CONTENTS

List of Contributors  XIX

SECTION 1: Introduction

Chapter 1
The discipline of Clinical Pharmacology (Markus Müller)  3

Chapter 2
Current issues in drug development (Markus Müller)  7

1 Historical success  7
2 The dawn of a molecular era, the “druggable genome” and market fragmentation  8
3 Innovation and stagnation  10
4 The development of EBM methodology  12
5 Issues in preclinical and clinical drug development  12
6 The role of academic medicine  15
7 Confidence crisis and public opinion  15
8 Conclusion  16
Case Study: Pfizer  16

Chapter 3
Current issues in drug regulation (Marcus Müller,
Hans-Georg Eichler)  19

1 The drug regulators’ decision-making  19
2 Authorizing a medicinal product in the EU  20
   2.1 The Centralized Authorization  22
   2.2 The Mutual Recognition Procedure (MRP)
      and the Decentralized Procedure (DCP)  23
   2.3 The national procedure  24
Contents

3 Regulatory life-cycle management of medicinal products 24
   3.1 From efficacy to post-marketing relative effectiveness assessment 25
   3.2 Pharmacovigilance and signal detection 26
   3.3 Risk management plans (RMPs) 27
   3.4 When should a medicinal product be authorized? 28
Case Study: Efailizumab (Raptiva) 29

Chapter 4
Current issues in drug reimbursement (Anna Bucsics) 33

1 Introduction 33
2 Reimbursement principles in general 34
3 Relative effectiveness – background 35
4 Relative effectiveness case study – data submitted for reimbursement in Austria
   (Anna Bucsics, Valerie Nell-Duxneuner) 36
   4.1 Introduction 36
   4.2 Methods 36
   4.3 Results 37
   4.4 Interpretation 38
5 MEDEV – local payers vs. global payers 38
6 The Pharmaceutical Forum 39
7 Results 41
   7.1 Good principles 41
   7.2 Data for relative effectiveness assessment 43
   7.3 Networking 44
8 Looking forward 45
   8.1 EUnetHTA 45
   8.2 USA – comparative effectiveness research 45
9 In the future – building a European system of assessing relative effectiveness 46
   9.1 Developing the methodology 46
   9.2 Validating estimates of relative effectiveness 46
   9.3 Designing and performing the studies we need 46
   9.4 Leading the way 47

SECTION 2: Clinical Trials

Chapter 5
Ethics in clinical research (Ernst Singer, Christiane Druml) 53

1 Development of world-wide standards in clinical research ethics 53
2 Research Ethics Committees today – function and composition 56

VI
3 Research Ethics Committees – issues of debate 57
  3.1 Increasing workload 57
4 Compensation for committee members 59
Case Study: “Roaring sixties” in clinical research – The Beecher Article 59

Chapter 6
Good Clinical Practice (GCP) and scientific misconduct
(Brigitte Bloechl-Daum) 63

1 Introduction 63
2 Historic background 63
  2.1 The Prussian directive and the case of Neisser 64
    2.1.1 The Neisser case 64
  2.2 Federal Food and Drugs Act of 1906 64
  2.3 The sulfanilamide disaster and the “Food, Drug and Cosmetic
      Act” 1938 64
  2.4 Second World War crimes 65
    2.4.1 Unit 731 65
    2.4.2 Nazi experiments 65
  2.5 Nuremberg trial and Nuremberg Code 65
  2.6 Thalidomide (contergan) tragedy 66
  2.7 Declaration of Helsinki 66
3 Development of Good Clinical Practice Guidelines 66
4 International Conference of Harmonization (ICH) 67
  4.1 ICH parties 67
    4.1.1 European Commission – European Union (EU) 67
    4.1.2 European Federation of Pharmaceutical Industries
         and Associations (EFPIA) 68
    4.1.3 US Food and Drug Administration (FDA) 68
    4.1.4 Pharmaceutical Research and Manufacturers of America
         (PhRMA) 68
    4.1.5 Ministry of Health, Labour and Welfare, Japan
         (MHLW) 68
    4.1.6 Japan Pharmaceutical Manufacturers Association
         (JPMA) 68
  4.2 ICH observers 68
  4.3 ICH Steering Committee 69
5 ICH TOPIC E6, Note of Guidance for Good Clinical Practice (CPMP/ICH/135/95) –
   the Principles of ICH GCP 69
6 The three “main players” of ICH–GCP – Ethics Committee, Investigator
   and Sponsor 70

VII
Contents

6.1 Institutional review board/independent Ethics Committee (IRB/IEC) 70
6.2 Investigator 70
   6.2.1 Investigator’s qualifications and agreements 70
   6.2.2 Adequate resources 71
   6.2.3 Medical care of trial subjects 71
   6.2.4 Communication with IRB/IEC 72
   6.2.5 Compliance with protocol 72
   6.2.6 Investigational product(s) 72
   6.2.7 Randomization procedures and unblinding 72
   6.2.8 Informed consent of trial subjects 72
   6.2.9 Should study participants receive payment? 73
   6.2.10 Should there be a different standard for paying healthy subjects as opposed to patient-subjects? 74
6.2.11 Patient information 74
6.2.12 The informed consent process 75
6.2.13 Records and reports 76
6.2.14 Case record form (CRF) 76
6.2.15 Archiving 77
6.2.16 Progress reports 77
6.2.17 Safety reporting 77
6.2.18 Serious adverse event 77
6.2.19 Suspected unexpected serious adverse event (SUSAR) 78
6.2.20 Causality assessment 78
6.2.21 Premature termination or suspension of a trial 79
6.2.22 Final reports 79
6.3 Sponsor 79
   6.3.1 Quality assurance and quality control 80
   6.3.2 Additional responsibilities of the sponsor 80
7 Deficiencies of GCP 80
   7.1 Is ICH–GCP just a “bronze standard”? 80
   7.2 ICH–GCP and academic research 81
8 Summary 81

Research misconduct 82

1 What is research misconduct? 82
2 Forms of research misconduct 82
3 How common is research misconduct or fraud? 83
4 Conclusion 84
Case Study: Medical research in a global world 84

VIII
Chapter 7
Phase-I studies and first-in-human trials (Ulla Derhaschnig, Bernd Jilma)  89

1 Introduction  89
2 Definition phase I  89
3 General considerations for phase-I studies, trial design and study protocol  91
4 Preclinical development  91
5 Choice of subjects, study population  92
6 Dose finding  93
7 Route and rate of administration  93
8 Clinical environment  94
Case Study: Anti-CD28 antibody first-in-man trial  95

Chapter 8
Clinical trials – intervention studies (Michael Wolzt, Stefan Aschauer)  101

1 Introduction  101
2 Types of clinical trials  101
   2.1 Purpose  102
   2.2 Definition  102
3 Randomization  103
   3.1 The basic idea, like most good things is very simple  103
   3.2 Simple randomization  104
   3.3 Permuted block randomization  104
   3.4 Stratified randomization  104
   3.5 Pseudo – randomization  105
   3.6 Allocation concealment  105
4 Blinding  106
   4.1 Human behaviour is influenced by what we know or believe  106
5 Different study designs  107
   5.1 Parallel group design  107
   5.2 Cross-over design  108
   5.3 Factorial design  108
6 Study endpoint  109
7 Interim analyses  109
Case Study: The cardiac arrhythmia suppression trial (CAST)  110
Chapter 9
Observational studies (Harald Herkner, Christoph Male) 113

1 Introduction 113
2 Methodological principles 115
  2.1 Study population 115
  2.2 Data sources 116
    2.2.1 Exposure 117
    2.2.2 Outcome 118
  2.3 Measurement issues 118
  2.4 Measures of association and impact 119
  2.5 Interpreting an effect: bias, confounding, and sampling error 121
    2.5.1 Bias 121
    2.5.2 Confounding 122
    2.5.3 Sampling variation 123
3 Overview of study design types 123
  3.1 Descriptive studies 124
  3.2 Analytical study designs 125
    3.2.1 Cross-sectional study 126
    3.2.2 Cohort study – principles and practical example 126
    3.2.3 Case-control study – principles and a practical example 129
      3.2.3.1 The cases 130
      3.2.3.2 The controls and the source population 131
      3.2.3.3 Measurement of the main exposure factor 132
      3.2.3.4 Handling potential confounders 132
      3.2.3.5 Analysis and results 133
      3.2.3.6 Summary of case control studies 134
    3.2.4 Case-crossover studies 134
  3.3 Meta-analysis of observational studies 135

Case Study (cohort study): The risk of venous thrombosis in users of hormonal contraception 135

Chapter 10
Pharmacokinetics I: PK–PD approaches – antibiotic drug development (Sreedharan N. Sabarinath, Rajendra Pratap Singh, Hartmut Derendorf) 143

1 PK–PD approach 144
2 Microdialysis for measuring free drug concentrations 147
3 MD calibration methods 148
4 MD and tissue penetration of antibiotics 150
5 Microdialysis and PK–PD 150

X
6 Kill curves 151
7 Experimental settings of in vitro models 152
8 Conclusion 154

Chapter 11
**Pharmacokinetics II: $^{14}$C-labelled microdosing in assessing drug pharmacokinetics at Phase-0 (Graham Lappin)** 157

1 Origins of $^{14}$C-labelled tracers 157
2 Administration of $^{14}$C-drugs to humans 159
3 Accelerator Mass Spectrometry 159
   3.1 The emergence of microdosing 160
   3.2 Application of microdosing 161
4 Pharmacokinetic linearity 162
5 Microdosing and metabolism 164
6 Conclusions 165

Chapter 12
**Epidemiology and bio statistics (Gerhard Garhöfer, Leopold Schmetterer)** 167

1 Introduction 167
2 Measures of the disease frequency 167
   2.1 Prevalence 168
   2.2 Incidence 169
   2.3 Mortality 170
3 Relationship between prevalence, incidence and mortality 170
4 Survival analysis 171
5 Censored data 172
6 Case fatality rate 173
7 Risk, relative risk and attributable risk 173
8 Epidemiologic study designs 173
9 Statistical measures 174
   9.1 Why use statistics? 174
   9.2 Variables 174
   9.3 Presentation of variables 175
10 Population and sample 175
   10.1 Hypothesis testing and the $p$ value 175
   10.2 Post hoc analysis or “fishing for results” 176
   10.3 Multiple testing 177
   10.4 Correlation analysis 177
   10.5 Association and causation 178
Contents

10.5.1 Association strength 178
10.5.2 Temporal relationship 178
10.5.3 Dose-response relationship 178
10.5.4 Constancy 179
10.5.5 Plausibility 179
10.5.6 Experiment 179
10.5.7 Specificity 179

Case Study: Multiple post-hoc comparisons in the “Second International Study of Infarct Survival (ISIS-2)” 179

Chapter 13
Placebo effects and placebo control in clinical trials
(Magdalena Pitz, Johannes Pleiner) 181

1 The recent debate about research ethics in placebo controlled trials (PCTs) 182
2 Placebo vs. active control 183
3 The issue of “assay sensitivity” 184
4 Placebo controlled trial: ethical or not? 184
5 Criteria for justification of placebo 186
Case Study: Placebo Surgery 187

SECTION 3: Tools in Clinical Pharmacology

Chapter 14
Tools in clinical pharmacology – imaging techniques
(Martin Bauer, Oliver Langer) 193

1 Introduction 193
2 Positron emission tomography (PET) 195
3 Single photon emission computed tomography (SPECT) 198
4 Optical imaging 198
5 Magnetic resonance imaging (MRI) 199
6 Computed tomography (CT) 200
7 Ultrasound imaging 200
Case Study: Using PET in drug development – apreptan 200

Chapter 15
Current concepts of pharmacogenetics, pharmacogenomics, and the “druggable” genome (Wolfgang M. Schmidt) 205

1 Genetic variation in the human genome: biological basis of pharmacogenetics 206

XII
Chapter 16
Biomarkers (Volker Wacheck) 225

Introduction 225
2 Why do molecular targeting drugs fail in current clinical drug development? 227
3 Biomarker in clinical drug development 229
4 How biomarkers may improve clinical drug development 231
5 Biomarker as surrogate endpoints 234
6 Outlook 236
Case Study: Cholesterol as biomarker and surrogate endpoint for cardiovascular disease 237

Chapter 17
Molecular tools in drug research – translational medicine
(Sandra Eder, Volker Wacheck) 241

Introduction 241
2 Molecular tools for drug target identification 242
  2.1 At the nucleotide level 243
  2.2 At the protein level 247
3 Molecular tools for target validation 249
  3.1 Target (over)expression 250
  3.2 Target downregulation 251
  3.3 Conditional target regulation 254
4 Molecular tools for monitoring pharmacodynamics in translational studies 255
Case Study: Re-translational studies – the case of ACE2 258
SECTION 4: Topics in Clinical Pharmacology

Chapter 18
Pharmaceutical drug safety (*Martin Brunner*) 263

1 Introduction 263
2 Thalidomide – a disaster as starting point for the methodical assessment of drug safety 265
3 During drug development only frequent ADRs can be detected 266
4 ADR reporting and worldwide pharmacovigilance 267
5 Spontaneous reporting systems 268
6 Drug safety issues after Lipobay and Vioxx 272
7 Recent and future developments in pharmacovigilance 272
8 Conclusions 274
Case Study 1: Cerivastatin – the withdrawal of a blockbuster drug is needed to expose problems with drug safety systems 274
Case Study 2: Micafungin – safety issues prompt EMA to demand submission of a risk management strategy as a condition of market authorization in the European Union (if not otherwise specified, the EMA public assessment report, EPAR [38] was quoted) 276

Chapter 19
Drug interactions (*Markus Zeitlinger*) 281

1 Definition 281
2 Relevance of interactions 281
3 Categories of interaction 281
4 Factors promoting interactions and their clinical relevance 282
5 Most important mechanisms of interactions according to the ADME schemata 284
   5.1 ADME – interactions based on drug absorption 284
6 ADME – interactions based on drug distribution 286
   6.1 ADME – interactions based on drug metabolism 292
   6.2 Examples for clinically relevant interactions based on CYP3A4 295
   6.3 ADME – interactions based on drug excretion 297
7 Management of potential drug interactions 297
Case Study: Interactions based on a drug class: antibiotics 298

XIV
Chapter 20
“Non-chemical” drugs: biologicals, protein therapeutics, vaccines and antisense therapeutics (Markus Müller) 309

1 Introduction 309
2 A need for alternatives to traditional chemicals 310
3 Specifics of the development process of biologicals 311
4 Protein therapeutics (PTs) 314
5 Vaccines (group III PTs) 316
6 Antisense approaches and aptamers 317
Case Study: Alzheimer vaccine 318

Chapter 21
Development of Advanced Therapy Medicinal Products – a case for early scientific advice (Bernd Jilma) 323

1 Introduction 323
2 Cell-based medicinal products (CBMPs) 325
3 Efficacy and safety challenges 325
   3.1 Patient integration 325
   3.2 Characterization 326
4 Gene therapy medicinal products (GTMP) 327
5 Development challenges and strategies to address them 327
   5.1 Vector manufacture 327
   5.2 Achieving stable gene expression 328
   5.3 Clinical efficacy and safety 328
6 Combined ATMPs 328
7 Involvement of CAT in ATMP development 329
Definitions of Advanced Therapy medicinal products in the European Pharmaceutical legislation) 330
Tasks of the CAT 331
EMA information and guidelines 332

Chapter 22
Individualized medicine (Markus Müller) 333

1 The current concept 335
2 A history of dose individualization 336
3 Pharmacogenetics and biomarkers 338
Contents

4 The unmet need – improving the benefit-risk ration and effectiveness of drugs 339
5 Improving the benefit/risk profile by biomarker tests 340
Case Study: Warfarin dosing 342

Chapter 23
Generics, biosimilars, enantiomers and me-toos (George Wade, Brigitte Bloechl-Daum) 345

1 Generics 345
   1.1 Regulatory background 346
   1.2 Patent protection, data protection and marketing protection for new products 347
   1.3 Salts, esters 348
   1.4 Bioequivalence 349
   1.5 Bioequivalence – some special issues 352
      1.5.1 Narrow therapeutic index drugs (NTIDs) 352
      1.5.2 Highly variable drug products (HVDP) 353
      1.5.3 Chiral drugs, enantiomers 353
      1.5.4 $t_{\text{max}}$ 353
      1.5.5 Drugs which are not orally absorbed 354
      1.5.6 Inhaled drugs 354
      1.5.7 Bioequivalence of intravenous products? complex parenterals 354

2 Biosimilars 356
   2.1 Complexity 356
   2.2 Biosimilars: General issues 357
   2.3 Regulatory experience 358

3 Enantiomers 358
   3.1 Sophisticated nonsense? 358
   3.2 Rationale for the development of chirally pure drugs 359
   3.3 Pharmacodynamic and kinetic differences between enantiomers 360
   3.4 Recent regulatory experience of the Chiral Switch: a word of caution 361

4 Me-toos 362
   4.1 Background 362
   4.2 What are “me-too” drugs? 363
   4.3 How many “me-too” drugs are enough? 364
   4.4 Is First-in-class also best-in-class? 364
   4.5 Are incentives for drugs that are “first in class” or hurdles for “me-too” drugs called for? 365

XVI
4.6 What is a drug class? 366
4.7 Is there a “class effect”? 366

Case Study: Class effect with proton pump inhibitors 366

Chapter 24
Special situations, market fragmentation I: orphan drugs
for rare diseases (Brigitte Bloechl-Daum, Florence Butlen-Ducuing,
Jordi Linares-Garcia) 369

1 What are rare diseases? 369
2 What are orphan drugs? 369
3 The orphan drug legislation 370
4 The Committee on Orphan Medicinal Products (COMP) 370
5 Orphan incentives 371
6 What are the criteria for orphan designation? 371
7 General requirements for a valid condition for orphan designation 373
   8.1 Some examples for a positive opinion for orphan designation 374
   8.2 Negative opinions 374
   8.3 Reason for negative opinions – subsetting – no significant benefit 375
      8.3.1 Subsetting/valid condition 375
      8.3.2 Significant benefit 376
9 Confirmation of orphan status at the time of marketing authorization 377
10 Challenging marketing exclusivity for orphan medicinal products 378
11 Success of the orphan programme 379
   11.1 Designated orphan medicines 379
   11.2 Marketing authorizations for orphan medicines 380
12 Discussion 381
13 Useful links 385

Chapter 25
Special situations, market fragmentation II: sex differences
(Ghazaleh Gouya) 387

1 Expanding scope of gender and sex differences 387
2 Sex versus gender 388
3 Sex matters 388
   3.1 Physiologic variability 388
   3.2 Pharmacokinetics – sex differences 389
   3.3 Pharmacodynamic – sex differences 389
   3.4 Female specific aspects 390
   3.5 Adverse drug reactions 390
Contents

3.6 Clinical trials – women’s representation 391
   3.6.1 History 391
   3.6.2 Barriers of participation in clinical trials 392
4 Regulatory changes to include women in clinical trials 392
5 Pregnancy 392
6 From sex differences to individual differences: where the science is taking us 393
Case Study: Cardiovascular disease and women 393

Chapter 26
Special situations III: Medicines for Children (Christoph Male) 403

1 Children as therapeutic orphans 403
2 Hurdles to drug development for children 404
   2.1 Ethical and legal aspects 404
   2.2 Lack of public acceptance 405
   2.3 Methodological challenges of clinical studies in children 405
   2.4 Lack of research infrastructures and paediatric research networks 405
   2.5 Low economic potential of paediatric indications for pharmaceutical industry 406
3 Regulatory initiatives to improve paediatric drug development 406
   3.1 Paediatric initiatives in the USA 406
   3.2 EU Paediatric Regulation 407
      3.2.1 Requirements and rewards 407
      3.2.2 Paediatric Investigation Plan 408
      3.2.3 Paediatric Committee 408
      3.2.4 Collateral measures 409
4 Points to consider for a Paediatric Investigation Plan 409
   4.1 Paediatric indications 409
   4.2 Child-appropriate formulations 410
   4.3 Juvenile animal studies 410
   4.4 Clinical Pharmacology studies in children 411
   4.5 Clinical efficacy and safety studies 412
Case Study: Paediatric Investigation Plan for Clopidogrel 413

About the authors 419
Keyword index 427

XVIII