction, 70
3.2.2 Phase II Conjugation Biotransformation Reactions, 71
3.2.2.1 UDP-Glucuronosyltransferase (UGT), 71
3.2.2.2 Other Conjugation Reactions: Sulfonyltransferase, Glutathione-S-Transferases, Methyl Transferases, and N-Acetyl Transferases, 75
3.2.3 Phase III Metabolism, 77
3.2.4 Localization of Drug Metabolism in Organ Cells, 78

3.3 Metabolic Clearance as a Critical Factor Influencing Drug Action and Safety, 78
3.3.1 Effect of Physiological Factors on Drug Metabolism-Mediated Drug Clearance, 80
3.3.1.1 Protein Binding, 81
3.3.1.2 Hepatic Blood Flow (Q_{H}), 82
3.3.1.3 Liver Size Relative to Body Weight, 82
3.3.1.4 Milligram Microsomal Protein per Gram of Liver, 82
3.3.2 Role of Drug Transporters, 82
3.3.3 Effect of Age on Drug Metabolism and Clearance, 84
3.3.4 Effect of Hormones on Metabolic Clearance and Gender Difference in Drug Metabolism, 86
3.3.5 Effects of Disease on Drug Metabolism, 86
3.3.6 Genetic Polymorphism and Ethnic Variability Effect on Metabolic Clearance, 87

3.4 Species Differences in Drug Metabolism, 89

3.5 Translational Technologies and Methodologies and Regulatory Recommendation for Drug Metabolism, 91
3.5.1 In Vitro Models of Drug Metabolism, 92
3.5.1.1 Single-cDNA Expressed Enzymes, 92
3.5.1.2 Subcellular Fractions, 93
CONTENTS

3.5.1.3 Cellular Systems, 94
3.5.2 In Vivo Models of Drug Metabolism, 95
3.5.2.1 Preclinical Animal Studies, 95
3.5.2.2 Genetically Modified Animal/Chimeric Mouse Model/Ex Vivo/In Situ Organ Perfusion, 96

References, 98

4 Excretion: Principle, Methods, and Applications for Better Therapy

4.1 Outline of Drug Excretion and Mechanisms, 111
4.2 Excretion of Drugs in Humans as Function of Drug Transporters, 112
4.2.1 Biliary and Renal Excretion, 112
4.2.1.1 Biliary Excretion, 113
4.2.1.2 Renal Excretion, 115
4.2.2 Drug Transporter Function in Renal Excretion, 118
4.3 Translational Tools to Determine the Biliary and Renal Clearance, 119
4.3.1 In Vitro Methods in Determination of Biliary Clearance, 119
4.3.2 In Vitro Methods in Determination of Renal Clearance, 122
4.3.3 In Vivo Methods in Determination of Biliary and Renal Clearances, 125
4.3.3.1 MBSs in Humans, 125
4.3.4 In Vivo Model to Study Excretion and Toxicity: Chimeric Mice with Humanized Liver, 128
4.4 Impairment of Drug Elimination, 128
4.4.1 Hepatic Impartment: Cholestasis, 128
4.4.2 Renal Impartment: Chronic Kidney Disease (CKD), 130

References, 133

5 Drug–Drug Interaction: From Bench to Drug Label

5.1 Introduction: The Impact of Drug–Drug Interaction on Drug Disposition and Drug Safety, 139
5.2 DDIs Implicated with Drug-Metabolizing Enzymes (DMEs) and Drug Metabolism, 141
5.2.1 DDI Mediated by P450 Inhibition, 141
5.2.1.1 In Vitro P450 Inhibition Models and Methodologies, 142
5.2.1.2 Translating In Vitro P450 Inhibition Data to Clinical DDI, 144
5.2.2 Mechanism-Based P450 Inactivation DDI, 146
5.2.2.1 Translating the In Vitro Information to Clinical Pharmacology Investigation, 147
5.2.3 DDI Mediated by P450 Induction, 152
CONTENTS

5.2.3.1 In Vitro P450 Induction Models and Methodologies, 152
5.2.3.2 Translating In Vitro P450 Induction Data to Clinical DDI, 156
5.3 Incidence of DDI Due to Drug Transporters, 158
  5.3.1 DDI-Mediated Uptake Transporters, 159
  5.3.2 DDI-Mediated Efflux Transporters, 162
5.4 Clinical DDI, 163
  5.4.1 DDI in Pediatric Patients, 164
  5.4.2 Clinical DDI Study Designs, 166
  5.4.3 Statistical Approach in Clinical DDI Studies, 168
5.5 Conclusion, 169
References, 169

6 General Toxicology: Principle, Methods, and Applications 179

6.1 Introduction: The History of Toxicology, 179
6.2 The Multifaceted Field of Toxicology, 183
  6.2.1 Various Disciplines in Toxicology, 183
  6.2.2 Principles of Toxicology, 184
6.3 Characteristics of Toxicants, Toxins, and Exposures, 184
  6.3.1 Use Classes, 185
  6.3.2 Characteristics of Exposure, 186
  6.3.3 Length of Exposure, 186
  6.3.4 Routes of Exposure, 187
  6.3.5 Dose Response, 187
  6.3.6 Tolerance, 188
6.4 Adverse Drug Reactions: Idiosyncratic and Drug-Induced Liver Injury (DILI), 188
  6.4.1 Idiosyncratic Drug Reactions (IDRs), 188
  6.4.2 Drug-Induced Liver Injury, 190
6.5 In Vitro Determination of Reactive Metabolite Formation, Oxidative Stress, Mitochondrial Damage, and Nephrotoxicity, 193
6.6 Present and Future for Assessing Toxicity in Drug Discovery and Development, 197
References, 200

7 Toxicokinetics and Toxicity Testing in Drug Development 205

7.1 Introduction: Toxicokinetics and Its Relationship with Pharmacokinetics and ADME in Preclinical Development, 205
7.2 Types of Preclinical Dosing that Support Toxicokinetics, 206
  7.2.1 Single-Dose Toxicity Studies, 207
  7.2.2 Repeated-Dose Toxicity Studies, 207
7.3 Pharmacokinetic Parameters in Support of Toxicokinetic Assessments, 209
  7.3.1 Area Under the Curve (AUC), 209
  7.3.2 Maximum Plasma Concentration (C_{max}) and Time of Maximum Concentration (T_{max}), 210
  7.3.3 Clearance, 210
  7.3.4 Apparent Volume of Distribution (V_d), 211
  7.3.5 Apparent Volume of Distribution at Steady State (V_{dss}), 211
  7.3.6 Half-Life (t_{1/2}), 212
  7.3.7 Bioavailability (F%), 212

7.4 Genotoxicity, Oncogenicity, Reproductive Toxicity versus Toxicogenomics and Biomarkers in Preclinical Species, 213
  7.4.1 Genotoxicity Studies, 213
  7.4.2 Carcinogenicity (Oncogenicity) Studies, 214
  7.4.3 Reproductive Toxicity Studies, 214
  7.4.4 Toxicogenomics Studies, 215

7.5 Drug Metabolism and Drug Related-Toxicities, 215
References, 218

8 PBPK Modeling and In Silico Prediction for ADME and Drug–Drug Interaction 221
  8.1 Introduction: Computational Assessment of ADME and Drug–Drug Interaction (DDI) within Pharmaceutical R&D Paradigm, 221
  8.2 PBPK Models for ADMET and DDI, 223
    8.2.1 General PBPK Model and Physiological Parameters that Affect Drug Disposition, 223
    8.2.2 Simple Organ-Based PBPK Models, 227
      8.2.2.1 PBPK for Liver, 227
      8.2.2.2 Whole-Body PBPK Models, 229
    8.2.3 PBPK Model for DDI, 230
    8.2.4 PBPK and Genetic Polymorphism, 232
  8.3 In Silico Prediction of ADMET, 232
    8.3.1 Significance of Using In Silico Modeling: In Silico versus PBPK Modeling, 233
    8.3.2 Methods for In Silico ADMET Prediction, 233
      8.3.2.1 Data Modeling, 233
      8.3.2.2 Molecular Modeling, 234
  8.4 Applications of In Silico Models in ADME, DDI, and Drug Toxicity, 234
    8.4.1 Prediction of the Rate of Metabolism, 235
    8.4.2 DDI of Metabolism, 235
    8.4.3 Identifying Substrates for Transporters, 235
References, 236
9 Translational Tools toward Better Drug Therapy in Human Populations 241

9.1 Introduction: Translational ADMET and its Therapeutic Value, 241

9.2 Translational Bioinformatics and Biomarkers: Utilization for Better Drug Therapy, 244
  9.2.1 In Cancer, 245
  9.2.2 In Chronic Kidney Disease (CKD), 245
  9.2.3 Role of Biomarkers in CNS, 246
  9.2.4 Biomarkers in Diabetes and Their Role in AD, 247

9.3 Genomics and Pharmacogenomics in Translational ADMET, 249
  9.3.1 Influence of Pharmacogenomics on Drug Metabolism-Mediated Drug Development, 250
  9.3.2 Influence of Pharmacogenomics on Drug Transporter-Mediated Drug Development, 255

9.4 Translational ADMET, Approaches and Tools, 257
  9.4.1 From Bedside to Bench to Bedside: POC Investigations, 257
    9.4.1.1 Individualized Antifungal Drug Therapy in Pediatric Patients, 257
    9.4.1.2 “From Bedside to Bench” in Rare Pediatric Leukemia, 261
  9.4.2 From Juvenile Animal Model to Human Adult, 262
  9.4.3 Use of Chimeric Rodents with Humanized Liver as a Translation Model in Bridging the Gap between Preclinical and Clinical Trials in ADMET, 263

9.5 Scaling of PK in Prediction of Human PK and Dosing, 264
  9.5.1 From Adult PK to Pediatric: Calculation of In Vivo CL in Children, 264
  9.5.2 From Animal PK to Human Dose, 268
    9.5.2.1 CL and PK/TK Modeling in Predicting Clinical Dose, 270

References, 271

10 Phase 1–Phase 3 Clinical Studies, Procedures, Responsibilities, and Documentation 277


10.2 General Clinical Study Design: Enrollment, Responsibilities, and Documentation, 282
  10.2.1 Clinical Study Protocol, 283
  10.2.2 Patient Selection and Eligibility Criteria, 284
  10.2.3 Typical Study Design Features, 285
    10.2.3.1 Randomized Clinical Trials, 285
    10.2.3.2 Blinding versus Masking, 286
10.2.4 Responsibilities: IRBs, Regulatory Authorities, Sponsor, PI, Patients, 287
  10.2.4.1 Institutional Review Boards, 287
  10.2.4.2 Role of Regulatory Agencies, 287
  10.2.4.3 Responsibility of Sponsor, 289

10.3 Integration of Clinical Trials with Preclinical Absorption, Distribution, Metabolism, and Excretion (ADME), Drug–Drug Interaction (DDI), and Pharmacogenomics in Investigating, 290
  10.3.1 Assessment of DDI and Disposition, 290
  10.3.2 Mechanism Underlying Drug Therapy (Aromatase Inhibitors) for Breast Cancer, 295
  10.3.3 Mechanism Underlying Drug Therapy (Metformin) for Type 2 Diabetes, 297

10.4 Clinical Pharmacology Studies of Special Populations, 298
  10.4.1 Pediatrics and Geriatrics, 299
  10.4.2 Renal Impaired, 300
  10.4.3 Hepatic Impaired, 300
  10.4.4 Genetic Polymorphic Populations, 301
  10.4.5 Different Ethnic Populations, 302

References, 302

11 Regulatory Submission: MIST and Drug Safety Assessment 307

11.1 Drug Development and Approval Processes According to the Food and Drug Administration (FDA), European Medicines Agency (EMA), and Other Regulatory Authorities, 307

11.2 Studies Required for IND and NDA, 309
  11.2.1 Types of INDs, Types of Information, and Timelines, 309
    11.2.1.1 Chemistry and Manufacturing Control, 309
    11.2.1.2 Pharmacology/Toxicology, 310
    11.2.1.3 Pharmacology and Drug Distribution (21 CFR 312.23(a)(8)(I)), 310
    11.2.1.4 Toxicology Data Present Regulations (21 CFR 312.23(a)(8)(ii)(a)), 310
    11.2.1.5 Medical Review, 310
    11.2.1.6 Safety Review, 311
    11.2.1.7 Statistical Review, 311
    11.2.1.8 Timelines and Clinical Hold Decision, 311
    11.2.1.9 Notify Sponsor, 311
  11.2.2 Metabolites in Safety Testing (MIST) Regulation—Safety Assessments in Humans, 311
  11.2.3 Highlights of the AAPS 2013 MIST Symposium, 314
    11.2.3.1 ICH M3(R2) and Metabolite Issues, 314
    11.2.3.2 Early Assessment of MIST Liability of a Clinical Drug Candidate without the Use of Radiolabel, 316
11.2.3.3 MIST: How Do We Deal with Surprises? 316
11.2.3.4 A Simple LC-MS/MS Method for Evaluating MIST Coverage, 316

11.3 Drug Labeling and Black Box Warning, 317
 11.3.1 Sections Included in Drug Label, 319
    11.3.1.1 Drug Dosing, 319
    11.3.1.2 Age in Drug Labeling, 319
    11.3.1.3 Renal and Hepatic Impairment, 320
    11.3.1.4 Drug Metabolism, 320
    11.3.1.5 Genetic Polymorphism, Ethnic Differences, 322

References, 323

Index 327