

VOLUME TWO

Second Edition

Handbook of
**Pharmaceutical
Manufacturing
Formulations**

Uncompressed Solid Products



SARFARAZ K. NIAZI

informa
healthcare

Contents

Preface to the Series—Second Edition v
Preface to the Series—First Edition viii
Preface to the Volume—First Edition ix
About the Author xi

PART I REGULATORY AND MANUFACTURING GUIDELINES

1. U.S. FDA Good Manufacturing Practices	2
I. Introduction	2
II. U.S. FDA cGMP Guidelines	2
A. General Provisions	4
Part 210—cGMP in Manufacturing, Processing, Packaging, or Holding of Drugs; General	4
Part 211—cGMP for Finished Pharmaceuticals	5
III. Amendments to Part 211	18
IV. U.S. FDA cGMP Overview Checklist	19
V. Drug Master Files and Certifications	23
A. Types of DMFs	23
Glossary	23
2. GMP Audit Template, EU Guidelines	27
3. Guideline on the Common Technical Document for the Registration of Pharmaceuticals for Human Use	47
Background	47
Scope of the Guideline	47
General Principles	47
Organization of the Common Technical Document	47
Organization of the Common Technical Document for the Registration of Pharmaceuticals for Human Use	48
Granularity of Document	48
Definition of a Document	48
Document Pagination and Segregation	54
Section Numbering Within Documents	54
Table of Contents Formatting	54
Module 2	54
Module 3	54
Module 4	54
Module 5	54
Organization of Module 3	55
Module 2: Common Technical Document Summaries	55
2.3: Quality Overall Summary	55
Introduction	55
2.3.S Drug Substance (Name, Manufacturer)	55
2.3.S.1 General Information (Name, Manufacturer)	55

2.3.S.2 Manufacture (Name, Manufacturer)	55
2.3.S.3 Characterization (Name, Manufacturer)	55
For NCE:	55
For Biotech:	55
For NCE and Biotech:	55
2.3.S.4 Control of Drug Substance (Name, Manufacturer)	55
2.3.S.5 Reference Standards or Materials (Name, Manufacturer)	56
2.3.S.6 Container Closure System (Name, Manufacturer)	56
2.3.S.7 Stability (Name, Manufacturer)	56
2.3.P Drug Product (Name, Dosage Form)	56
2.3.P.1 Description and Composition of the Drug Product (Name, Dosage Form)	56
2.3.P.2 Pharmaceutical Development (Name, Dosage Form)	56
2.3.P.3 Manufacture (Name, Dosage Form)	56
2.3.P.4 Control of Excipients (Name, Dosage Form)	56
2.3.P.5 Control of Drug Product (Name, Dosage Form)	56
2.3.P.6 Reference Standards or Materials (Name, Dosage Form)	56
2.3.P.7 Container Closure System (Name, Dosage Form)	56
2.3.P.8 Stability (Name, Dosage Form)	56
2.3.A Appendices	56
2.3.A.1 Facilities and Equipment (Name, Manufacturer)	56
Biotech:	56
2.3.A.2 Adventitious Agents Safety Evaluation (Name, Dosage Form, Manufacturer)	56
2.3.A.3 Excipients	56
2.3.R Regional Information	56
Module 3: Quality	56
Scope of the Guideline	56
3.1 Table of Contents of Module 3	57
3.2 Body of Data	57
3.2.S Drug Substance (Name, Manufacturer)	57
3.2.S.1 General Information (Name, Manufacturer)	57
3.2.S.1.1 Nomenclature (Name, Manufacturer)	57
3.2.S.1.2 Structure (Name, Manufacturer)	57
NCE:	57
Biotech:	57
3.2.S.1.3 General Properties (Name, Manufacturer)	57
3.2.S.2 Manufacture (Name, Manufacturer)	57
3.2.S.2.1 Manufacturer(s) (Name, Manufacturer)	57
3.2.S.2.2 Description of Manufacturing Process and Process Controls (Name, Manufacturer)	57
NCE:	57

- Biotech: 57
- Batch(es) and scale definition 57
- Cell culture and harvest 57
- Purification and modification reactions 57
- Filling, storage, and transportation (shipping) 58
- 3.2.S.2.3 Control of Materials (Name, Manufacturer) 58
- Biotech: 58
- Control of source and starting materials of biological origin 58
- Source, history, and generation of the cell substrate 58
- Cell banking system, characterization, and testing 58
- 3.2.S.2.4 Controls of Critical Steps and Intermediates (Name, Manufacturer) 58
- 3.2.S.2.5 Process Validation and/or Evaluation (Name, Manufacturer) 58
- Biotech: 58
- 3.2.S.2.6 Manufacturing Process Development (Name, Manufacturer) 58
- NCE: 58
- Biotech: 58
- 3.2.S.3 Characterization (Name, Manufacturer) 59
- 3.2.S.3.1 Elucidation of Structure and Other Characteristics (Name, Manufacturer) 59
- NCE: 59
- Biotech: 59
- 3.2.S.3.2 Impurities (Name, Manufacturer) 59
- 3.2.S.4 Control of Drug Substance (Name, Manufacturer) 59
- 3.2.S.4.1 Specification (Name, Manufacturer) 59
- 3.2.S.4.2 Analytical Procedures (Name, Manufacturer) 59
- 3.2.S.4.3 Validation of Analytical Procedures (Name, Manufacturer) 59
- 3.2.S.4.4 Batch Analyses (Name, Manufacturer) 59
- 3.2.S.4.5 Justification of Specification (Name, Manufacturer) 59
- 3.2.S.5 Reference Standards or Materials (Name, Manufacturer) 59
- 3.2.S.6 Container Closure System (Name, Manufacturer) 59
- 3.2.S.7 Stability (Name, Manufacturer) 59
- 3.2.S.7.1 Stability Summary and Conclusions (Name, Manufacturer) 59
- 3.2.S.7.2 Postapproval Stability Protocol and Stability Commitment (Name, Manufacturer) 59
- 3.2.S.7.3 Stability Data (Name, Manufacturer) 59
- 3.2.P Drug Product (Name, Dosage Form) 59
- 3.2.P.1 Description and Composition of the Drug Product (name, dosage form) 59
- 3.2.P.2 Pharmaceutical Development (Name, Dosage Form) 59
- 3.2.P.2.1 Components of the Drug Product (Name, Dosage Form) 60
- 3.2.P.2.1.1 Drug substance (name, dosage form) 60
- 3.2.P.2.1.2 Excipients (name, dosage form) 60
- 3.2.P.2.2 Drug Product (Name, Dosage Form) 60
- 3.2.P.2.2.1 Formulation development (name, dosage form) 60
- 3.2.P.2.2.2 Overages (name, dosage form) 60
- 3.2.P.2.2.3 Physicochemical and biological properties (name, dosage form) 60
- 3.2.P.2.3 Manufacturing Process Development (Name, Dosage Form) 60
- 3.2.P.2.4 Container Closure System (Name, Dosage form) 60
- 3.2.P.2.5 Microbiological Attributes (Name, Dosage Form) 60
- 3.2.P.2.6 Compatibility (Name, Dosage Form) 60
- 3.2.P.3 Manufacture (Name, Dosage Form) 60
- 3.2.P.3.1 Manufacturer(s) (Name, Dosage Form) 60
- 3.2.P.3.2 Batch Formula (Name, Dosage Form) 60
- 3.2.P.3.3 Description of Manufacturing Process and Process Controls (Name, Dosage Form) 60
- 3.2.P.3.4 Controls of Critical Steps and Intermediates (Name, Dosage Form) 61
- 3.2.P.3.5 Process Validation and/or Evaluation (Name, Dosage Form) 61
- 3.2.P.4 Control of Excipients (Name, Dosage Form) 61
- 3.2.P.4.1 Specifications (Name, Dosage Form) 61
- 3.2.P.4.2 Analytical Procedures (Name, Dosage Form) 61
- 3.2.P.4.3 Validation of Analytical Procedures (Name, Dosage Form) 61
- 3.2.P.4.4 Justification of Specifications (Name, Dosage Form) 61
- 3.2.P.4.5 Excipients of Human or Animal Origin (Name, Dosage Form) 61
- 3.2.P.4.6 Novel Excipients (Name, Dosage Form) 61
- 3.2.P.5 Control of Drug Product (Name, Dosage Form) 61
- 3.2.P.5.1 Specification(s) (Name, Dosage Form) 61
- 3.2.P.5.2 Analytical Procedures (Name, Dosage Form) 61
- 3.2.P.5.3 Validation of Analytical Procedures (Name, Dosage Form) 61
- 3.2.P.5.4 Batch Analyses (Name, Dosage Form) 61
- 3.2.P.5.5 Characterization of Impurities (Name, Dosage Form) 61
- 3.2.P.5.6 Justification of Specification(s) (Name, Dosage Form) 61
- 3.2.P.6 Reference Standards or Materials (Name, Dosage Form) 61
- 3.2.P.7 Container Closure System (Name, Dosage Form) 61
- 3.2.P.8 Stability (Name, Dosage Form) 61
- 3.2.P.8.1 Stability Summary and Conclusion (Name, Dosage Form) 61
- 3.2.P.8.2 Postapproval Stability Protocol and Stability Commitment (name, dosage form) 62
- 3.2.P.8.3 Stability Data (Name, Dosage Form) 62
- 3.2.A Appendices 62
- 3.2.A.1 Facilities and Equipment (Name, Manufacturer) 62
- Biotech: 62
- 3.2.A.2 Adventitious Agents Safety Evaluation (Name, Dosage Form, Manufacturer) 62
- For nonviral adventitious agents: 62
- For viral adventitious agents: 62
- Materials of biological origin 62
- Testing at appropriate stages of production 62
- Viral testing of unprocessed bulk 62
- Viral clearance studies 62
- 3.2.A.3 Excipients 62

3.2.R Regional Information	62	4.2 Study Reports	67
3.3 Literature References	63	4.3 Literature References	68
Organization of Module 4	63	Appendix A	68
Nonclinical Overview and Nonclinical Summaries of Module 2		Tables and Figures for Written Summaries	68
Module 2: Common Technical Document Summaries	63	Appendix B	68
General Principles of Nonclinical Overview and Summaries	63	The Nonclinical Tabulated Summaries— Templates	68
2.4 Nonclinical Overview	63	The Nonclinical Tabulated Summaries— Templates	68
General Aspects	63	Module 5: Clinical Study Reports	68
Content and Structural Format	63	Clinical Overview and Clinical Summary of Module 2	68
2.6 Nonclinical Written and Tabulated Summaries	64	Module 2: Common Technical Document Summaries	68
Nonclinical Written Summaries	64	2.5: Clinical Overview	68
Introduction	64	Preamble	68
General Presentation Issues	64	Detailed Discussion of Content of the Clinical Overview Sections	69
Use of Tables and Figures	64	2.5.1 Product Development Rationale	69
Content of Nonclinical Written and Tabulated Summaries	64	2.5.2 Overview of Biopharmaceuticals	69
2.6.1 Introduction	64	2.5.3 Overview of Clinical Pharmacology	69
2.6.2 Pharmacology Written Summary	65	2.5.4 Overview of Efficacy	69
2.6.2.1 Brief Summary	65	2.5.5 Overview of Safety	70
2.6.2.2 Primary Pharmacodynamics	65	2.5.6 Benefits and Risks Conclusions	70
2.6.2.3 Secondary Pharmacodynamics	65	2.5.7 Literature References	71
2.6.2.4 Safety Pharmacology	65	2.7: Clinical Summary	71
2.6.2.5 Pharmacodynamic Drug Interactions	65	Preamble	71
2.6.2.6 Discussion and Conclusions	65	Table of Contents	71
2.6.2.7 Tables and Figures	65	2.7.1 Summary of Biopharmaceutical Studies and Associated Analytical Methods	71
2.6.3 Pharmacology Tabulated Summary (See Appendix B)	65	2.7.1.1 Background and Overview	71
2.6.4 Pharmacokinetics Written Summary	65	2.7.1.2 Summary of Results of Individual Studies	71
2.6.4.1 Brief Summary	65	2.7.1.3 Comparison and Analyses of Results across Studies	71
2.6.4.2 Methods of Analysis	65	2.7.1.4 Appendix	71
2.6.4.3 Absorption	65	2.7.2 Summary of Clinical Pharmacology Studies	72
2.6.4.4 Distribution	65	2.7.2.1 Background and Overview	72
2.6.4.5 Metabolism (Interspecies Comparison)	65	2.7.2.2 Summary of Results of Individual Studies	72
2.6.4.6 Excretion	65	2.7.2.3 Comparison and Analyses of Results across Studies	72
2.6.4.7 Pharmacokinetic Drug Interactions	65	2.7.2.4 Special Studies	72
2.6.4.8 Other Pharmacokinetic Studies	65	Example 1: Immunogenicity	73
2.6.4.9 Discussion and Conclusions	65	Example 2: Clinical microbiology	73
2.6.4.10 Tables and Figures	66	2.7.2.5 Appendix	73
2.6.5 Pharmacokinetics Tabulated Summary (See Appendix B)	66	2.7.3 Summary of Clinical Efficacy	73
2.6.6 Toxicology Written Summary	66	2.7.3.1 Background and Overview of Clinical Efficacy	73
2.6.6.1 Brief Summary	66	2.7.3.2 Summary of Results of Individual Studies	73
2.6.6.2 Single-Dose Toxicity	66	2.7.3.3 Comparison and Analyses of Results across Studies	74
2.6.6.3 Repeat-Dose Toxicity (Including Supportive Toxicokinetics Evaluation)	66	2.7.3.3.1 Study Populations	74
2.6.6.4 Genotoxicity	66	2.7.3.3.2 Comparison of Efficacy Results of all Studies	74
2.6.6.5 Carcinogenicity (Including Supportive Toxicokinetics Evaluations)	66	2.7.3.3.3 Comparison of Results in Subpopulations	74
2.6.6.6 Reproductive and Developmental Toxicity (Including Range-Finding Studies and Supportive Toxicokinetics Evaluations)	66	2.7.3.4 Analysis of Clinical Information Relevant to Dosing Recommendations	75
2.6.6.7 Local Tolerance	66	2.7.3.5 Persistence of Efficacy and/or Tolerance Effects	75
2.6.6.8 Other Toxicity Studies (If Available)	66	2.7.3.6 Appendix	75
2.6.6.9 Discussion and Conclusions	67	2.7.4 Summary of Clinical Safety	75
2.6.6.10 Tables and Figures	67	2.7.4.1 Exposure to the Drug	76
2.6.7 Toxicology Tabulated Summary (See Appendix B)	67	2.7.4.1.1 Overall Safety Evaluation Plan and Narratives of Safety Studies	76
Nonclinical Tabulated Summaries	67		
Module 4: Nonclinical Study Reports	67		
4.1 Table of Contents of Module 4	67		

2.7.4.1.2 Overall Extent of Exposure	76	5.3.4.1 Healthy Subject PD and PK/PD Study Reports	82
2.7.4.1.3 Demographic and Other Characteristics of Study Population	76	5.3.4.2 Patient PD and PK/PD Study Reports	82
2.7.4.2 Adverse Events	76	5.3.5 Reports of Efficacy and Safety Studies	82
2.7.4.2.1 Analysis of Adverse Events	76	5.3.5.1 Study Reports of Controlled Clinical Studies Pertinent to the Claimed Indication	83
2.7.4.2.1.1 Common Adverse Events	77	5.3.5.2 Study Reports of Uncontrolled Clinical Studies	83
2.7.4.2.1.2 Deaths	78	5.3.5.3 Reports of Analyses of Data from More than One Study	83
2.7.4.2.1.3 Other Serious Adverse Events	78	5.3.5.4 Other Study Reports	83
2.7.4.2.1.4 Other Significant Adverse Events	78	5.3.6 Reports of PostMarketing Experience	83
2.7.4.2.1.5 Analysis of Adverse Events by Organ System or Syndrome	78	5.3.7 Case Report Forms and Individual Patient Listings	83
2.7.4.2.2 Narratives	78	5.4 Literature References	83
2.7.4.3 Clinical Laboratory Evaluations	78	1. General Questions	83
2.7.4.4 Vital Signs, Physical Findings, and Other Observations Related to Safety	79	Format or Content?	83
2.7.4.5 Safety in Special Groups and Situations	79	CTD training	85
2.7.4.5.1 Intrinsic Factors	79	2. Questions Regarding Location Issues	85
2.7.4.5.2 Extrinsic Factors	79	General Issues	85
2.7.4.5.3 Drug Interactions	79	3. Associated Information Located in Different Sections	86
2.7.4.5.4 Use in Pregnancy and Lactation	79	3.1 Polymorphism	86
2.7.4.5.5 Overdose	79	3.2 Particle Size	86
2.7.4.5.6 Drug Abuse	79	3.3 Impurities	86
2.7.4.5.7 Withdrawal and Rebound	79	3.4 New Location of Quality Information for Investigational Formulations	87
2.7.4.5.8 Effects on Ability to Drive or Operate Machinery or Impairment of Mental Ability	79	3.5 Where Would the Information Related to Nonviral Adventitious Agents be Placed Within Module 3.2?	87
2.7.4.6 Postmarketing Data	80	6. Safety	94
2.7.4.7 Appendix	80	7. Efficacy	94
2.7.5 Literature References	80	ISS/ISE	95
2.7.6 Synopses of Individual Studies	80		
Summary of Bioavailability Studies	80		
Summary of In vitro Dissolution Studies	80		
Summary of Drug–Drug Interaction PK Studies	80		
Module 5: Clinical Study Reports	80		
Preamble	80		
Detailed Organization of Clinical Study Reports and Related Information in Module 5	80		
5.1 Table of Contents of Module 5	80	4. Process Validation: General Principles and Practices	98
5.2 Tabular Listing of All Clinical Studies	81	I. Introduction	98
5.3 Clinical Study Reports	81	II. Background	98
5.3.1 Reports of Biopharmaceutical Studies	81	III. Statutory and Regulatory Requirements for Process Validation	99
5.3.1.1 Bioavailability (BA) Study Reports	81	IV. Recommendations	99
5.3.1.2 Comparative BA and BE Study Reports	81	A. General Considerations for Process Validation	99
5.3.1.3 In Vitro –In Vivo Correlation Study Reports	81	B. Specific Stages and Activities of Process Validation in the Product Lifecycle	99
5.3.1.4 Reports of Bioanalytical and Analytical Methods for Human Studies	81	1. Stage 1—Process Design	100
5.3.2 Reports of Studies Pertinent to Pharmacokinetics Using Human Biomaterials	81	2. Stage 2—Process Qualification	100
5.3.2.1 Plasma Protein Binding Study Reports	81	3. Stage 3—Continued Process Verification	102
5.3.2.2 Reports of Hepatic Metabolism and Drug Interaction Studies	81	V. Concurrent Release of Performance Qualification Batches	103
5.3.2.3 Reports of Studies Using Other Human Biomaterials	81	VI. Documentation	103
5.3.3 Reports of Human PK Studies	81	VII. Analytical Methodology	103
5.3.3.1 Healthy Subject PK and Initial Tolerability Study Reports	82	References	103
5.3.3.2 Patient PK and Initial Tolerability Study Reports	82		
5.3.3.3 Intrinsic Factor PK Study Reports	82	5. Bioequivalence Regulatory Compliance	104
5.3.3.4 Extrinsic Factor PK Study Reports	82	I. Background	104
5.3.3.5 Population PK Study Reports	82	II. Regulatory Aspects	105
5.3.4 Reports of Human Pharmacodynamic (PD) Studies	82	III. Equivalence Documentation for Marketing Authorization	105
		IV. Therapeutic Classification	106

- V. Topics Related to Regulatory Compliance 106
 - A. Is a BE Study Required? 106
 - B. Prior Review 109
- VI. Record Maintenance 109
- VII. Clarification on Requirements 110
 - A. In Which Cases Is It Allowed to Use a Wider Acceptance Range for the Ratio of C_{max} ? 110
 - B. When Can Subjects Classified as Outliers Be Excluded from the Analysis in BE Studies? 110
 - C. If One Side of the 90% CI of a PK Variable for Testing BE Lies on 0.80 or 1.25, Can We Conclude that the Products Are Bioequivalent? 111
 - D. In Which Cases May a Nonparametric Statistical Model Be Used? 111
 - E. When Should Metabolite Data Be Used to Establish BE? 111
 - F. When Using Metabolite Data to Establish BE, May One Use the Same Justification for Widening the C_{max} Acceptance Criteria as in the Case of the Parent Compound? 111
 - G. What is a “Highly Variable Drug or Drug Product”? 111
 - H. What Are the Conditions for Using Urinary PK Data for BE Assessment? 112
 - I. Standardization of BE Studies with Regard to Food Intake. How Strictly Should the Guideline Be Interpreted? 112
 - J. Worldwide Considerations 112
- VIII. Postapproval Changes 113
 - A. NDAs: BA and BE Studies 113
 - B. Waivers of In Vivo BE Studies (Biowaivers): NDAs and aNDAs 113
 1. Beaded Capsules—Lower Strength 113
 2. Tablets—Lower Strength 113
 - C. Risk-Based BE 113
 - D. Typical Examples of Complex BE 115
 1. Digoxin 115
 2. Levothyroxine 115
 3. Warfarin Sodium 115
 4. Albuterol Metered-Dose Inhalers 116
 - E. General PK Study Design and Data Handling 116
 1. Study Conduct 116
 2. Sample Collection and Sampling Times 117
 3. Subjects with Predose Plasma Concentrations 117
 4. Data Deletion due to Vomiting 117
 5. PK Information Recommended for Submission 117
 6. BE Demonstration Measures 117
 7. CI Values 117
 8. Statistical Information for AUC_{0-T} , $AUC_{0-\infty}$, and C_{max} 117
 - F. Measurement Indices 117
 - G. Dose Selection 117
 - H. Multiple Strengths of Solid Oral Dosage Forms 117
 - I. Manufacturing of Pilot Batch (“Biobatch”) 118
 - J. Dosing by Labeled Concentration 118
 - K. Single Dose vs. Multiple Dose Studies 118
 - L. Guidelines on the Design of a Single-Dose Study 118
 - M. Guidelines for Multiple-Dose Study 118
 - N. Fed vs. Fasted State 119
 - O. Pharmacological End-Point Studies 119
 - P. Clinical End-Point Studies 119
 - Q. Analytical Methods 120
 1. Assay Consideration 120
 - Concentration range and linearity 120
 - Limit of detection 120
 - Limit of quantitation 120
 - Specificity 120
 - Accuracy (Recovery) 120
 - Precision 120
 - Analyte stability 120
 - Analytical system stability 120
 - QC samples 121
 - Replicate and repeat analyses 121
 - Summary of samples to be run with each analysis 121
 - R. Sampling Time Considerations 121
 - S. Protein Binding 121
 - T. Subject Number 121
 - U. Crossover and Parallel Design Considerations 121
 - V. Duration of Washout Time for Crossover Study 122
 - W. Fed BE Studies 122
 - X. Food Effects on Drug Products 122
 - Y. Recommendations for Immediate-Release Drugs: 122
 - Z. Recommendations For Modified-Release Products 122
 1. Study Design 123
 2. General Design 123
 3. Subject Selection 123
 4. Dosage Strength 123
 5. Test Meal 123
 6. Administration 123
 7. Sample Collection 123
 8. Data Analysis and Labeling 123
 - Parent Drug vs. Metabolites 124
 - Enantiomers vs. Racemates 124
 - Drug Products with Complex Mixtures as the Active Ingredients 124
 - Long Half-Life Drugs 124
 - First-Point C_{max} 124
 - Orally Administered Drugs Intended for Local Action 125
 - Sprinkles 125
 - Special Vehicles 125
 - Locally Acting GI Drugs 125

Animal Drug BE Testing	125
Reference Product	126
Reference	126

6. Bioequivalence Regulatory Review Process and Audit 127

Background	127
Protocols	127
Productivity Documentation	127
Methods Validation for Abbreviated New Drug Applications	128
Good Laboratory Practices	128
Types of Inspections	129
Inspections	129
FDA Audit Plans	133
PART I—Background	133
PART II—Implementation	134
Objective	134
Program Management Instructions	134
PART III—Inspectional	134
Operations	134
PART IV—Analytical	135
PART V—Regulatory/Administrative Strategy	135
Clinical Testing	135
Analytical Testing	135
Bioequivalence Inspection Report	136
PART I—Facilities and Procedures (Clinical and Analytical)	136
Electronic Records and Signatures	136
Clinical Data and Operations	137
General	137
Inspection Procedures	137
Study Responsibility and Administration	137
Protocol	137
Subjects' Records	137
Other Study Records	138
Consent of Human Subjects	138
Institutional Review Board	138
Sponsor	138
Test Article Accountability	138
Records Retention	138
Abbreviated Report Format	138
I. Analytical Data and Operations	139
References	141

7. EU Guidelines to Good Manufacturing Practice 142

1.1. Objective	142
1.2. Scope	142
2. Quality Management	143
2.1. Principles	143
2.2. Responsibilities of the Quality Unit(s)	143
2.3. Responsibility for Production Activities	144
2.4. Internal Audits (Self-Inspection)	144
3. Personnel	144
3.1. Personnel Qualifications	144
3.2. Consultants	144
4. Buildings and Facilities	145
4.1. Design and Construction	145
4.2. Utilities	145
4.3. Water	145

4.4. Containment	145
4.5. Lighting	145
4.6. Sewage and Refuse	145
4.7. Sanitation and Maintenance	146
5. Process Equipment	146
5.1. Design and Construction	146
5.2. Equipment Maintenance and Cleaning	146
5.3. Calibration	146
5.4. Computerized Systems	146
6. Documentation and Records	147
6.1. Documentation System and Specifications	147
6.2. Equipment Cleaning and Use Record	147
6.3. Records of Raw Materials, Intermediates, API Labeling, and Packaging Materials	147
6.4. Master Production Instructions (Master Production and Control Records)	147
6.5. Batch Production Records (Batch Production and Control Records)	148
6.6. Laboratory Control Records	148
6.7. Batch Production Record Review	148
7. Materials Management	149
7.1. General Controls	149
7.2. Receipt and Quarantine	149
7.3. Sampling and Testing of Incoming Production Materials	149
7.4. Storage	149
7.5. Reevaluation	149
8. Production and In-Process Controls	149
8.1. Production Operations	149
8.2. Time Limits	150
8.3. In-Process Sampling and Controls	150
8.4. Blending Batches of Intermediates or APIs	150
8.5. Contamination Control	150
9. Packaging and Identification Labeling of APIs and Intermediates	151
9.1. General	151
9.2. Packaging Materials	151
9.3. Label Issuance and Control	151
9.4. Packaging and Labeling Operations	151
10. Storage and Distribution	151
10.1. Warehousing Procedures	151
10.2. Distribution Procedures	151
11. Laboratory Controls	152
11.1. General Controls	152
11.2. Testing of Intermediates and APIs	152
11.3. Validation of Analytical Procedures—See section 12.	152
11.4. Certificates of Analysis	152
11.5. Stability Monitoring of APIs	153
11.6. Expiry and Retest Dating	153
11.7. Reserve/Retention Samples	153
12. Validation	153
12.1. Validation Policy	153
12.2. Validation Documentation	153
12.3. Qualification	153
12.4. Approaches to Process Validation	154
12.5. Process Validation Program	154

- 12.6. Periodic Review of Validated Systems 154
 - 12.7. Cleaning Validation 154
 - 12.8. Validation of Analytical Methods 155
 - 13. Change Control 155
 - 14. Rejection and Reuse of Materials 155
 - 14.1. Rejection 155
 - 14.2. Reprocessing 155
 - 14.3. Reworking 155
 - 14.4. Recovery of Materials and Solvents 155
 - 14.5. Returns 156
 - 15. Complaints and Recalls 156
 - 16. Contract Manufacturers (including Laboratories) 156
 - 17. Agents, Brokers, Traders, Distributors, Repackers, and Relabellers 156
 - 17.1. Applicability 156
 - 17.2. Quality Management 156
 - 17.3. Repackaging, Relabeling and Holding of APIs and Intermediates 156
 - 17.4. Stability 157
 - 17.5. Transfer of Information 157
 - 17.6. Handling of Returns 157
 - 18. General 157
 - 18.1. Cell Bank Maintenance and Record Keeping 158
 - 18.2. Cell Culture/Fermentation 158
 - 18.3. Harvesting, Isolation, and Purification 158
 - 18.4. Viral Removal/Inactivation steps 158
 - 19. APIs for Use in Clinical Trials 158
 - 19.1. General 158
 - 19.2. Quality 159
 - 19.3. Equipment and Facilities 159
 - 19.4. Control of Raw Materials 159
 - 19.5. Production 159
 - 19.6. Validation 159
 - 19.7. Changes 159
 - 19.8. Laboratory Controls 159
 - 19.9. Documentation 159
- Glossary 159
- 8. Preapproval Inspections 163**
- I. Introduction 163
 - A. Background 163
 - B. Objective 163
 - C. Triggering of Inspections 164
 - D. Inspections/Audits 165
 - 1. Manufacturing Process 165
 - i. Drug Product (Dosage Form) 165
 - ii. Drug Substance (Bulk Drug Chemical) 165
 - 2. Reprocessing 165
 - 3. Laboratory 165
 - 4. Components 165
 - 5. Building and Facilities 165
 - 6. Equipment 165
 - 7. Packaging and Labeling Controls 165
 - II. Regulatory/Administrative Strategy 165
 - A. General 165
 - B. Process Validation 166
 - C. Key Elements 166
- D. Strategies for Preinspection 166
 - E. International Inspection 168
 - F. Product Stability Data 169
 - G. Validation of Processes 170
 - H. Change Control 172
 - 1. Cleaning Validation 172
 - 2. Analytical Methods Validation 173
 - 3. Computer System Validation 173
 - PART 11—Electronic Records; Electronic Signatures 173
 - Subpart A—General Provisions 173
 - Sec. 11.1 Scope 173
 - Sec. 11.2 Implementation. 173
 - Sec. 11.3 Definitions. 174
 - Subpart B—Electronic Records 174
 - Sec. 11.10 Controls for closed systems. 174
 - Sec. 11.30 Controls for open systems. 174
 - Sec. 11.50 Signature manifestations. 175
 - Sec. 11.70 Signature/record linking. 175
 - Subpart C—Electronic Signatures 175
 - Sec. 11.100 General requirements. 175
 - Sec. 11.200 Electronic signature components and controls. 175
 - Sec. 11.300 Controls for identification codes/ passwords. 175
 - I. Documentation Standards 176
 - 1. Development History Report 176
 - 2. Deviation Records 176
 - 3. Installation, Operational, and Performance Qualification 177
 - 4. Organizational Chart 177
 - 5. Products List 177
 - 6. Drawings 177
 - 7. Stability Data 177
 - 8. SOPs 177
 - 9. Training Records 177
 - 10. Validation Records 177
 - 11. Technology Transfer and Scale-Up 177
 - 12. Quality Policy 178
 - 13. Vendor Approval 178
 - 14. Outside Contractors 178
- 9. Formulation Factors in Uncompressed Dosage Forms 179**
- I. Relative Humidity 179
 - II. Surface Area 179
 - III. Sieve Analysis 179
 - IV. Particle Size Distribution 179
 - V. Powder Flow Properties 180
 - VI. Real, Tapped, and Bulk Density 180
 - VII. Solid Handling 180
 - VIII. Mixing of Powders 181
 - IX. Oral Powders 181
 - X. Capsules 181

XI. FDA Classification of Capsule Types 181
 XII. FDA Classification of Powders 182
 XIII. Inhalers and Lung Delivery 182
 XIV. Problems in Powder Handling 182
 XV. Capsulation Equipment 183
 XVI. Capsule Finishing 183
 XVII. Modified-Release Products 183
 XVIII. Clinical Test Supplies and Placebos 183
 XIX. Coated Particles 183
 XX. Mixing Mechanisms 183
 XXI. Segregation Mechanisms 183
 XXII. Mixing Equipment 183
 XXIII. Milling 184
 References 184

10. Bioequivalence Testing Protocols 185

11. Dissolution Testing of Uncompressed Solid Dosage Forms 197

12. Approved Excipients in Uncompressed Solid Dosage Forms 204

PART II MANUFACTURING FORMULATIONS

Uncompressed Solids Formulations 229

Acebutolol Hydrochloride Capsules 229
 Aceclofenac Instant Granules 229
 Acetaminophen and Diphenhydramine Hydrochloride Hot Therapy Sachets 230
 Acetaminophen Capsules (500 mg) 230
 Acetaminophen, Doxylamine, and Caffeine Effervescent 231
 Acetaminophen Instant Granules 231
 Acetaminophen Instant Granules 232
 Acetaminophen Instant Granules 232
 Acetaminophen, Pseudoephedrine Hydrochloride, Chlorpheniramine Hot Therapy Sachet 233
 Acetaminophen, Pseudoephedrine Hydrochloride Hot Therapy Sachet 233
 Acetaminophen Swallow Capsules 234
 Acetazolamide Sustained-Release Capsules 234
 Acetylcysteine Sachets 234
 Acitretin Capsules 235
 Acrivastine and Pseudoephedrine Hydrochloride Capsules 235
 Acrivastine and Pseudoephedrine Hydrochloride Capsules 235
 Acyclovir Capsules 235
 Acyclovir Capsules 235
 Adenosine Monophosphate Topical Powder 236
 Aluminum Acetate Powder 236
 Aluminum Hydroxide and Magnesium Carbonate Dry Syrup 236
 Aminosalicic Acid Granules 236
 Amlodipine Besylate and Benazepril Hydrochloride Capsules 237
 Amlodipine Besylate and Benazepril Hydrochloride Capsules 237
 Amlodipine Besylate Capsules 237
 Amlodipine Free Base Capsules 238
 Amlodipine Maleate Capsules 238

Amoxicillin and Bromhexine Hydrochloride Capsules 238
 Amoxicillin and Clavulanic Acid Powder for Suspension, 125 mg and 31.25 mg per 5 mL (Amoxil) 239
 Amoxicillin and Clavulanic Acid Powder for Suspension 239
 Amoxicillin and Clavulanate Potassium for Suspension 240
 Amoxicillin and Clavulanate Potassium for Suspension 240
 Amoxicillin Powder for Suspension (125 and 250 mg) 241
 Amoxicillin Trihydrate Capsules (250 and 500 mg) 241
 Ampicillin Dry Syrup (5% = 500 mg/10 mL) 242
 Ampicillin Powder for Suspension 242
 Ampicillin Trihydrate Capsules 242
 Ampicillin Trihydrate Capsules for Suspension 243
 Ampicillin Trihydrate Powder for Suspension 243
 Antibacterial and Bacterial Culture Capsules 244
 Antifungal Foot Powder 244
 Antioxidant Eye Nutrition Supplement Capsules 245
 Aspartame Granules in Sachets 245
 Aspartame Powder in Sachets 245
 Aspirin and Chlorpheniramine Powder 245
 Aspirin-Coated Crystals 245
 Aspirin and Phenylpropanolamine Powder 246
 Aspirin Microencapsulated Sustained-Release Capsules 246
 Aspirin, Salicylamide, and Caffeine Powder 246
 Azithromycin Suspension 246
 Azithromycin Capsules 247
 Azithromycin Capsules 247
 Azithromycin Capsules 247
 Azithromycin Capsules and Oral Suspension 248
 Azithromycin for Oral Suspension 248
 Azithromycin for Oral Suspension 249
 Azithromycin Sachets for Oral Suspension 249
 Balsalazide Disodium Capsules 250
 Benazepril Hydrochloride and Amlodipine Besylate Capsules 250
 Benazepril Hydrochloride and Amlodipine Besylate Capsules 250
 Bisacodyl Colonic Delivery Capsules 251
 Brompheniramine and Pseudoephedrine Capsules 251
 Budesonide Capsules 252
 Budesonide Inhalation Powder 252
 Butalbital and Acetaminophen Capsules 252
 Calcitonin (Salmon) Capsules 253
 Calcitriol Capsules 254
 Calcium Carbonate Microencapsulated Sustained-Release Capsules 254
 Camptothecin Capsules 254
 Carbamazepine Extended-Release Capsules 255
 Cefaclor Capsules 256
 Cefdinir Capsules and Oral Suspension 256
 Cefixime for Oral Suspension 256
 Cefpodoxime Proxetil for Oral Suspension 256
 Cefprozil for Oral Suspension 256
 Ceftributen Capsules and Oral Suspension 257
 Ceftributen for Oral Suspension 257

- Cefuroxime for Oral Suspension 257
 Celecoxib Capsules 258
 Celecoxib Tablets Celebrex 258
 Cellulose Triacetate Liquefiable Topical Powder 258
 Cephalexin Capsules 259
 Cephalexin Powder for Oral Suspension 259
 Cephradine Capsules 259
 Cephradine Powder for Suspension 260
 Cevimeline Capsules 260
 Cevimeline Capsules 260
 Chlordiazepoxide Hydrochloride Capsules 261
 Chlordiazepoxide Hydrochloride Capsules 261
 Chloroxylenol and Chlorhexidine Topical Powder 261
 Chlorpromazine Sustained-Release Capsules 262
 Cimetidine Microencapsulated Sustained-Release Capsules 262
 Citrate Effervescent Powder 262
 Clindamycin Capsules 263
 Clindamycin Capsules (150 mg) 263
 Clofibrate Capsules 263
 Clonidine Sustained-Release Capsules 263
 Clorazepate Dipotassium Capsules 264
 Coated Spheroids 264
 Crospovidone Water-Dispersible Tablets 265
 Cyanocobalamin Tablets 265
 Cyclosporin A Capsules 265
 Dantrolene Sodium Capsules 266
 Dextroamphetamine Sulfate Capsules 266
 Diclofenac and Misoprostol Capsules 266
 Diclofenac Spherized Pellets for Sustained-Release Coating (30%) 266
 Diclofenac Sustained-Release Capsules 266
 Diclofenac Granules 267
 Didanosine Delayed-Release Capsules 268
 Didanosine Delayed-Release Capsules Enteric-Coated Beadlets 268
 Didanosine for Oral Suspension 268
 Diethyl Toluamide Topical Powder 268
 Difluoromethylornithine-Alpha Capsules 269
 Diltiazem Hydrochloride Extended-Release Capsules 270
 Diphenhydramine Hydrochloride Capsules 271
 Dipyridamole and Aspirin Extended-Release Capsules 271
 Divalproex Sodium Capsules 271
 Divalproex Sodium Coated Particle Capsules 271
 Dofetilide Capsules 271
 Doxepin Hydrochloride Capsules 271
 Doxycycline Capsules 271
 Doxycycline Hyclate Capsules 272
 Doxycycline Hyclate Capsules 272
 Doxycycline Hydrochloride Capsules and Oral Suspension 272
 Efavirenz Capsules 272
 Enalapril Maleate Capsules 272
 Enalapril Maleate Capsules 272
 Eplerenone Capsules 273
 Erythromycin and Bromhexine Powder for Suspension 274
 Erythromycin and Sulfisoxazole Granules for Suspension 275
 Erythromycin Delayed-Release Capsules 276
 Erythromycin Delayed-Release Capsules 276
 Erythromycin Ethylsuccinate for Oral Suspension 276
 Erythromycin Ethylsuccinate for Oral Suspension (200 mg/5 mL) 277
 Erythromycin Stearate for Oral Suspension 278
 Erythromycin Stearate for Oral Suspension 279
 Erythropoietin Capsules 280
 Esomeprazole Magnesium Capsules 281
 Estramustine Phosphate Capsules 281
 Ethosuximide Capsules 281
 Etodolac Capsules 281
 Felbamate for Oral Suspension 281
 Fenofibrate Capsules 281
 Fenofibrate Capsules 281
 Fenofibrate Capsules 282
 Fexofenadine Hydrochloride Capsules 282
 Fexofenadine Hydrochloride Capsules 282
 Fluconazole for Oral Suspension 283
 Flucytosine Capsules 283
 Fluoxetine Capsules 283
 Fluoxetine Hydrochloride Capsules 283
 Fluoxetine Hydrochloride Instant and Weekly Capsules 284
 Flutamide Capsules 284
 Fluticasone Propionate and Salmeterol Xinafoate Inhalation Powder 284
 Fluvastatin Sodium Capsules 284
 Fluvastatin Sodium Capsules 284
 Formoterol Fumarate Inhalation Powder 285
 Formoterol Fumarate Inhaler Capsules 285
 Fosfomycin Tromethamine Sachets 285
 Gabapentin Capsules 285
 Gabapentin Capsules 285
 Ganciclovir Capsules 285
 Ganciclovir Capsules 285
 Gemfibrozil Capsules 286
 Glycoprotein IIa/IIb Capsules 286
 Guaifenesin Sustained-Release Capsules 287
 Herbal AIDS Treatment Capsules 287
 Histidine Capsules 287
 Human Growth Hormone Capsules 288
 Hydrochlorothiazide and Triamterene Capsules 289
 Hydrochlorothiazide Capsules 289
 Hydroxyzine Pamoate Capsules and Oral Suspension 289
 Hyoscyamine Sulfate Capsules 289
 Ibuprofen Microencapsulated Sustained-Release Capsules 289
 Ibuprofen and Domperidone Maleate Capsules 290
 Ibuprofen and Domperidone Maleate Effervescent Granules 290
 Ibuprofen Sustained-Release Capsules 290
 Ifosfamide Capsules 292
 Imatinib Mesylate Capsules 292
 Indinavir Sulfate Capsules 292
 Indinavir Sulfate Capsules 292
 Indomethacin Capsules 292
 Indomethacin Capsules 293
 Indomethacin Capsules 293
 Indomethacin Capsules (25 mg) 294
 Indomethacin Capsules (50 mg) 294

- Indomethacin Powder for Hard Gelatin Capsules (160 mg) 295
 Indomethacin Microencapsulated Sustained-Release Capsules 295
 Indomethacin Sustained-Release Capsules 296
 Insulin Capsules 297
 Iron–Polysaccharide Complex Capsules 298
 Isometheptene Mucate, Dichloralphenazone, and Acetaminophen Capsules 298
 Isosorbide Mononitrate Capsules (20 mg) 298
 Isradipine Capsules 299
 Itraconazole Capsules 299
 Itraconazole Capsules 299
 Ketoprofen and Misoprostol Capsules 299
 Ketoprofen Capsules 300
 Lansoprazole Capsules 300
 Lansoprazole Delayed-Release Capsules 300
 Lincomycin Capsules 300
 Linezolid Oral Suspension 301
 Lipase, Amylase, and Protease Capsules 301
 Lithium Carbonate Capsules 301
 Loperamide and Trimebutine Capsules 301
 Lopinavir–Ritonavir Capsules 301
 Loracarbef Capsules and Oral Suspension 301
 Loxapine Succinate Capsules 302
 Magaldrate Instant Powder or Dry Syrup 302
 Magaldrate Instant Powder or Dry Syrup 302
 Magnesium Oxide Capsules 302
 Mefenamic Acid Capsules 302
 Mesalamine Capsules 303
 Mesalamine Colonic Delivery Capsules 303
 Methsuximide Capsules 303
 Methylphenidate Capsules 303
 Methylphenidate Capsules 303
 Methylphenidate Immediate- and Extended-Release Capsules 304
 Methyltestosterone Capsules 304
 Metoclopramide Hydrochloride Sustained-Release Capsules 304
 Metyrosine Capsules 305
 Miconazole Nitrate Foot and Itch Powder 305
 Midodrine Capsules 305
 Mineral Powder for Topical Herpes Simplex 306
 Minocycline Hydrochloride Capsules 306
 Mixed Amphetamine Salt Capsules 306
 Mixed Amphetamine Salts Enteric-Release Capsules 306
 Morphine Sulfate Capsules 307
 Morphine Sulfate Controlled-Release Capsules 307
 Morphine Sulfate Sustained-Release Capsules 308
 Multivitamin Effervescent Granules 308
 Multivitamin Effervescent Granules 309
 Multivitamin Instant Granules 310
 Multivitamin Instant Granules 311
 Mycophenolate Mofetil Capsules and Oral Suspension 311
 Nanoparticle Polymer Particle Powders 311
 Nelfinavir Mesylate Oral Powder 312
 Nelfinavir Mesylate Oral Powder 312
 Nilvadipine Capsules 312
 Nitrofurantoin Capsules 312
 Nitrofurantoin Sustained-Release Capsules 312
 Nizatidine Capsules 313
 Nizatidine Capsules 313
 Nystatin Powder 313
 Omeprazole and Piroxicam Capsules 313
 Omeprazole Capsules 314
 Omeprazole Capsules 314
 Omeprazole Delayed-Release Capsules 315
 Oral Rehydration Salt (45 mEq) 315
 Orlistat Capsules 316
 Orlistat Capsules 316
 Oseltamivir Phosphate Capsules and Oral Suspension 316
 Oxcarbazepine Oral Suspension 316
 Oxycodone Hydrochloride and Acetaminophen Capsules 316
 Oxytetracycline Hydrochloride Capsules 317
 Oxytetracycline Hydrochloride, Sulfamethizole, and Phenazopyridine Hydrochloride Capsules 317
 Pancrelipase Capsules 317
 Pancrelipase Capsules Enteric-Coated Microspheres 317
 Penicillamine Capsules 317
 Pentosan Polysulfate Sodium Capsules 317
 Pentostatin Capsules 318
 pH-Sensitive Coated Spheroids 318
 Phenobarbital and Hyoscyamine Sulfate Capsules 319
 Phenoxybenzamine Hydrochloride Capsules 319
 Phentermine Capsules 319
 Phentermine Hydrochloride Capsules 319
 Phenytoin Sodium Extended-Release Capsules 319
 Piroxicam and Beta-Cyclodextrin Topical Powder 319
 Piroxicam Capsules 320
 Piroxicam Capsules 320
 Piroxicam Capsules 320
 Polyethylene Glycol 3350 Powder for Reconstitution 321
 Polythiazide Capsules 321
 Potassium Chloride Extended-Release Capsules 321
 Potassium Chloride for Oral Solution 321
 Potassium Chloride Microencapsulated Sustained-Release Capsules 321
 Potassium Chloride Powder (20 mEq) 322
 Prazosin and Polythiazide Capsules 322
 Prednisolone Targeted-Release Capsules 322
 Procarbazine Hydrochloride Capsules 323
 Prochlorperazine Sustained-Release Capsules 323
 Propoxyphene Hydrochloride, Caffeine, and Aspirin Capsules 323
 Propoxyphene Hydrochloride Capsules 323
 Propranolol Hydrochloride and Hydrochlorothiazide Capsules 323
 Propranolol Hydrochloride Long-Acting Capsules 323
 Propranolol Hydrochloride Multiple Bead Capsules 323
 Propranolol Hydrochloride Sustained-Release Capsules 324
 Propranolol Timed- and Sustained-Release Capsules 325
 Proton Pump Inhibitor Powder for Reconstitution for Oral Use 325

Proton Pump Inhibitor Powder for Reconstitution for Oral Use	326	Tiotropium Inhalation Powder	334
Pseudoephedrine Hydrochloride Capsules	326	Tolmetin Sodium Capsules	334
Pseudoephedrine Hydrochloride Capsules	326	Tolterodine Capsules	334
Pseudoephedrine and Guaifenesin Capsules	326	Tolterodine Capsules	334
Pseudoephedrine Hydrochloride Capsules	326	Topiramate Capsules	335
Psyllium and Dioctyl Sodium Sulfosuccinate Powder	327	Tretinoin Capsules	335
Psyllium and Docusate Sodium Wafer	327	Triamterene and Hydrochlorothiazide Capsules	335
Psyllium Husk Granules	327	Triamterene Capsules	335
Ranitidine Effervescent Granules	327	Triclosan and Zinc Foot Deodorant Powder	335
Ribavirin Capsules	327	Triclosan and Zinc Undecylenate Powder	336
Rifabutin Capsules	327	Trientine Hydrochloride Capsules	336
Rifampicin Capsules	327	Trimebutine Capsules	336
Rifampin and Isoniazid Capsules	328	Trimethoprim and Sulfamethoxazole Oral Suspension	337
Rivastigmine Tartrate Capsules	328	Trimipramine Maleate Capsules	337
Salmeterol Xinafoate Capsules	328	Troleandomycin Capsules	337
Salmeterol Xinafoate Inhalation Powder	328	Typhoid Vaccine Live Oral Capsules	337
Salmeterol Xinafoate Inhalation Powder	328	Valsartan and Hydrochlorothiazide Capsules	338
Saquinavir Mesylate Capsules	328	Valsartan Capsules	338
Selegiline Hydrochloride	328	Valsartan Capsules	338
Sevelamer Hydrochloride Capsules	328	Vancomycin Hydrochloride Capsules	339
Sibutramine Hydrochloride Capsules	328	Venlafaxine Capsules	339
Sibutramine Hydrochloride Capsules	329	Verapamil Hydrochloride Capsules	339
Simethicone Instant Granules (60 mg and 120 mg)	329	Verapamil Hydrochloride Capsules	339
Stavudine Capsules	329	Verapamil Hydrochloride Sustained-Release Capsules	340
Succimer Capsules	329	Vincamine Capsules	341
Sucralafate Granules	329	Vinpocetine Multiple Bead Capsules	341
Sulfamethoxazole + Trimethoprim Dry Syrup (400 mg + 80 g/10 mL)	330	Vitamin B Complex, Amino Acids, and Magnesium Effervescent Granules (Sugar-Free)	342
Tacrine Hydrochloride Capsules	330	Vitamin B Complex + Amino Acid + Magnesium Effervescent Granules (Sugar-free)	342
Tacrolimus Capsules	330	Vitamin B Complex and Vitamin C Instant Granules	342
Tacrolimus Capsules	330	Vitamin C and Calcium Carbonate Effervescent Powder	343
Talc, Crospovidone, and Starch Topical Powder	330	Zanamivir Powder	343
Tamsulosin Hydrochloride Capsules	331	Zanamivir Powder	343
Tamsulosin Hydrochloride Capsules	331	Zidovudine Capsules	343
Temazepam Capsules	331	Zidovudine Capsules	343
Temozolomide Capsules	332	Zinc Oxide and Cornstarch Powder	344
Terazosin Capsules (1–10 mg) Hytrin	332	Ziprasidone Hydrochloride Capsules	344
Terazosin Capsules	332	Ziprasidone Hydrochloride Capsules	344
Terazosin Hydrochloride Capsules	332	Zonisamide Capsules	344
Terfenadine Oral Granules Directions	332	Zonisamide Capsules	344
Tetracycline Hydrochloride Capsules	332	Commercial Pharmaceutical Formulations	345
Thalidomide Capsules	333		
Theophylline Sustained-Release Capsules	333		
Thiothixene Capsules	333		
Tibolone Capsules	333		
		<i>Index</i>	355