

CONTENTS

Chapter 1. An Introduction to the U.S. New Drug Approval Process	1
The FDA and the Food, Drug and Cosmetic Act	2
New Drug Development and Approval: A Brief Overview of the Principal Steps	3
Chapter 2. Nonclinical Drug Testing	11
Trends in Nonclinical Testing	12
FDA Guidance on Nonclinical Testing Requirements	14
Types of Nonclinical Studies	15
Pharmacology Studies	15
Toxicity Studies	17
Acute Toxicity Studies	17
Subacute or Subchronic Studies	18
Chronic Toxicity Testing	19
Carcinogenicity Studies	20
Special Toxicity Studies	23
Reproductive Toxicity Studies	24
Genotoxicity Studies	25
Toxicokinetic Studies	26
FDA Standards for Nonclinical Testing: Good Laboratory Practice (GLP)	27
Chapter 3. The IND	31
Types of INDs	32
The “Exploratory” or Screening IND	32
Investigator INDs	34
Emergency Use INDs	34
Treatment INDs	34
The Applicability of the IND	34
IND Content and Format Requirements	35
Cover Sheet (Form FDA 1571)	39
Table of Contents	39
Introductory Statement	39
General Investigational Plan	39
Investigator’s Brochure	40
Clinical Protocols	43
Chemistry, Manufacturing, and Controls Information	49
Animal Pharmacology and Toxicology Information	53
Previous Human Experience with the Investigational Drug	54
Additional Information	54
Pharmacogenomic Data and the IND	55
Submitting the IND	55
IND Maintenance Requirements	57
Protocol Amendments	57
IND Safety Reports	57
Annual Reports	60
Information Amendments	61

Chapter 4. CDER and the IND Review Process	63
The FDA's Center for Drug Evaluation and Research	63
CDER's Review Divisions	66
Division of Oncologic Drug Products	76
Division of Biological Oncology Products	68
Division of Medical Imaging and Hematology Products	68
Division of Cardiovascular and Renal Products	69
Division of Neurology Products	69
Division of Psychiatry Products	69
Division of Metabolism and Endocrinology Products	69
Division of Pulmonary and Allergy Products	70
Division of Anesthesia, Analgesia, and Rheumatology Products	70
Division of Reproductive and Urologic Drug Products	70
Division of Gastroenterology Products	70
Division of Dermatology and Dental Products	70
Division of Anti-Infective and Ophthalmology Products	71
Division of Antiviral Drug Products	71
Division of Special Pathogen and Transplant Products	71
Office of Nonprescription Products	72
Inside the FDA's Drug Review Divisions	72
The IND Review Process	74
Initial Processing of the IND	76
The IND within the Review Division	77
Pharmacology Review	77
Chemistry Review	78
Clinical Review	78
Microbiology Review	78
The 30-Day Review Clock	79
The Clinical Hold	80
IND Status	83
Chapter 5. The Clinical Development of New Drugs	85
The FDA's Role in Clinical Trials	92
The Structure of Clinical Trials	94
Phase 1 Clinical Trials	97
PK/PD and Phase 1 Trials	99
Sponsor Information/Data Submissions During Clinical Trials	100
Phase 2 Clinical Trials	101
End-of-Phase 2 Meetings and Other FDA-Sponsor Communication During Clinical Trials	103
Phase 3 Clinical Trials	106
Pivotal Clinical Studies	107
Standards for Pivotal Trials	109
Clinical Trials and the Safety Data Base	112
Completing a Drug's Clinical Study	114
Phase 4 Clinical Studies	117
Chapter 6. Good Clinical Practices (GCP)	119
Recent Developments in GCP	120
Responsibilities of the Sponsor	122
Selecting Investigators and Monitors	122

Chapter 4. CDER and the IND Review Process	63
The FDA's Center for Drug Evaluation and Research	63
CDER's Review Divisions	66
Division of Oncologic Drug Products	76
Division of Biological Oncology Products	68
Division of Medical Imaging and Hematology Products	68
Division of Cardiovascular and Renal Products	69
Division of Neurology Products	69
Division of Psychiatry Products	69
Division of Metabolism and Endocrinology Products	69
Division of Pulmonary and Allergy Products	70
Division of Anesthesia, Analgesia, and Rheumatology Products	70
Division of Reproductive and Urologic Drug Products	70
Division of Gastroenterology Products	70
Division of Dermatology and Dental Products	70
Division of Anti-Infective and Ophthalmology Products	71
Division of Antiviral Drug Products	71
Division of Special Pathogen and Transplant Products	71
Office of Nonprescription Products	72
Inside the FDA's Drug Review Divisions	72
The IND Review Process	74
Initial Processing of the IND	76
The IND within the Review Division	77
Pharmacology Review	77
Chemistry Review	78
Clinical Review	78
Microbiology Review	78
The 30-Day Review Clock	79
The Clinical Hold	80
IND Status	83
Chapter 5. The Clinical Development of New Drugs	85
The FDA's Role in Clinical Trials	92
The Structure of Clinical Trials	94
Phase 1 Clinical Trials	97
PK/PD and Phase 1 Trials	99
Sponsor Information/Data Submissions During Clinical Trials	100
Phase 2 Clinical Trials	101
End-of-Phase 2 Meetings and Other FDA-Sponsor Communication During Clinical Trials	103
Phase 3 Clinical Trials	106
Pivotal Clinical Studies	107
Standards for Pivotal Trials	109
Clinical Trials and the Safety Data Base	112
Completing a Drug's Clinical Study	114
Phase 4 Clinical Studies	117
Chapter 6. Good Clinical Practices (GCP)	119
Recent Developments in GCP	120
Responsibilities of the Sponsor	122
Selecting Investigators and Monitors	122

Informing Investigators	124
Review of Ongoing Investigations	125
Recordkeeping and Record Retention	126
Disposition of Unused Drug Supplies	126
Sponsors and Data Safety Monitoring Boards	126
Responsibilities of Investigators	127
Control of the Product	128
Recordkeeping and Record Retention	128
Investigator Reports	128
Assurance of IRB Review	128
Handling of Controlled Substances	128
The Institutional Review Board (IRB)	129
Informed Consent	130

Chapter 7. The New Drug Application (NDA)133

The History of the NDA	135
NDA Content and Format Requirements	137
The Common Technical Document/Electronic Common Technical Document	137
The Fundamentals of NDA Submissions	145
The Archival, Review, and Field Copies of the NDA	146
Application Form	150
The Index	150
Labeling	150
The “Content of Labeling” Section	150
The NDA Summary	151
Chemistry Section	152
Nonclinical Pharmacology and Toxicology Section	160
Human Pharmacokinetics and Bioavailability Section	161
Microbiology Section	162
Clinical Data Section	163
Safety Update Report Section	166
Statistical Section	167
Pediatric Assessment	167
Case Report Tabulations Section	168
Case Report Forms Section	169
Patent Information	170
Patent Certification	170
Establishment Description	170
Debarment Certification	170
Field Copy Certification	170
User Fee Cover Sheet (Form FDA 3397)	170
Financial Information Section	171
Other Information	172
Other Possible Elements of the NDA: RiskMAPs, REMS and Pharmacogenomic Data	172
The NDA and Risk Minimization Action Plans	173
REMS	174
Pharmacogenomic Data and the NDA	175
Complete versus Partial NDA Submissions	176
The GRMPs and the Wisdom of Complete NDA Filings	176
PDUFA, the Rolling NDA, and the Reviewable Unit Pilot	178
Pre-NDA Meetings	179

Informing Investigators	124
Review of Ongoing Investigations	125
Recordkeeping and Record Retention	126
Disposition of Unused Drug Supplies	126
Sponsors and Data Safety Monitoring Boards	126
Responsibilities of Investigators	127
Control of the Product	128
Recordkeeping and Record Retention	128
Investigator Reports	128
Assurance of IRB Review	128
Handling of Controlled Substances	128
The Institutional Review Board (IRB)	129
Informed Consent	130

Chapter 7. The New Drug Application (NDA)133

The History of the NDA	135
NDA Content and Format Requirements	137
The Common Technical Document/Electronic Common Technical Document	137
The Fundamentals of NDA Submissions	145
The Archival, Review, and Field Copies of the NDA	146
Application Form	150
The Index	150
Labeling	150
The “Content of Labeling” Section	150
The NDA Summary	151
Chemistry Section	152
Nonclinical Pharmacology and Toxicology Section	160
Human Pharmacokinetics and Bioavailability Section	161
Microbiology Section	162
Clinical Data Section	163
Safety Update Report Section	166
Statistical Section	167
Pediatric Assessment	167
Case Report Tabulations Section	168
Case Report Forms Section	169
Patent Information	170
Patent Certification	170
Establishment Description	170
Debarment Certification	170
Field Copy Certification	170
User Fee Cover Sheet (Form FDA 3397)	170
Financial Information Section	171
Other Information	172
Other Possible Elements of the NDA: RiskMAPs, REMS and Pharmacogenomic Data	172
The NDA and Risk Minimization Action Plans	173
REMS	174
Pharmacogenomic Data and the NDA	175
Complete versus Partial NDA Submissions	176
The GRMPs and the Wisdom of Complete NDA Filings	176
PDUFA, the Rolling NDA, and the Reviewable Unit Pilot	178
Pre-NDA Meetings	179

Assembling and Submitting the NDA	181
Amending the NDA	181
Chapter 8. The NDA Review Process	183
The NDA Review Process in the PDUFA Era	183
A Profile of the NDA Review Process	187
Initial Processing of the NDA	188
Processing Within the Drug Review Division	188
The FDA's Refuse-to-File Authorities	190
PDUFA and Early Notification of NDA Issues	194
The Preapproval Inspection	195
The Primary Review Process	197
Clinical Review	197
Pharmacology/Toxicology Reviewer	198
Chemistry Reviewer	198
Statistical Reviewer	198
Biopharmaceutics Reviewer	198
Microbiology Reviewer	198
Bioresearch Monitoring Reviewer	199
Mid-Review CDER/Sponsor Communications	199
Emerging Elements of the NDA Review Process: RiskMAPs, REMS, and Pharmacogenomic Data	201
Reaching an Institutional Decision on the NDA	203
The Formal Action on an NDA	205
FDA Action Letters	207
Approval Letter	207
Approvable Letter	209
Not-Approvable Letter	210
Applicant Responses to Approvable or Not-Approvable Letters	211
Final Printed Labeling	212
Draft Package Labeling	213
The FDA's Review of Draft Labeling	215
Sponsor Rights During the NDA Review Process	216
The Right to a Timely Review	216
The Right to Meetings	218
The Right to Protest and Appeal FDA Actions/Decisions	220
The Right to Confidentiality	222
Proposed Changes to NDA Confidentiality Standards	224
Chapter 9. The FDA's Priority Review Policy	225
Therapeutic Rating	226
Assigning the Therapeutic Rating	227
Chemical Classification	228
CDER's Prioritization Policy at Work	230
The Impact of CDER's Priority Review Policy	230
Patterns in Priority/Standard Designations for New Drugs	231
Chapter 10. Advisory Committees and the Drug Approval Process	233
A Look at Committee Membership	236
Conflict of Interest Standards for Committee Members	237
When CDER Uses Advisory Committees	240

Assembling and Submitting the NDA	181
Amending the NDA	181
Chapter 8. The NDA Review Process	183
The NDA Review Process in the PDUFA Era	183
A Profile of the NDA Review Process	187
Initial Processing of the NDA	188
Processing Within the Drug Review Division	188
The FDA's Refuse-to-File Authorities	190
PDUFA and Early Notification of NDA Issues	194
The Preapproval Inspection	195
The Primary Review Process	197
Clinical Review	197
Pharmacology/Toxicology Reviewer	198
Chemistry Reviewer	198
Statistical Reviewer	198
Biopharmaceutics Reviewer	198
Microbiology Reviewer	198
Bioresearch Monitoring Reviewer	199
Mid-Review CDER/Sponsor Communications	199
Emerging Elements of the NDA Review Process: RiskMAPs, REMS, and Pharmacogenomic Data	201
Reaching an Institutional Decision on the NDA	203
The Formal Action on an NDA	205
FDA Action Letters	207
Approval Letter	207
Approvable Letter	209
Not-Approvable Letter	210
Applicant Responses to Approvable or Not-Approvable Letters	211
Final Printed Labeling	212
Draft Package Labeling	213
The FDA's Review of Draft Labeling	215
Sponsor Rights During the NDA Review Process	216
The Right to a Timely Review	216
The Right to Meetings	218
The Right to Protest and Appeal FDA Actions/Decisions	220
The Right to Confidentiality	222
Proposed Changes to NDA Confidentiality Standards	224
Chapter 9. The FDA's Priority Review Policy	225
Therapeutic Rating	226
Assigning the Therapeutic Rating	227
Chemical Classification	228
CDER's Prioritization Policy at Work	230
The Impact of CDER's Priority Review Policy	230
Patterns in Priority/Standard Designations for New Drugs	231
Chapter 10. Advisory Committees and the Drug Approval Process	233
A Look at Committee Membership	236
Conflict of Interest Standards for Committee Members	237
When CDER Uses Advisory Committees	240

How Advisory Committees Function	241
Committee Meeting Scheduling and Practices	242
How Influential Are CDER's Advisory Committees?	244
What Sponsors Should Know About Advisory Committees	245
Chapter 11. Beyond Approval: Postmarketing Drug Manufacturer Regulatory Responsibilities . . .	247
General Reporting Requirements	248
Field Alert Reports	248
Annual Reports	248
Other Reports	251
Adverse Drug Experience Reporting Requirements	252
Key Definitions Relevant to Adverse Drug Experience Reporting	254
Adverse Drug Experience Reporting Requirements	255
Pending Revisions to the FDA's Postmarketing AE Reporting Requirements	259
Current Good Manufacturing Practice (cGMP)	261
The Pharmaceutical cGMPs for the 21st Century Initiative	262
The FDA's cGMP Standards	264
The Enforcement of cGMP	267
Phase 4 Commitments	268
FDAAA and New FDA Powers to Require Postmarketing Studies/Trials	268
Trends in Postmarketing Commitments for New Drugs	272
Post-Approval Risk Management	272
Chapter 12. The Supplemental NDA and Postapproval Changes to Marketed Drugs	275
Recent History of Regulatory Reform and sNDAs	275
When to Submit Supplemental versus Original NDAs	276
Supplemental NDA Submission Requirements	277
Postmarketing Manufacturing Changes	278
FDAMA and Postmarketing Manufacturing Changes	278
SUPAC and sNDAs for Manufacturing Changes	279
CDER's PQAS and Manufacturing Supplements	280
Expedited Review for NDA Chemistry Supplements	281
"Bundled" CMC Supplements	281
Labeling Changes	282
Pursuing New Indications for Approved Drugs	283
Submission and Approval Trends for Efficacy Supplements	284
Chapter 13. The FDA's Orphan Drug Development Program	285
The FDA and Orphan Drugs: A Brief History	286
The Significance of Orphan Drug Designation	286
Obtaining Orphan Drug Designation	287
A Look at Orphan Drug Incentives	289
Marketing Exclusivity	290
Tax Credits	292
Protocol Assistance	292
FDA Grants and Contracts	293
The FDA Approval Process: Advantages for Orphan Drugs?	293
Chapter 14. CDER's Bioresearch Monitoring Program	295
A Brief History of the Bioresearch Monitoring Program	297
The Clinical Investigator Compliance Program	298

How Advisory Committees Function	241
Committee Meeting Scheduling and Practices	242
How Influential Are CDER's Advisory Committees?	244
What Sponsors Should Know About Advisory Committees	245
Chapter 11. Beyond Approval: Postmarketing Drug Manufacturer Regulatory Responsibilities . . .	247
General Reporting Requirements	248
Field Alert Reports	248
Annual Reports	248
Other Reports	251
Adverse Drug Experience Reporting Requirements	252
Key Definitions Relevant to Adverse Drug Experience Reporting	254
Adverse Drug Experience Reporting Requirements	255
Pending Revisions to the FDA's Postmarketing AE Reporting Requirements	259
Current Good Manufacturing Practice (cGMP)	261
The Pharmaceutical cGMPs for the 21st Century Initiative	262
The FDA's cGMP Standards	264
The Enforcement of cGMP	267
Phase 4 Commitments	268
FDAAA and New FDA Powers to Require Postmarketing Studies/Trials	268
Trends in Postmarketing Commitments for New Drugs	272
Post-Approval Risk Management	272
Chapter 12. The Supplemental NDA and Postapproval Changes to Marketed Drugs	275
Recent History of Regulatory Reform and sNDAs	275
When to Submit Supplemental versus Original NDAs	276
Supplemental NDA Submission Requirements	277
Postmarketing Manufacturing Changes	278
FDAMA and Postmarketing Manufacturing Changes	278
SUPAC and sNDAs for Manufacturing Changes	279
CDER's PQAS and Manufacturing Supplements	280
Expedited Review for NDA Chemistry Supplements	281
"Bundled" CMC Supplements	281
Labeling Changes	282
Pursuing New Indications for Approved Drugs	283
Submission and Approval Trends for Efficacy Supplements	284
Chapter 13. The FDA's Orphan Drug Development Program	285
The FDA and Orphan Drugs: A Brief History	286
The Significance of Orphan Drug Designation	286
Obtaining Orphan Drug Designation	287
A Look at Orphan Drug Incentives	289
Marketing Exclusivity	290
Tax Credits	292
Protocol Assistance	292
FDA Grants and Contracts	293
The FDA Approval Process: Advantages for Orphan Drugs?	293
Chapter 14. CDER's Bioresearch Monitoring Program	295
A Brief History of the Bioresearch Monitoring Program	297
The Clinical Investigator Compliance Program	298

Data Audit Inspection Program	299
For Cause Inspection Program	300
Bioequivalency/Bioavailability Inspection Program	301
Post-Inspectional FDA Actions	303
The Sponsor/Monitor Compliance Program	303
The Inspection of Drug Sponsors	304

Chapter 15. Accelerated Drug Approval/Expanded Access Programs 307

Recent Developments in Expanded Access/Accelerated Development Programs	309
The Treatment IND	310
Treatment Use for Immediately Life-Threatening Conditions	311
Treatment Use for Serious Conditions	312
Obtaining FDA Permission for Treatment Use	312
The Sale of Investigational Drugs	313
The FDA's Accelerated Drug Development Program (Subpart E)	317
Eligibility for Accelerated Development	317
The Cornerstone of Accelerated Development: Early FDA-Sponsor Consultation	318
Restructuring Clinical Trials	318
Accelerated Drug Approval Program (Subpart H)	320
Eligibility for Accelerated Approval	324
The Parallel Track Program	325
The Oncology Initiative	325
Fast Track Initiative	327
Qualifying for Fast Track Status	328
Seeking a Fast Track Designation	330
Fast Track and the Rolling NDA	331
Industry Success Rates in Obtaining Fast Track Status	332
FDA Proposal to Overhaul Experimental Drug Access Programs	333

Chapter 16. The Pediatric Studies Initiative 339

Historical Development	339
The Carrot: FDAMA Pediatric Exclusivity as Reauthorized Under the Best Pharmaceuticals for Children Act (BPCA)	340
Off-Patent Incentive Program	343
Modifications to the Pediatric Exclusivity Program Under the 2007 Reauthorization of BPCA	344
The Stick: The FDA's 1998 Rule as Codified Under the Pediatric Research Equity Act (PREA)	345
Modifications to Required Pediatric Assessment Under the 2007 Reauthorization of PREA	348
Incorporating Pediatric Studies into Drug Development Planning	350
Planning Considerations I: What Types of Studies Will Be Needed?	350
Planning Considerations II: How Often Will New Formulations be Needed?	354
Planning Considerations III: When Should Pediatric Studies Be Initiated?	356
Planning Considerations IV: What Information Resources Are Available?	357
The Present	358
The Future	360

Data Audit Inspection Program	299
For Cause Inspection Program	300
Bioequivalency/Bioavailability Inspection Program	301
Post-Inspectional FDA Actions	303
The Sponsor/Monitor Compliance Program	303
The Inspection of Drug Sponsors	304

Chapter 15. Accelerated Drug Approval/Expanded Access Programs 307

Recent Developments in Expanded Access/Accelerated Development Programs	309
The Treatment IND	310
Treatment Use for Immediately Life-Threatening Conditions	311
Treatment Use for Serious Conditions	312
Obtaining FDA Permission for Treatment Use	312
The Sale of Investigational Drugs	313
The FDA's Accelerated Drug Development Program (Subpart E)	317
Eligibility for Accelerated Development	317
The Cornerstone of Accelerated Development: Early FDA-Sponsor Consultation	318
Restructuring Clinical Trials	318
Accelerated Drug Approval Program (Subpart H)	320
Eligibility for Accelerated Approval	324
The Parallel Track Program	325
The Oncology Initiative	325
Fast Track Initiative	327
Qualifying for Fast Track Status	328
Seeking a Fast Track Designation	330
Fast Track and the Rolling NDA	331
Industry Success Rates in Obtaining Fast Track Status	332
FDA Proposal to Overhaul Experimental Drug Access Programs	333

Chapter 16. The Pediatric Studies Initiative 339

Historical Development	339
The Carrot: FDAMA Pediatric Exclusivity as Reauthorized Under the Best Pharmaceuticals for Children Act (BPCA)	340
Off-Patent Incentive Program	343
Modifications to the Pediatric Exclusivity Program Under the 2007 Reauthorization of BPCA	344
The Stick: The FDA's 1998 Rule as Codified Under the Pediatric Research Equity Act (PREA)	345
Modifications to Required Pediatric Assessment Under the 2007 Reauthorization of PREA	348
Incorporating Pediatric Studies into Drug Development Planning	350
Planning Considerations I: What Types of Studies Will Be Needed?	350
Planning Considerations II: How Often Will New Formulations be Needed?	354
Planning Considerations III: When Should Pediatric Studies Be Initiated?	356
Planning Considerations IV: What Information Resources Are Available?	357
The Present	358
The Future	360