CONTENTS

Preface xi
List of Contributors xiii

1 Introduction: History of Metabolite Safety in Drug Development 1
   Dennis A. Smith and Suzanne L. Iverson
   1.1 People, Events, and Reaction, 1
   1.2 The Rise of Industrial Drug Metabolism, 2
   1.3 The Appearance of Mist, 4
   1.4 The Journey Triggered by Thalidomide: Would Present Science have Made a Difference?, 5
   1.5 Key Events from Thalidomide to Mist, 8
   1.6 The Purpose of this Book, 13
   References, 14

2 “Mist” and other Metabolite Guidelines in the Context of Industrial Drug Metabolism 17
   Gordon J. Dear and Angus N. R. Nedderman
   2.1 A Historical Perspective, 17
   2.2 The Emergence of the Regulatory Guidance Documents, 23
   2.3 Impact of the Guidelines, 30
   2.4 Future Directions, 32
   References, 37
3 Metabolite Technology: Qualitative and Quantitative 45

Gordon J. Dear and Andrew McEwen

3.1 Introduction, 45
3.2 Clinical Samples, 46
3.3 Preclinical Samples, 48
3.4 Radiolabeled Test Compounds, 51
3.5 Mass Spectrometry, 55
3.6 NMR Spectroscopy, 65
3.7 Accelerator Mass Spectrometry, 72
References, 75
Further Reading, 85

4 In Vitro Methods for Evaluation of Drug Metabolism: Identification of Active and Inactive Metabolites and the Enzymes that Generate them 87

R. Scott Obach, Amit S. Kalgutkar, and Deepak K. Dalvie

4.1 Introduction, 87
4.2 In Vitro Methods for Metabolite Profiling and Identification, 88
  4.2.1 In Vitro Systems We Use: Most Complex to Simplest, 88
  4.2.2 Criteria for Selecting the Most Appropriate In Vitro System for In Vitro Metabolite Profiling, 92
4.3 Application of In Vitro Methods for Metabolite Profiling in Drug Discovery and Development, 96
  4.3.1 In Vitro Metabolite Profiling and Identification in the Early Drug Discovery Stage, 96
  4.3.2 In Vitro Metabolite Profiling and Identification in the Late Drug Discovery Stage: Selection of Candidate Compounds for Further Development, 98
  4.3.3 In Vitro Metabolite Profiling and Identification in the Drug Development Stage: Support of Candidate Compounds for New Drug Registration, 101
4.4 How Well Do In Vitro Metabolite Profiles Represent In Vivo Metabolite Profiles?, 103
4.5 Pharmacologically Active Metabolites and their Identification, 104
  4.5.1 When Is a Metabolite Considered Active?, 104
  4.5.2 Experimental Approaches to Reveal Active Metabolites, 106
4.6 Conclusion, 108
References, 108

5 Integrated Reactive Metabolite Strategies 111

J. Gerry Kenna and Richard A. Thompson

5.1 Introduction, 111
5.2 Role of RMs in Toxicity, 114
5.3 Strategies for Predicting, Assessing, and Derisking RM-Mediated Toxicity, 118
  5.3.1 Assessing RM Hazard: Awareness/Avoidance, 118
  5.3.2 Assessing RM Risk: Covalent Binding and Dose, 122
CONTENTS

7.7 Soft Drug Approach, 198
    7.7.1 Soft Corticosteroids, 199
    7.7.2 PDE4 Inhibitors, 200

7.8 Exposure to Metabolites and Risk of Adverse Events, 202
    7.8.1 Drug Interaction Potential, 204
    7.8.2 Toxicities and Safety Concerns, 205

References, 206

8 In Silico Modeling of Metabolite Kinetics 213
    Lu Gaohua, Howard Burt, Helen Humphries, Amin Rostami-Hodjegan, and Masoud Jamei

8.1 Introduction, 213
    8.1.1 Why Do We Need to Model Metabolite PK?, 213
    8.1.2 Brief Review of Existing PBPK Models of Metabolites, 214

8.2 Simcyp Approach to Modeling Metabolite PBPK, 215
    8.2.1 Parent/Metabolite PBPK Model Structure, 215
    8.2.2 Formation/Absorption of the Metabolite, 217
    8.2.3 Distribution of Metabolite, 219
    8.2.4 Elimination of Metabolite, 222
    8.2.5 Interaction of Metabolite, 222

8.3 Model Verifications, 223
    8.3.1 Comparison of Prediction versus Observation, 223
    8.3.2 What-If Simulation Examples, 223

8.4 Discussion, 230
    8.4.1 Role of M&S in Handling Metabolites, 230
    8.4.2 How to Deal with Multiple Metabolites, 231
    8.4.3 Role of M&S of Metabolites in Regulatory Submissions, 232

8.5 Concluding Remarks, 232
    8.5.1 What has been Achieved?, 232
    8.5.2 Future Works, 232

Glossary, 233
Superscription, 233
Subscription, 234
References, 234

9 Introduction to Case Studies 239
    Suzanne L. Iverson

References, 242

10 A Mass Balance and Metabolite Profiling Study of Sonidegib in Healthy Male Subjects Using Microtrace Approach 243
    Piet Swart, Frederic Lozac’h, and Markus Zollinger

10.1 Introduction to the Study, 243
10.2 Radioactive Dose Limitations, 245
10.3 Results, 246
10.4 Metabolite Profiling and Identification, 249
Acknowledgments, 258
References, 258

11 Dealing with Reality: When is it Necessary to Qualify and Quantify Metabolites? Some Case Studies 261
Deepak K. Dalvie, R. Scott Obach, and Amit S. Kalgutkar

11.1 Introduction, 261
11.2 Case Study 1, 261
11.3 Case Study 2, 265
11.4 Case Study 3, 268
References, 271

12 The Value of Metabolite Identification and Quantification in Clinical Studies. Some Case Studies Enabling Early Assessment of Safety in Humans: GlaxoSmithKline 275
Jackie Bloomer, Claire Beaumont, Gordon J. Dear, Stephanie North, and Graeme Young

12.1 GW644784: Species-Specific Metabolites, 276
12.2 Danirixin: Assessment of Victim Drug Interaction Risk Using Bile Sampling, 279
12.3 Sitamaquine: Unique, Active, and Possible Genotoxic Metabolites and Human Radiolabel Study Not Feasible, 280
12.5 GW766994: Consideration of Steady-State Kinetics and Multiple Analytical Methodologies for an Accurate Assessment of Human Metabolism, 288
References, 290

13 The Importance of Dose- and Time-Dependent Pharmacokinetics During Early Metabolite Safety Assessment in Humans 293
Laurent Leclercq, Marc Bockx, Hilde Bohets, Hans Stieltjes, Vikash Sinah, and Ellen Scheers

References, 303

14 Mist and the Future 305
B. Kevin Park and Dennis A. Smith

14.1 Introduction, 305
14.2 Mist and Pharmacology, 306
14.3 Reactive Metabolites, Pharmacology, and Mist, 309
14.4 Implications of Drug Bioactivation and Covalent Binding for Mist, 309
CONTENTS

14.5 Drug Bioactivation and Drug Hepatotoxicity, 311
14.6 Drug-Conjugate Formation and Drug Hypersensitivity, 313
14.7 Drug Bioactivation, Conjugate Formation, and Drug Hypersensitivity, 315
14.8 Toward a Mist Strategy for Reactive Metabolites, 317
References, 318

Index 323