EARLY DRUG DEVELOPMENT

Strategies and Routes to First-in-Human Trials

Edited by

MITCHELL N. CAYEN
Cayen Pharmaceutical Consulting, LLC
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CONTENTS

Contributors xix
Foreword xxi
Preface xxiii

PART I INTRODUCTION

1 Drug Discovery and Early Drug Development 3
   Mitchell N. Cayen

   1.1 The Drug Discovery and Development Scene, 3
       1.1.1 Pharmaceutical Research and Development Challenges, 3
       1.1.2 Attrition During Discovery and Development, 5
       1.1.3 Corporate Strategy Perspectives, 6

   1.2 Drug Discovery, 8
       1.2.1 Target Identification, 8
       1.2.2 Hit-to-Lead Identification, 9
       1.2.3 Lead Optimization Strategies, 10

   1.3 Pre-FIH Drug Development, 12
       1.3.1 Introduction, 12
       1.3.2 Pre-FIH Toxicology, 12
       1.3.3 Formulation and Drug Delivery, 13
       1.3.4 Pre-FIH Drug Metabolism and Pharmacokinetics, 14

   1.4 The FIH Trial, 15

   1.5 The Regulatory Landscape, 16
PART II LEAD OPTIMIZATION STRATEGIES

2 ADME Strategies in Lead Optimization 27
   Amin A. Nomeir
   2.1 Introduction, 27
   2.2 Absorption, 30
      2.2.1 Permeability, 32
      2.2.2 Efflux Transport, 35
   2.3 Distribution, 36
      2.3.1 Plasma Protein Binding, 36
      2.3.2 Brain Uptake, 40
      2.3.3 Tissue Distribution, 41
   2.4 Metabolism, 42
      2.4.1 In Vitro Metabolism Studies, 42
   2.5 Excretion, 61
   2.6 Pharmacokinetics, 64
   2.7 Prioritizing ADME Screens, 68
   2.8 In Silico ADME Screening, 69
   2.9 The Promise of Metabolomics, 76
   2.10 Conclusions, 78
      References, 79

3 Prediction of Pharmacokinetics and Drug Safety in Humans 89
   Peter L. Bullock
   3.1 Introduction, 89
   3.2 Prediction of Human Pharmacokinetic Behavior, 91
      3.2.1 In Vitro Models for Predicting Intestinal Absorption,
           Intrinsic Hepatic Clearance, and Drug Interactions, 92
      3.2.2 In Vivo Models for Predicting Pharmacokinetic
           Behavior, 107
3.3 Prediction of Drug Safety, 113
  3.3.1 In Vitro Approaches for Predicting Drug Safety, 114
  3.3.2 In Vivo and Ex Vivo Methods for Predicting Drug Safety, 116
  3.3.3 In Silico Methods for Predicting Drug Safety, 119

3.4 Conclusions, 120

References, 121

4 Bioanalytical Strategies 131

Christopher Kemper

4.1 Introduction, 131
  4.1.1 Bioanalysis: The Primary Basis for Pharmacokinetic and Pharmacodynamic Evaluations, 131
  4.1.2 Regulatory Initiatives in Bioanalysis, 132

4.2 Basic Bioanalytical Techniques and Method Development, 133
  4.2.1 Sample Preparation, 133
  4.2.2 Component Separation, 139
  4.2.3 Detection, 144
  4.2.4 Ligand-Binding Assays, 149
  4.2.5 Integration of Method Development Components: Example with LC-MS/MS, 154

4.3 Bioanalytical Method Validation, 156
  4.3.1 Introduction to Validation, 156
  4.3.2 The Primary Metrics: Acceptance Criteria, 157
  4.3.3 Additional Validation Criteria, 165

4.4 Special Issues with Ligand-Binding Assays, 168
  4.4.1 Characterization, 168
  4.4.2 Selectivity Issues, 168
  4.4.3 Matrix Effects, 168
  4.4.4 Quantification Issues, 169

4.5 Partial and Cross-Validations, 169

4.6 Application of Validated Methods to Sample Analyses: Some Perspectives, 170
  4.6.1 Stability, 171
  4.6.2 Calibration Curves, 172
  4.6.3 Quality Control Samples, 172
  4.6.4 Analytical Notes, 172
  4.6.5 Acceptance Criteria, 173
CONTENTS

4.6.6 Repeat Analyses of Incurred Samples, 174
4.6.7 Sample Stability and Incurred Samples, 176
4.6.8 Scientific Versus Production Issues, 177
4.6.9 Documentation, 178
4.6.10 Resources, 179

4.7 Risk-Based Paradigms: Discovery and Development Support, 188
4.7.1 Logistics and Discovery, 189
4.7.2 Early Involvement of Consultants and CROs, 192
4.7.3 Metabolites: Bioanalytical Issues Pre-FIH, 193
4.7.4 Racemic Mixtures, 194

4.8 The Road to “First in Human”, 194
4.8.1 Clinical Collaboration Prior to Initiation of the FIH Trial, 195

4.9 International Perspectives, 196
4.9.1 European Union, 196
4.9.2 Japan, 197
4.9.3 India, 197

4.10 Conclusions, 198

References, 199

PART III  BRIDGING FROM DISCOVERY TO DEVELOPMENT

5 Chemistry, Manufacturing, and Controls: The Drug Substance and Formulated Drug Product 207
Örn Almarsson and Christopher J. Galli

5.1 Introduction, 207

5.2 Pre-NCE Activities and CMC Development, 208
5.2.1 Rationale for CMC Involvement in Discovery, 208
5.2.2 Pharmaceutical Properties, 209
5.2.3 CMC Interactions with Discovery at NCE Selection, 212
5.2.4 Biopharmaceuticals, 214

5.3 CMC Considerations at the NCE Stage, 216
5.3.1 Solid-State Compounds, 216
5.3.2 Selection of Development Form (Crystalline State), 217
5.3.3 Characterization of Drug Substance (Preformulation), 220

5.4 NCE-to-GLP Transition (Bridging from Discovery to Pre-FIH Development), 222
CONTENTS

5.4.1 Drug Synthesis and Formulation for Toxicity Studies: Meeting the Delivery Objectives, 222
5.4.2 Bridging to Formulations for FIH Studies, 224

5.5 CMCs to Meet Clinical Trial Material Requirements, 229
5.5.1 Drug Substance Comparability with Material Used in Pre-FIH GLP Studies, 229
5.5.2 Good Manufacturing Practices, 230
5.5.3 Analytical Development for Assay of Drug Substance and Drug Product, 230
5.5.4 Placebos and Blinding, 235

5.6 CMC Strategic Considerations, 236
5.6.1 Interactions Across Disciplines, 236
5.6.2 Outsourcing (and Insourcing) CMC Work, 237

5.7 Case Studies, 238
5.7.1 Indinavir, 238
5.7.2 Doxorubicin Peptide Conjugate, 241

5.8 Evolution of Drug Development: Implications for CMCs in the Future, 244

Resources, 245

References, 247

6 Nonclinical Safety Pharmacology Studies Recommended for Support of First-in-Human Clinical Trials 249

Duane B. Lakings

6.1 Introduction and Overview, 249
6.2 Timing of Safety Pharmacology Studies, 252
6.3 CNS Safety Pharmacology, 254
6.4 Cardiovascular Safety Pharmacology, 254
6.4.1 Study Designs, 254
6.4.2 Additional Information on QT-Interval Prolongation or Delayed Ventricular Repolarization, 267
6.5 Respiratory System Safety Pharmacology, 267
6.6 Renal/Urinary Safety Pharmacology, 274
6.7 Gastrointestinal System Safety Pharmacology, 274
6.8 Autonomic Nervous System Safety Pharmacology, 275
6.9 Other Systems, 276
6.10 Discussion and Conclusions, 277

References, 279

PART IV  PRE-IND DRUG DEVELOPMENT

7  Toxicology Program to Support Initiation of a Clinical Phase I Program for a New Medicine  283

Hugh E. Black, Stephen B. Montgomery, and Ronald W. Moch

7.1  Introduction, 283

7.2  Toxicology Support of Discovery, 284

7.3  Goals of the Pre-FIH Toxicology Program, 285

7.4  Importance of a Clinical Review of the Nonclinical Pharmacology Data, 286

7.5  Take the Time to Plan Appropriately, 286

7.6  The Active Pharmaceutical Ingredient, 286

7.6.1  Availability Issues, 286

7.6.2  Impurity Considerations, 287

7.6.3  Inactive Ingredients, 288

7.7  Timely Conduct of In Vitro Assays, 288

7.7.1  Comparative In Vitro Metabolism, 288

7.7.2  Genetic Toxicology, 289

7.8  Development of Validated Bioanalytical and Analytical Assays, 290

7.8.1  Validated Bioanalytical Assay for Determining Plasma Concentrations of the NCE, 290

7.8.2  Validated Analytical Assays for Dosing Solutions or Suspensions, 290

7.8.3  Validated Assays for Dosing Solution Stability, 291

7.9  Planning for the Conduct of Toxicity Studies, 291

7.9.1  Timing of the IND/CTA, 291

7.9.2  The Danger of Shortcuts, 292

7.9.3  Pilot In Vivo Studies for Dose Selection and Bleeding Time Determinations, 292

7.10  GLP Toxicology Program, 293

7.10.1  Toxicology Requirements for Initiating an FIH Trial, 294

7.10.2  Toxicology Protocols, 295

7.10.3  Study Monitoring, 302
8 Toxicokinetics in Support of Drug Development 309

Gary Eichenbaum, Vangala Subrahmanyam, and Alfred P. Tonelli

8.1 Introduction, 309
8.2 Historical Perspectives, 310
8.3 Regulatory Considerations, 311
8.4 Factors to Consider in the Design of Toxicokinetic Studies, 312
  8.4.1 Drug Supply Requirements, 312
  8.4.2 Species Selection, 313
  8.4.3 API Properties: Salt/Crystal Form, Particle Size, and Impurities, 314
  8.4.4 Dose-Related Exposure, 314
  8.4.5 Changes in Pharmacokinetics Following Multiple Dosing, 315
  8.4.6 Selection of Dosing Vehicles, 316
  8.4.7 Bioanalytical Method, 316
  8.4.8 Evaluation of Metabolites, 317
  8.4.9 Evaluation of Enantiomers, 321
  8.4.10 Matrix Considerations, 321
  8.4.11 Number of Animals, 322
  8.4.12 Gender, 322
  8.4.13 Dose Selection, 323
  8.4.14 Dose Volume, 324
  8.4.15 Blood Sampling Variables, 324
  8.4.16 Sampling Times, 329
  8.4.17 Considerations with Biopharmaceutics, 331
  8.4.18 Practical Considerations in Planning a Toxicokinetic Program, 332
8.5 Toxicokinetic Parameter Estimates and Calculations, 332
  8.5.1 Data Analysis (Noncompartmental Versus Compartmental), 332
  8.5.2 Noncompartmental Kinetic Parameters, 333
  8.5.3 Statistics and Outliers, 338
  8.5.4 Physiologically Based Toxicokinetic Modeling, 338
8.6 Interpretation of Toxicokinetic Data, 339
  8.6.1 Review of In-life Results, 339
  8.6.2 Protocol Deviations, 339
  8.6.3 Confirmation of Exposure and Evaluation of Dose Proportionality, 339
  8.6.4 Exposure after Single and Multiple Dosing: Accumulation Perspectives, 341
  8.6.5 Gender Effects, 343
  8.6.6 Relationship to Toxicology Findings, 344
  8.6.7 Midstudy Changes in Dosing Duration or Dose Level, 345

8.7 Role of Toxicokinetics in Different Types of Toxicity Studies, 345
  8.7.1 Acute Studies, 346
  8.7.2 Dose-Range-Finding and Tolerability Studies, 346
  8.7.3 Subchronic Studies (Two Weeks to Three Months), 347
  8.7.4 Chronic Studies (Six to 12 Months), 347
  8.7.5 Safety Pharmacology and Specialty Studies, 347
  8.7.6 Genetic Toxicology, 348
  8.7.7 Reproductive Toxicology, 348
  8.7.8 Carcinogenicity Studies, 349
  8.7.9 Bridging Toxicity Studies, 350

8.8 Role of Toxicokinetics in Integrated Safety Assessment, 350
  8.8.1 Safety Margins: Role in Setting Clinical Doses for FIH Studies, 350
  8.8.2 Role of Protein Binding and Blood Partitioning, 352
  8.8.3 Toxicokinetics: Caution about Safety Margins, 353
  8.8.4 Safety Margins for Different Toxicity Profiles, 354

8.9 Conclusions, 355

References, 355

9 Good Laboratory Practice
  Anthony B. Jones, Kathryn Hackett-Fields, and Shari L. Perlstein

9.1 Introduction, 361

9.2 Hazard and Risk, 363

9.3 U.S. GLP Regulations, 366
  9.3.1 Subpart A: General Provisions, 367
  9.3.2 Subpart B: Organization and Personnel, 369
  9.3.3 Subpart C: Facilities, 376
  9.3.4 Subpart D: Equipment, 376
  9.3.5 Subpart E: Testing Facilities Operation, 377
9.3.6 Subpart F: Test and Control Articles, 378  
9.3.7 Subpart G: Protocol for and Conduct of a Nonclinical Laboratory Study, 379  
9.3.8 Subpart J: Reports and Records, 384  
9.3.9 Disqualification of Testing Facilities, 387  

9.4 GLPs in the Bioanalytical Laboratory, 387  
9.4.1 Organization and Personnel, 389  
9.4.2 Equipment and Testing Facilities Operation, 389  
9.4.3 Some Challenges in the Bioanalytical Laboratory, 391  

9.5 Moving Into the Future: A Closing Overview, 393  

9.6 Appendixes, 395  
  Appendix 9.1: Preambles—Perspectives on GLP Requirements, 395  
  Appendix 9.2: International Regulations, 396  
  Appendix 9.3: Paraphrased FDA GLP Definitions, 398  
  Appendix 9.4: FDA Inspections, 399  
  Appendix 9.5: Critical Phase Inspections—What, Why, How, and When?, 401  
  Appendix 9.6: Test System, 402  
  Appendix 9.7: 21 CFR Part 11, 402  
  Appendix 9.8: SOP Generation and Review, 408  
  Appendix 9.9: Study Director’s Responsibilities, 411  
  Appendix 9.10: Regulatory Requirements for the Study Protocol, 413  

References, 416  

PART V PLANNING THE FIRST-IN-HUMAN STUDY AND REGULATORY SUBMISSION  

10 Estimation of Human Starting Dose for Phase I Clinical Programs  
Lorrene A. Buckley, Parag Garhyan, Rafael Ponce, and Stanley A. Roberts  

10.1 Introduction, 423  

10.2 Characteristics of Well-Behaved Therapeutic Candidates, 424  

10.3 Regulatory Guidances for FIH-Enabling Nonclinical Safety Assessment: General Principles, 426  

10.4 Nonclinical Pharmacokinetics and Pharmacodynamics for Human Dose Projection, 427
10.5 Establishing the First-in-Human Dose, 427
   10.5.1 Phase I Clinical Trial Support: Use of the NOAEL-Based Approach, 428
   10.5.2 Estimating a Human Dose, 432

10.6 Phase I Clinical Trial Support: Use of the MABEL or Pharmacologically Active Dose, 439
   10.6.1 Predicting the MABEL and PAD in Humans, 441

10.7 Support of Exploratory Clinical Studies, 445

10.8 Considerations in the Design of Phase I Trials, 446
   10.8.1 Toxicological Considerations, 446
   10.8.2 Differences Between Animals and Humans That May Modify Exposure or Response, 447
   10.8.3 Healthy Human Subjects or Patients, 448

10.9 Interdisciplinary Partnerships, 448
   10.9.1 Chemistry, Manufacturing, and Control, 448
   10.9.2 Regulatory Affairs, 449
   10.9.3 Clinical, 449

10.10 Beyond the FIH Dose, 450

10.11 Concluding Perspective, 450

10.12 Four Case Studies, 451

References, 459

11 Exploratory INDs/CTAs

Mitchell N. Cayen

11.1 Introduction, 465

11.2 Regulatory Background, 467
   11.2.1 FDA Single-Dose Toxicity Guidance, 467
   11.2.2 European Position Paper on Microdose Clinical Trials, 467
   11.2.3 FDA Critical Path Initiative, 468
   11.2.4 FDA Guidance on Exploratory IND Studies, 469
   11.2.5 Belgium National Guidance on Exploratory Trials, 472
   11.2.6 The ExpIND (or ExpCTA) Submission, 473

11.3 Experience and Various Perspectives on ExpINDs or ExpCTAs, 474
   11.3.1 Microdose Studies, 475
   11.3.2 Pharmacological Dose and MOA Studies, 479
11.4 Some Reactions and Perspectives on the ExpIND/ExpCTA Initiative, 480
  11.4.1 What an ExpIND/ExpCTA Can Do, 481
  11.4.2 What an ExpIND/ExpCTA Cannot Do, 481
  11.4.3 Some Potential Drawbacks or Challenges in the Conduct of an ExpIND/ExpCTA Program, 482

11.5 What Is an Ideal Candidate for an ExpIND/ExpCTA?, 484

11.6 Conclusions, 484

References, 486

12 Unique Considerations for Biopharmaceutics 489
Laura P. Andrews and James D. Green

12.1 Introduction and Background, 489

12.2 Selection of the Molecule: Contrasts to Small-Molecule Considerations, 490
  12.2.1 Utility of Animal Efficacy Models, 491
  12.2.2 In Vitro Activity Profiling, Sequence Homology, and the Use of Homologous Molecules for Nonclinical Efficacy and Safety Assessments, 491
  12.2.3 In Vivo Profiling of Biopharmaceutical Activity, 492

12.3 Production and Process Considerations in Pre-FIH Development, 493

12.4 Bioanalytical Assay Considerations, 495

12.5 Objectives and Implementation of Pre-FIH Safety Assessment Programs, 496
  12.5.1 ICH S6 Guideline, 496
  12.5.2 Considerations and Typical Program Designs for Nonclinical Safety Assessment of Biopharmaceutics, 497

12.6 Post-IND Considerations: Support of Phases II and III and Registration, 507
  12.6.1 Changes in Production and Process, and Impact on Completed Studies, 507

12.7 The TeGenero Incident and Implications for Biopharmaceutic Nonclinical Safety Evaluation Programs, 508

12.8 Conclusions, 509

References, 510
13 Project Management and International Regulatory Requirements and Strategies for First-in-Human Trials 513
Carolyn D. Finkle and Judith Atkins

13.1 Introduction: Initiate Product Development with the End in Mind, 513

13.2 Importance of Project Management, 516

13.3 FDA Input Early and Often, 518

13.4 IND Submission in the United States, 519

13.5 Global Clinical Trials, 521

13.6 Clinical Trial Applications, 523
  13.6.1 Europe, 523
  13.6.2 Canada, 526
  13.6.3 Australia, 528
  13.6.4 Latin America, 530
  13.6.5 China, 534
  13.6.6 India, 535
  13.6.7 Japan, 537

13.7 Conclusions, 539

References, 539

14 First-in-Human Regulatory Submissions 543
Mary M. Sommer, Mark Ammann, Ulf B. Hillgren, Kathleen J. Kovacs, and Keith Wilner

14.1 Introduction, 543

14.2 Submission Strategies, 544
  14.2.1 Regulatory Environment, 545
  14.2.2 Clinical Considerations, 546

14.3 First-in-Human Dossiers, 549
  14.3.1 Introduction, 549
  14.3.2 General Considerations for Dossier Preparations, 549
  14.3.3 Coordination of the Disciplines, 553
  14.3.4 Document Preparation, 557

14.4 United States: Investigational New Drug Application, 559
  14.4.1 Regulatory Perspective, 559
  14.4.2 Chemistry, Manufacturing, and Controls, 565
  14.4.3 Nonclinical Sections, 574
  14.4.4 Clinical Components, 580
CONTRIBUTORS

Örn Almarsson, Alkermes, Inc., Waltham, Massachusetts
Mark Ammann, United BioSource Corporation, Ann Arbor, Michigan
Laura P. Andrews, Genzyme Corporation, Framingham, Massachusetts
Judith Atkins, Paraxel International Inc., Waltham, Massachusetts
Hugh E. Black, Hugh E. Black & Associates, Inc., Sparta, New Jersey
Lorrene A. Buckley, Eli Lilly and Company, Indianapolis, Indiana
Peter L. Bullock, Paul P. Carbone Cancer Center, University of Wisconsin, Madison, Wisconsin
John Caldwell, University of Liverpool, Liverpool, United Kingdom
Mitchell N. Cayen, Cayen Pharmaceutical Consulting, LLC, Bedminster, New Jersey
Gary Eichenbaum, Johnson & Johnson Pharmaceutical Research and Development, Raritan, New Jersey
Kathryn Hackett-Fields, QualiStat, Inc., Helmetta, New Jersey
Carolyn D. Finkle, MedImmune, Gaithersburg, Maryland
Christopher J. Galli, TransForm Pharmaceuticals/ChemPharm LEX, Johnson & Johnson Pharmaceutical Research and Development, Lexington, Massachusetts
Parag Garhyan, Eli Lilly and Company, Indianapolis, Indiana
James D. Green, Biogen Idec, Inc., Cambridge, Massachusetts
Ulf B. Hillgren, Pfizer Global Research and Development, Groton, Connecticut
Christopher Kemper, Pharmanet Development Group, Princeton, New Jersey
Kathleen J. Kovacs, Pfizer Global Research and Development, Groton, Connecticut
Duane B. Lakings, DSE Consulting, Inc., Elgin, Texas
Ronald W. Moch, Hugh E. Black & Associates, Inc., Rockville, Maryland
Amin A. Nomeir, Schering-Plough Research Institute, Kenilworth, New Jersey
Shari L. Perlstein, Pfizer Global Research and Development, Groton, Connecticut
Rafael A. Ponce, ZymoGenetics, Seattle, Washington; presently at: Amgen Inc., Seattle, Washington
Stanley A. Roberts, CoxX Research LLC, San Diego, California
Mary M. Sommer, Pfizer Global Research and Development, Groton, Connecticut
Vangala Subrahmanyam, Sai Advantium Pharma Ltd., Hinjewadi, Pune, India
Alfred P. Tonelli, Johnson & Johnson Pharmaceutical Research and Development, Raritan, New Jersey
Keith Wilner, Pfizer Global Research and Development, La Jolla, California
FOREWORD

From 1950 to the late 1990s, the global pharmaceutical industry was responsible for a series of advances that addressed major disease areas and led to significant improvements in public health and quality of life. In no particular order, these treatments may be exemplified by drugs (a) controlling blood pressure, and latter, blood cholesterol; (b) controlling gastric acid secretion; (c) controlling female fertility; and (d) progressively addressing major cancers, so that many tumor types are now treated as chronic diseases rather than terminal illnesses. The reader will be able to add many other examples to this list. Although these years were also marked by instances of patients harmed by drug treatments, most notably thalidomide in the early 1960s, the introduction of new therapies has revolutionized medical care for many people, created new personal freedoms, and is a major factor in the increase in life expectancy achieved in many countries over the past 50 or more years.

In recent years, the ability of the pharmaceutical industry to sustain this remarkable contribution has been challenged. Although we have seen a huge growth both in scientific understanding in the biomedical sciences and in the technical feasibility of many aspects of drug research and development, these advances have not been accompanied by corresponding increases in research productivity: put very simply, the research and development pipeline of new medicines has gotten blocked, so that fewer and fewer new agents reach the market each year. The reasons for this are many and varied. Making new compounds with interesting and therapeutically relevant biological activity is a challenge, but those that are produced lack other key features of usable drugs. In recent years it has proved very difficult indeed to develop such active compounds into novel medicines. The business model used by many pharmaceutical companies is not capable of infinite replication. The development of more “blockbuster” drugs, which have underpinned much of the growth seen from the mid-1970s onward, is now less and less likely in times when science seeks to stratify drug development and medicine seeks individualized therapies. The protection of intellectual
property and the maximization of marketing exclusivity are now more important than ever and come under pressure from health care providers, who emphasize the need for low-cost generic prescribing as one means to address the escalation of costs. The regulatory environment in the early twenty-first century is both sophisticated and questioning in all jurisdictions and is supported by the very high expectations of the public in terms of both the efficacy and safety of new therapies. It is to be hoped that recent developments in this area, such as the U.S. Food and Drug Administration’s Critical Path and the European Union’s Innovative Medicines Initiative, will bear fruit, but there have been few successes thus far.

Against this background, this new volume provides an invaluable guide to the earliest and most critical stages of drug development, getting promising new chemicals into humans quickly, effectively, and safely, to provide information of maximum benefit for critical decision making. The Editor, who has a lifetime of experience in exactly this arena, has identified a series of key topics and matched them to well-qualified authors, resulting in an extremely helpful handbook to guide the experienced investigator and novice alike through what can all too easily be a mine field.

Drug development is simultaneously an art and a science. It depends on excellent science in all of the various chemical, biological, and clinical disciplines that contribute, but at present at least the coordination of the management of all of the resources required as well as critical and fully informed decision making is best regarded as an art. It is my view that this new volume represents a substantial contribution by providing an integrated approach to an area that has suffered from excessive fragmentation.

JOHN CALDWELL

Pro-Vice-Chancellor and Dean of the Faculty of Medicine
University of Liverpool, United Kingdom
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PREFACE

During my career in the pharmaceutical industry in Canada and the United States, initially as a bench scientist and subsequently in managing departments in big pharma companies, and now as an industry consultant, I have never ceased to view the drug discovery and development paradigm with a combination of excitement, awe, wonder, and caution. There are many reasons for this mix of emotions. First, the discovery and development of successful medicines represent hugely complex challenges, with what seems to be a constantly shifting end zone. Our learning curve about the etiology and treatment of disease, coupled with the numerous changes in regulatory climate, help contribute, in my view, to make successful pharmaceutical development one of the most difficult of business enterprises. The second and probably more fundamental reason for these feelings is that the more I have learned over the years about how foreign compounds interface with living organisms, the more I realize that there is so much that I will never learn or understand. This is a sobering thought. Those of us who are in the business of developing medicines to treat human disease are doing the best we can to assure that we do not put patients at risk and that there is a high likelihood of therapeutic success. Given the complexity of the human body, the best we can hope for, based on all our advances over several millennia, is that successful therapeutics continue to morph from hit-and-miss to higher odds of positive outcomes in larger percentages of the target population. We still have a long way to go. It continues to amaze me that in most therapeutic areas, we have only reached the stage where we are merely alleviating disease symptoms rather than curing the actual disease.

It is therefore not surprising that the road to successful drug development has many twists, turns, and intersections, and that many travelers take different routes. It is critical to note that the path must eventually lead not to the submission of a new drug application (NDA), but to the attainment of an approvable NDA. The primary goal of this book is to describe those routes that have the greatest likelihood of a successful journey during the initial stages of the voyage.
[i.e., up to the first-in-human (FIH) trial]. The authors who provide these perspectives have had decades of experience in both big and small pharma companies, biotechnology companies, contract research organizations, regulatory affairs, and various aspects of consulting. Each chapter focuses on a specific discipline that contributes to the late discovery and early development of new candidate drugs, and is designed to describe the state-of-the-science, challenges, strategies, and “how to” regarding study designs and data interpretation. Many basic concepts are described and explained. The text can be used as a primer for new investigators as well as a resource for the experienced. It should be noted that each author is presenting the topic from his or her viewpoint and perspectives and that for the most part, no one size fits all. Indeed, given the fact that no single discipline can stand on its own, there is some overlap between chapters, and the reader may therefore obtain different viewpoints on similar topics (e.g., safety assessment of metabolites in Chapters 2, 3, 8, and 9; the TGN1412 monoclonal antibody human toxicity issue in Chapters 10 and 12). For example, approaches will vary based on such factors as:

- Small-molecule versus biotherapeutic drug
- Route of drug administration
- Frequency of drug administration
- Target disease
- Corporate resources, goals, portfolio management, and competitive landscape

We decided early where on the drug development path to end this book, and that was in the planning (but not implementation) of an FIH study. However, the more difficult decision was deciding where to begin. For various reasons, including the fact that there are numerous excellent published treatises on the discovery process, we decided arbitrarily to start at the point where a new chemical entity (NCE) has been shown to possess pharmacological activity in an initial screen (hit-to-lead), and then proceed to the next step toward the process of selection as a candidate drug (lead optimization). Accordingly, there is extensive discussion of those disciplines and activities necessary to demonstrate that the FIH trial will have a high likelihood of success; these disciplines include toxicology, safety pharmacology, CMC (chemistry, manufacturing, and controls), ADME (absorption, distribution, metabolism, and excretion), pharmacokinetics and toxicokinetics, GLPs (good laboratory practices), bioanalysis, regulatory submissions, and related activities. It is emphasized that there is no such thing as the perfect drug candidate, whether from the efficacy or safety viewpoint; as Sir Harold Macmillan pointed out: “To be alive at all involves some risk.”

One of my personal challenges when I begin consultation with a pharmaceutical company is to learn the lexicon which is the in-house language but which may not be readily transparent to new visitors. We have tried to be consistent within and have decided arbitrarily to use such terms as FIH [rather than FTIM
(first time in man)], NCE [rather than NME (new molecular entity) or NCD (new candidate drug)], and nonclinical (rather than preclinical, though both will be found).

I would like to thank Jonathan Rose at John Wiley & Sons for inviting me to put this book together and for his guidance during the process. I am very grateful to the authors of the various chapters for their dedication and patience, and for providing this project with their vast array of experience and expertise.

It is my joy to dedicate this book to my wife, Judy, who was instrumental in encouraging me to take on this project and whose love and support were absolutely invaluable during its course.

MITCHELL N. CAYEN

Bedminster, New Jersey
September 2009
PART I

INTRODUCTION