

HANDBOOK OF
Pharmaceutical
Manufacturing
Formulations

Liquid Products

VOLUME 3

Sarfaraz K. Niazi



CRC PRESS

Table of Contents

PART I

Regulatory and Manufacturing Guidance..... 1

Chapter 1

Current Good Manufacturing Practice Considerations in Liquid Manufacturing 3

I. Introduction.....	3
II. Facilities.....	3
III. Equipment.....	3
IV. Raw Materials.....	4
V. Compounding.....	4
VI. Microbiological Quality.....	4
VII. Oral Suspensions.....	5
VIII. Product Specifications.....	5
IX. Process Validation.....	5
X. Stability.....	5
XI. Packaging.....	6

Chapter 2

Stability Testing of New Drug Substances and Products..... 7

I. Introduction.....	7
II. Drug Substance.....	7
A. General Case.....	8
B. Drug Substances Intended for Storage in a Refrigerator.....	8
C. Drug Substances Intended for Storage in a Freezer.....	8
D. Drug Substances Intended for Storage below -20°C.....	9
III. Drug Product.....	10
A. General Case.....	11
B. Drug Products Packaged in Impermeable Containers.....	11
C. Drug Products Packaged in Semipermeable Containers.....	11
D. Drug Products Intended for Storage in a Refrigerator.....	12
E. Drug Products Intended for Storage in a Freezer.....	13
F. Drug Products Intended for Storage below -20°C.....	13
IV. Glossary.....	14
References.....	16

Chapter 3

Container Closure Systems..... 17

I. Introduction.....	17
A. Definitions.....	17
B. Current Good Manufacturing Practice, the Consumer Product Safety Commission, and Requirements on Containers and Closures.....	17
C. Additional Considerations.....	17
II. Qualification and Quality Control of Packaging Components.....	18
A. Description.....	21
B. Information about Suitability.....	21

C.	Stability Data (Packaging Concerns).....	22
D.	Inhalation Drug Products.....	23
E.	Injection and Ophthalmic Drug Products.....	23
F.	Liquid-Based Oral and Topical Drug Products and Topical Delivery Systems.....	24
G.	Solid Oral Dosage Forms and Powders for Reconstitution.....	25
	1. Polyethylene Containers (USP <661>).....	26
	2. Single-Unit Containers and Unit-Dose Containers for Capsules and Tablets (USP <671>).....	26
	3. Multiple-Unit Containers for Capsules and Tablets (USP <671>).....	26
H.	Other Dosage Forms.....	26
III.	Postapproval Packaging Changes.....	27
IV.	Type III Drug Master Files.....	27
V.	Bulk Containers.....	27
	References.....	28

Chapter 4

	Preapproval Inspections.....	29
I.	Introduction.....	29
A.	Background.....	29
B.	Objective.....	29
C.	Triggering of Inspections.....	31
D.	Inspections/Audits.....	31
	1. Manufacturing Process.....	31
	2. Reprocessing.....	32
	3. Laboratory.....	32
	4. Components.....	32
	5. Building and Facilities.....	32
	6. Equipment.....	32
	7. Packaging and Labeling Controls.....	32
II.	Regulatory/Administrative Strategy.....	32
A.	General.....	32
B.	Process Validation.....	33
C.	Key Elements.....	33
D.	Strategies for Preinspection.....	33
E.	International Inspection.....	35
F.	Product Stability Data.....	37
G.	Validation of Processes.....	39
H.	Change Control.....	41
	1. Cleaning Validation.....	41
	2. Analytical Methods Validation.....	42
	3. Computer System Validation.....	43
I.	Documentation Standards.....	46
	1. Development History Report.....	47
	2. Deviation Records.....	47
	3. Installation, Operational, and Performance Qualification.....	47
	4. Organizational Chart.....	47
	5. Products List.....	47
	6. Drawings.....	48
	7. Stability Data.....	48
	8. SOPs.....	48
	9. Training Records.....	48
	10. Validation Records.....	48
	11. Technology Transfer and Scale-Up.....	48
	12. Quality Policy.....	49
	13. Vendor Approval.....	49
	14. Outside Contractors.....	49

Chapter 5	
Formulation Considerations of Liquid Products	51
I. Solubility	51
II. Chemical Modification	51
III. Preservation.....	52
IV. Sweetening Agents	52
V. Flavors.....	52
VI. Viscosity.....	52
VII. Appearance	52
VIII. Chemical Stability	52
IX. Physical Stability	52
X. Raw Material	53
XI. Manufacturing Equipment	53
XII. Manufacturing Directions	53
XIII. Packaging.....	53
XIV. Particle Size and Shape	54
XV. Suspensions.....	54
XVI. Emulsions.....	54
XVII. Powder for Reconstitution.....	55
XVIII. Nasal Spray Products	55
A. Inhalation Solutions and Suspensions	55
B. Inhalation Sprays.....	55
C. Pump Delivery of Nasal Products	56
D. Spray Content Uniformity for Nasal Products.....	56
E. Spray Pattern and Plume Geometry of Nasal Products	57
F. Droplet Size Distribution in Nasal Products	57
G. Particle Size Distribution for Nasal Suspensions	57
XIV. Emulsification and Solubilization	57
XV. Complexing	58
XVI. Hydrophilization	58
XVII. Stabilizing Suspensions.....	58

PART II

Manufacturing Formulations	59
Abacavir Sulfate Oral Solution.....	61
Acetaminophen Rectal Solution.....	61
Acetaminophen Drops.....	62
Acetaminophen Oral Suspension	63
Acetaminophen Suspension	64
Acetaminophen Syrup for Children.....	64
Acetaminophen Syrup.....	65
Acetaminophen Syrup.....	66
Acetaminophen, Chlorpheniramine, and Pseudoephedrine Syrup	67
Acyclovir Oral Suspension	68
Acyclovir Oral Suspension	68
Adapalene Solution	69
Atbendazole Oral Suspension	70
Atbendazole Suspension	71
Albuterol Inhalation Solution.....	71
Alpha-Bisabolol Aqueous Mouthwash Solution.....	72
Alpha-Bisabolol Buccal or Topical Solution.....	72
Alpha-Bisabolol Ethanolic Mouthwash Solution	72
Alpha-Bisabolol Mouthwash Solution.....	73

Aluminum Chloride Solution.....	73
Aluminum Hydroxide and Magnesium Hydroxide Suspension	74
Aluminum Hydroxide and Magnesium Hydroxide Suspension	75
Aluminum Hydroxide and Magnesium Hydroxide Suspension	75
Aluminum Hydroxide and Magnesium Hydroxide Suspension	76
Aluminum Hydroxide and Magnesium Hydroxide Suspension	76
Aluminum Hydroxide, Magnesium Hydroxide, and Simethicone Suspension	77
Aluminum Hydroxide, Magnesium Hydroxide, and Simethicone Suspension	77
Aluminum Hydroxide and Magnesium Carbonate Dry Syrup	78
Aminacrine Hydrochloride Topical Solution.....	78
Aminolevulinic Acid HCl for Topical Solution, 20%	79
Amoxicillin Powder for Suspension	79
Amoxicillin–Clavulanate Syrup.....	80
Ampicillin Powder for Suspension	81
Ampicillin Powder for Suspension.....	81
Ampicillin and Cloxacillin Oily Suspension	82
Amprenavir Capsules.....	82
Amprenavir Oral Solution.....	83
Anise Oil Solution	83
Antipyrine and Benzocaine Elixir.....	83
Apraclonidine Hydrochloride Ophthalmic Solution.....	83
Ascorbic Acid Solution.....	84
Atovaquone Suspension	84
Azelastine Hydrochloride Nasal Spray.....	85
Azithromycin Suspension	86
Azithromycin Suspension	86
Azulene Solution.....	87
Barium Sulfate Oral Suspension.....	87
Beclomethasone Dipropionate Inhalation Aerosol.....	88
Beclomethasone Dipropionate and Salbutamol Sulfate Nasal Spray	88
Benzethonium Chloride Solution.....	88
Benzethonium Chloride and Benzocaine Topical Anesthetic	89
Benzocaine and Tetracaine Topical Solution.....	89
Benzyl Benzoate Solution.....	89
Beta-Estradiol Vaginal Solution	89
Betamethasone Syrup.....	90
Bismuth Carbonate Suspension	90
Bismuth Subsalicylate Suspension.....	90
Bromazepam Drops	91
Bromhexine Hydrochloride Syrup — Alcohol Free	92
Bromhexine Hydrochloride Syrup.....	93
Budesonide Inhaler	94
Butamirate Citrate Syrup	94
Caffeine Citrate Oral Solution	95
Calcipotriene Solution.....	95
Calcitonin Nasal Spray.....	95
Calcium Carbonate and Guar Gum Suspension	96
Calcium Iodide and Ascorbic Acid Syrup.....	96
Carnitine and Coenzyme Q Solution.....	97
Cefaclor Suspension	98
Cefadroxil Monohydrate Oral Suspension	98
Cefpodoxime Proxetil Oral Suspension.....	98
Cefpodoxime Proxetil for Oral Suspension.....	99
Cefuroxime Axetil Suspension.....	99
Cetirizine Hydrochloride Syrup.....	99

Chlophedianol, Ipecac, Ephedrine, Ammonium Chloride, Carbinoxamine, and Balsam Tolu Syrup	100
Chloramphenicol Ophthalmic Solution	101
Chloramphenicol Palmitate Oral or Topical Emulsion	101
Chloroxylenol Surgical Scrub	101
Chlorpheniramine Maleate Syrup	102
Ciclopirox Topical Solution	103
Cimetidine Syrup	103
Ciprofloxacin Hydrochloride and Hydrocortisone Otic Suspension	104
Cisapride Suspension	105
Citalopram Hydrobromide Oral Solution	106
Clarithromycin Suspension	106
Clindamycin Phosphate Topical Solution	107
Clotrimazol Topical Solution	107
Codeine Phosphate and Acetaminophen Elixir	107
Colistin Sulfate, Neomycin, Thonzonium Bromide, and Hydrocortisone Otic Suspension	107
Cotrimoxazole Oral Suspension	108
Cromolyn Sodium Nasal Spray	109
Cromolyn Sodium Oral Concentrate	109
Cyclosporin Oral Solution	109
Cyclosporine Soft Gelatin Capsules	110
Desmopressin Acetate Nasal Spray	110
Dexamethasone Elixir	110
Dextromethorphan Solution	110
Dextromethorphan and Chlorpheniramine Maleate Solution	111
Dextromethorphan Liquid	112
Dextromethorphan Liquid	113
Dextromethorphan, Pseudoephedrine, and Chlorpheniramine Maleate Syrup	114
Dextrose, Levulose, and Phosphoric Acid Solution	114
Diclofenac Oral Solution	115
Diazepam Rectal Solution	115
Didanosine for Oral Solution	116
Digoxin Capsules	116
Digoxin Elixir Pediatric	116
Dihydroergotamine Mesylate Drops	117
Diphenhydramine and Ammonium Chloride Syrup	118
Diphenhydramine Hydrochloride Liquid	119
Dornase Alfa Inhalation Solution	119
Doxercalciferol Capsules	119
Dyphylline, Guaifenesin Elixir	119
Electrolyte Lavage Solution	120
Erythromycin Drops	121
Erythromycin Topical Solution	122
Estradiol Nasal Spray	122
Ethchlorvynol Gelatin Capsule 200 mg	123
Eucalyptol Solution	123
Eucalyptus and Mint Emulsion	124
Fentanyl Citrate Nasal Spray	124
Ferrous Sulfate Oral Solution	125
Ferrous Sulfate Oral Syrup	126
Fluconazole Oral Suspension	126
Flunisolide Spray	126
Fluocinonide Topical Solution	126
Fluorouracil Solution	127
Fluorouracil Topical Solution	127
Fluticasone Suspension Spray	127

Furosemide Syrup	127
Gabapentin Oral Solution.....	128
Galantamine Hydrobromide Oral Solution.....	128
Glucose, Fructose, and Phosphoric Acid Antiemetic Solution	128
Gramicidin Ophthalmic Solution.....	128
Guaifenesin, Pseudoephedrine, Carbinoxamine, and Chlophedianol Drops	129
Haloperidol Oral Liquid.....	130
Heparin Nasal Spray	130
Hydrocodone Bitartrate Elixir.....	130
Hydrocodone Polistirex Extended-Release Suspension	131
Hydromorphone Hydrochloride Oral Liquid.....	131
Hydroxyzine Pamoate Oral Suspension	131
Hyoscine Butylbromide Syrup.....	132
Hyoscyamine Sulfate Elixir	132
Ibuprofen Topical Solution.....	132
Ibuprofen Pediatric Suspension	133
Ibuprofen Solution.....	134
Ibuprofen Suspension.....	134
Ibuprofen Suspension, Sugar Free	134
Insulin Inhalation Spray	135
Ipratropium Bromide Inhalation Solution	135
Ipratropium Bromide Nasal Spray.....	135
Iron Infant Drops.....	136
Iron Polystyrene and Vitamin C Syrup.....	137
Isoproterenol Sulfate and Calcium Iodide Syrup	138
Isotretinoin Capsules.....	138
Itraconazole Oral Solution	138
Kaolin, Pectin, and Aluminum Hydroxide Suspension.....	139
Kaolin-Pectin Suspension	140
Ketoprofen Topical Solution	140
Ketotifen Syrup	141
Lamivudine Oral Solution.....	141
Levalbuterol Hydrochloride Inhalation Solution	141
Levocarnitine Oral Solution.....	141
Linezolid for Oral Suspension.....	142
Lithium Carbonate Solution.....	142
Lithium Citrate Syrup	142
Lomustine Nasal Spray	142
Loracarbef for Oral Suspension	142
Loratidine Syrup	143
Mafenide Acetate Topical Solution.....	143
Magaldrate Instant Powder for Dry Syrup	144
Magaldrate Suspension	144
Magaldrate with Simethicone Suspension.....	145
Mebendazole Oral Suspension.....	146
Mebendazole Suspension	147
Megestrol Acetate Oral Suspension.....	147
Menthol and Benzocaine Solution.....	148
Menthol Mouthwash	148
Mesalamine Rectal Suspension Enema	149
Mesalamine Rectal Suspension.....	149
Metformin Liquid.....	149
Metoclopramide Oral Solution.....	150
Metoclopramide Syrup.....	151
Metronidazole Suspension	152

Minoxidil Solution	153
Mint Oil Solution	153
Mint–Menthol Mouthwash	153
Mometasone Furoate Nasal Spray	154
Monosulfiram Solution	154
Multivitamin and Calcium Syrup	155
Multivitamin Drops	156
Multivitamin Syrup	156
Multivitamin Syrup	157
Multivitamin with Fluoride Infant Drops	158
Nafarelin Acetate Nasal Solution	159
Nevirapine Suspension	159
Nicotine Spray	159
Nimesulide Suspension	160
Nimodipine Capsules	160
Nitroglycerin Lingual Spray	160
Norephedrine Syrup	161
Nystatin Oral Suspension	162
Nystatin Suspension	163
Naproxen Suspension	163
Ofloxacin Otic Solution	163
Omeprazole Solution	164
Phenylpropanolamine Controlled-Release Capsule	164
Ondansetron Hydrochloride Dihydrate Oral Solution	165
Orciprenaline Sulfate and Clobutinol Hydrochloride Syrup	165
Oxitropium and Formeterol Nasal Spray	165
Oxycodone Hydrochloride Oral Concentrate Solution	165
Oxymetazoline Hydrochloride Congestion Nasal Spray	166
Oxymetazoline Hydrochloride Nasal Solution	166
Oxymetazoline Moisturizing Nasal Spray	166
Oxymetazoline Nasal Spray	167
Oxymetazoline Sinus Nasal Spray	167
Oxymetazoline Nasal Solution	167
Pheniramine Maleate Syrup	168
Phenobarbital, Hyoscyamine Sulfate, Atropine Sulfate, and Scopolamine Hydrobromide Elixir	168
Phenylephrine Tannate and Chlorpheniramine Tannate Pediatric Suspension	168
Phenylephrine Tannate and Pyrilamine Tannate Suspension	168
Phenylpropanolamine, Chlorpheniramine, Dextromethorphan, Vitamin C Syrup	169
Phenytoin Suspension	170
Pipenzolate Methyl Bromide and Phenobarbital Drops	171
Podofilox Solution	171
Polidocanol Wound Spray	172
Polyvinyl Pyrrolidone–Iodine Gargle Solution	172
Polyvinyl Pyrrolidone–Iodine Gargle Solution Concentrate	173
Polyvinyl Pyrrolidone–Iodine Liquid Spray	173
Polyvinyl Pyrrolidone–Iodine Mouthwash and Gargle Solution Concentrate	174
Polyvinyl Pyrrolidone–Iodine Scrub	174
Polyvinyl Pyrrolidone–Iodine Solution	175
Polyvinyl Pyrrolidone–Iodine Solution	175
Polyvinyl Pyrrolidone–Iodine Solution	175
Polyvinyl Pyrrolidone–Iodine Solution	176
Polyvinyl Pyrrolidone–Iodine Solution	176
Polyvinyl Pyrrolidone–Iodine Surgical Scrub	177
Polyvinyl Pyrrolidone–Iodine Surgical Scrub	177
Polyvinyl Pyrrolidone–Iodine Vaginal Douche Concentrate	177

Polyvinyl Pyrrolidone-Iodine Viscous Solution.....	178
Prednisone Oral Solution	178
Prednisolone Sodium Phosphate Oral Solution.....	178
Prednisolone Syrup	178
Progesterone Capsules	178
Promethazine Hydrochloride Syrup.....	179
Promethazine and Codeine Syrup.....	180
Promethazine and Dextromethorphan Syrup.....	180
Promethazine Rectal Solution.....	180
Promethazine Rectal Solution.....	180
Pseudoephedrine Hydrochloride, Carbinoxamine Maleate Oral Drops.....	181
Pseudoephedrine and Carbinoxamine Drops.....	182
Pseudoephedrine Hydrochloride Syrup	183
Ribavirin Inhalation Solution.....	184
Risperidone Oral Solution	184
Ritonavir Capsules	184
Ritonavir Oral Solution.....	184
Ritonavir and lopinavir Oral Solution	184
Rivastigmine Tartarate Oral Solution.....	184
Salbutamol Aerosol	185
Salbutamol Syrup Sugar Free	186
Salbutamol Syrup	186
Salicylic Acid Collodion	187
Salmeterol Xinafoate Inhalation Aerosol.....	187
Scopolamine Nasal Spray	188
Sertraline Hydrochloride Oral Concentrate	188
Sertraline Hydrochloride Solution	188
Simethicone Drops	189
Sirolimus Solution.....	190
Sodium Chloride Nasal Drops.....	190
Stavudine for Oral Suspension	190
Sucralafate Suspension.....	191
Sulfacetamide Sodium and Sulfur Cleanser and Suspension.....	191
Sulfadiazine and Trimethoprim Veterinary Oral Suspension	192
Sulfamethoxazole and Trimethoprim Suspension	193
Sulfamethoxazole and Trimethoprim Suspension	194
Sulfamethoxazole and Trimethoprim Suspension	194
Sulfathiazole Veterinary Oral Solution	194
Sulfidoxine Solution	195
Sulfidoxine and Pyrimethamine Suspension	195
Sumatriptan Nasal Spray.....	196
Terfenadine Oral Suspension	197
Terfenadine Suspension	198
Theophylline Sodium Glycinate Elixir.....	198
Thiabendazole Suspension	199
Thiothixene Oral Concentrate.....	199
Timolol Maleate Ophthalmic Drops	199
Tolnafate Foot Care Microemulsion	199
Tolu Balsam Cough Syrup.....	200
Tretinoin Solution.....	201
Triamcinolone Acetonide Nasal Spray	201
Triclosan Oral Solution.....	202
Triprolidine and Pseudoephedrine Hydrochloride Syrup.....	203
Tulobuterol Syrup.....	204
Undecylenic Acid and Chloroxylenol Solution.....	204

Urea Peroxide Ear Drop.....	205
Valproic Acid Capsules.....	205
Valproic Acid Syrup.....	205
Vancomycin Hydrochloride Oral Solution.....	205
Vitamin A and D Infant Drops.....	206
Vitamin A and Vitamin D3 Drops.....	207
Vitamin A and Vitamin D3 Oral Solution.....	207
Vitamin A and Vitamin D3 Syrup.....	207
Vitamin A and Vitamin E Drops.....	208
Vitamin A and Vitamin E Drops.....	208
Vitamin A Concentrate, Water-Miscible.....	208
Vitamin A Drops.....	209
Vitamin B-Complex Syrup.....	209
Vitamin B-Complex Syrup.....	210
Vitamin B-Complex Syrup.....	211
Vitamin B-Complex and Vitamin C Syrup.....	211
Vitamin B-Complex (without B12) Syrup.....	212
Vitamin B-Complex, A, C, D, and Calcium Drops.....	214
Vitamin B-Complex and Iron Syrup.....	215
Vitamin B-Complex and Vitamin C Syrup.....	216
Vitamin B-Complex, Vitamin C, and Iron Syrup.....	217
Vitamin B-Complex, Vitamin C, and Iron Syrup.....	218
Vitamin B-Complex, A, C, and D Syrup.....	219
Vitamin B-Complex, A, C, D, and E Pediatric Drops.....	220
Vitamin C Drops.....	221
Vitamin E and Benzocaine Solution.....	221
Vitamin E and Benzocaine Solution.....	222
Vitamin E Capsules.....	222
Vitamin E Drops.....	222
Vitamin E Drops.....	223
Vitamin E Solution with Ethanol.....	223
Vitamin E Solution with Ethanol.....	223
Xylometazoline Hydrochloride Nasal Solution.....	224
Xylometazoline Hydrochloride Children's Nasal Solution.....	224
Index.....	225