Contents

List	of Con	ntributors	xvii
Fore	eword		xxiii
		José Alonso	
Prej			XXV
Ack	nowled	lgments	xxvii
Par	t One	General Aspects of Chitosan	1
1	Chem	nical and Technological Advances in Chitins and Chitosans Useful for	
-		ormulation of Biopharmaceuticals	3
		rdo A. A. Muzzarelli	_
	1.1	Introduction	3
	1.2	Safety of Chitins and Chitosans	4
	1.3	Ionic Liquids: New Solvents and Reaction Media	5
	1.4	Chitin and Chitosan Nanofibrils	8
		1.4.1 Mechanically Isolated Nanofibrils in the Presence of Acetic Acid	8
		1.4.2 Nanochitosan Obtained from Partially Deacetylated Chitin or Deacetylated	0
	1.7	Nanochitin	9
	1.5	Electrospun Nanofibers	10
	1.6	Polyelectrolyte Complexes and Mucoadhesion	12
		1.6.1 Chitosan Polyelectrolyte Complexes Soluble in Alkaline Medium	14
		1.6.2 Polyelectrolyte Complexes of Regioselectively Oxidized Chitin	15
	1.7	1.6.3 Polyelectrolyte Complexes of Chitosan with Bacterial Cell Wall Components	15
	1.7	1	16
		nowledgments	16
	Refe	rences	16
2	-	cal Properties of Chitosan and Derivatives in Sol and Gel States	23
	Ü	uerite Rinaudo	
	2.1	Introduction	23
	2.2	Chitin	24
		2.2.1 Solid State of Chitin	24
		2.2.2 Solubility of Chitin	24
		2.2.3 Characterization of Chitin	26
		2.2.4 Processing of Chitin Solution and Physical Properties of Materials	28
	2.3	Chitosan	28
		2.3.1 Solubility of Chitosan	28
		2.3.2 Characterization of Chitosan	29

	2.4 Refe	 2.3.3 Processing of Chitosan-Based Materials 2.3.4 Complex Materials Based on Interacting Chitosan and Chitosan Derivatives Conclusions and Future Perspectives 	31 31 36 36
3		rption Promotion Properties of Chitosan and Derivatives Yamamoto	45
	3.1	Introduction	45
		Effect of Chitosan on the Intestinal Absorption of Poorly Absorbable Drugs	47
	3.3	Effect of Chitosan Derivatives on the Intestinal Absorption of Poorly Absorbable Drugs	47
	3.4		48
	3.5		51
	3.6	1	54
	Refe	erences	54
4		ompatibility and Biodegradation of Chitosan and Derivatives	57
	Ahma	nd Sukari Halim, Lim Chin Keong, Ismail Zainol, and Ahmad Hazri Abdul Rashid	
	4.1	Introduction	57
	4.2	Biocompatibility Evaluation of Chitosan and Derivatives	58
		4.2.1 <i>In Vitro</i> Biocompatibility	60
		4.2.2 In Vivo Biocompatibility	63
	4.3	4.2.3 Effect of Sterilization on Biocompatibility Biodegradation of Chitosan and Derivatives	64 65
	4.5	4.3.1 Factors Influencing the Biodegradation of Chitosan and Derivatives	67
		4.3.2 <i>In Vitro</i> Biodegradation of Chitosan and Derivatives	68
		4.3.3 <i>In Vivo</i> Biodegradation of Chitosan and Derivatives	69
	4.4		69
	Refe	erences	70
5	Teres	gical and Pharmacological Activity of Chitosan and Derivatives a Cunha, Branca Teixeira, Bárbara Santos, Marlene Almeida, avo Dias, and José das Neves	75
	5.1	Introduction	75
	5.2	Biological Activity	76
		5.2.1 Antimicrobial Activity	76
		5.2.2 Immune Effects and Anti-Inflammatory Activity	77
		5.2.3 Antioxidant Activity	78
		5.2.4 Anticancer Activity	79
		5.2.5 Blood Coagulation Effects 5.2.6 Articliohoric Activity	79
		5.2.6 Antidiabetic Activity5.2.7 Neuroprotective Activity	80 80
		5.2.8 Other Biological Activities	81
	5.3	Chitosan's Usefulness in Therapy and Alternative Medicine	82
		5.3.1 Wound Healing	82
		5.3.2 Obesity	82

			Contents	vii
		522	Dyslinidamia	02
			Dyslipidemia Dental Plaque	83 83
			Renal Failure	83
			Other Uses	84
	5.4		sions and Future Perspectives	84
		nowledgr		85
		erences	nents	85
		her Read	ing	92
6	Biolo	gical, Ch	nemical, and Physical Compatibility of Chitosan and Biopharmaceuticals	93
	Masa	yuki Ishil	hara, Masanori Fujita, Satoko Kishimoto, Hidemi Hattori, and Yasuhiro Kanatani	
	6.1	Introduc	ction	93
	6.2	Structur	ral Features of Chitosan and Its Derivatives	94
	6.3	Biocom	patibility for Chitosan and Its Derivatives	95
		6.3.1	Inflammatory Reaction	95
		6.3.2	Foreign Body Reaction	96
		6.3.3	Biocompatibility Testing	97
	6.4	Biocom	patibility of Photo-Cross-Linkable Chitosan Hydrogel	98
			Photo-Cross-Linkable Chitosan Hydrogel	98
			Photo-Cross-Linkable Chitosan Hydrogel as a Biological Adhesive	99
			Photo-Cross-Linkable Chitosan Hydrogel as a Wound Dressing	99
		6.4.4	, ,	99
	6.5		l and Chemical Compatibility of Chitosan and Its Derivatives	100
			Chitosan-Based Peptide and Protein Delivery Systems	101
			Chitosan-Based Gene Delivery Systems	101
		6.5.3	Physicochemical Characterization of Protein-, Peptide-, or	
			Gene-Loaded Chitosan-Based PECs	101
	6.6		sions and Future Perspectives	102
	Refe	erences		103
7	Appr	oaches fo	or Functional Modification or Cross-Linking of Chitosan	107
	A. An	itha, N. S	Sanoj Rejinold, Joel D. Bumgardner, Shanti V. Nair, and Rangasamy Jayakumar	
	7.1	Introduc	ction	107
	7.2	General	Awareness of Chitosan Cross-Linking Methods	108
		7.2.1	Chemical Cross-Linking	108
		7.2.2	Radiation Cross-Linking	111
		7.2.3	Physical Cross-Linking	111
	7.3	Modifie	d Chitosan: Synthesis and Characterization	112
		7.3.1	Synthesis of Water-soluble Chitosan Derivatives	112
		7.3.2	Thiolation	113
		7.3.3	Succinylation	113
		7.3.4	Chitosan-Grafted Polymers	115
	7.4		tions of Modified Chitosan and Its Derivatives in Drug Delivery	118
	7.5		sions and Future Perspectives	118
		nowledgr	ments	118
	Refe	erences		119

		Biopharmaceuticals Formulation and Delivery Aspects Using nd Derivatives	125
8	Forms	Chitosan and Derivatives in Conventional Biopharmaceutical Dosage Formulation Vasconcelos, Pedro Barrocas, and Rui Cerdeira	127
	8.1	Introduction	127
	8.2	Advantageous Properties of Chitosan and Its Derivatives	128
	8.3	Oral Administration	129
	8.4	Buccal Administration	131
	8.5	Nasal Administration	132
	8.6	Pulmonary Administration	132
		Transdermal Administration	133
		Conclusions and Future Perspectives	133
	Refere	ences	134
9	for Bio Franca	acture Techniques of Chitosan-Based Microparticles and Nanoparticles pharmaceuticals Ferrari, M. Cristina Bonferoni, Silvia Rossi, Giuseppina Sandri, rla M. Caramella	137
	9.1	Introduction	137
		Water-in-Oil Emulsion and Chemical Cross-linking	138
		Drying Techniques	141
		9.3.1 Spray Drying	141
		9.3.2 Supercritical Fluid Drying	142
		9.3.3 Electrospraying	143
	9.4	Ionic Cross-linking Methods	144
		9.4.1 Low-MW Molecules	145
		9.4.2 Macromolecules	148
	9.5	Coacervation and Precipitation Method	151
	9.6	Direct Interaction between Chitosan and Biopharmaceuticals	152
		9.6.1 DNA–Chitosan Interaction	152
		9.6.2 siRNA–Chitosan Interaction	153
		Conclusions and Future Perspectives	153
	Refere	ences	154
10		an and Derivatives for Biopharmaceutical Use: Mucoadhesive Properties ina Leithner and Andreas Bernkop-Schnürch	159
	10.1	Introduction	159
	10.2	Mucoadhesion	160
		10.2.1 The Mucus	160
		10.2.2 The Interaction of Mucoadhesives and Mucosa	160
		10.2.3 Mucoadhesion	160
		10.2.4 Chitosan as a Mucoadhesive Polymer	161
	10.3	Chitosan and Its Derivatives	161

				Contents	ix
		10.3.1	Overview		161
			Thiolated Chitosan		161
			Chitosan–EDTA and Chitosan–DTPA		164
			Trimethyl Chitosan		167
			Mono-N-Carboxymethyl Chitosan		168
			<i>N</i> -Sulfonato- <i>N</i> , <i>O</i> -Carboxymethylchitosan		168
			Hydrophobically Modified Chitosans		169
			PEGylated Chitosan		170
			Chitosan–Succinate and Chitosan–Phthalate		170
	10.4	-	rmaceutical Use of Chitosan and Its Derivatives		171
			Overview		171
			Oral Drug Delivery		171
			Nasal Drug Delivery		174
	10.5		Buccal Drug Delivery		175
			sions and Future Perspectives		175
	Refer	ences			176
11	Chitos	an-Base	d Systems for Mucosal Delivery of Biopharmaceuticals		181
	Sonia 1	Al-Qadi,	Ana Grenha, and Carmen Remuñán-López		
	11.1	Introdu	ction		181
	11.2	Importa	ant Challenges for the Delivery of Biopharmaceuticals by Mucosal Routes		182
	11.3	Interest	t in Chitosan for Mucosal Delivery of Biopharmaceuticals		184
		11.3.1	Chitosan Physicochemical Properties		184
		11.3.2	Biological Properties of Chitosan		185
		11.3.3	Mucoadhesive and Permeation-Enhancing Properties		186
		11.3.4	Chitosan Derivatives		187
	11.4		an-Based Delivery Nanosystems for Mucosal Delivery of Biopharmaceutic	als	188
			Oral Delivery of Biopharmaceuticals		189
			Nasal Delivery of Biopharmaceuticals		192
			Pulmonary Delivery of Biopharmaceuticals		195
			sions and Future Perspectives		200
		owledgm	nents		200
	Refer	ences			201
12			d Delivery Systems for Mucosal Vaccination d, Farnaz Esmaeili, and Simon Heuking		211
	12.1	Introdu	· ·		211
	12.1		nt Properties of Chitosan		211
	12.2		an in the Delivery of Protein and Subunit Vaccines		213
	12.3		an-Based Formulations of DNA Vaccines		215
	12.4		e Formulations Using Chitosan in Combination with Other Polymers		216
	12.5		an Derivatives in Vaccine Carrier Design		217
	12.0		N,N,N-Trimethyl Chitosan		217
			Nasal Delivery of TMC-Based Vaccine Formulations		218
		12.6.3	•		219
		12.0.3	I difficulty believely of Title Bused facettle I officiations		21)

x Contents

		12.6.4	Oral Delivery of TMC-Based Vaccine Formulations	219	
		12.6.5	Other Chitosan Derivatives	219	
	12.7	Conclus	sions and Future Perspectives	220	
	Refer	ences		220	
13	Chitos	an-Baseo	d Nanoparticulates for Oral Delivery of Biopharmaceuticals	225	
	Filipa	Antunes,	Fernanda Andrade, and Bruno Sarmento		
	13.1	Introdu	ction	225	
			ges on the Oral Delivery of Therapeutic Proteins	226	
			iges on the Oral Delivery of Genetic Material	227	
			Chitosan in the Protection of Biopharmaceuticals in the Gastrointestinal Tract	229	
			n-Based Nanoparticles for Oral Delivery of Therapeutic Proteins	232	
			n-Based Nanoparticles for Oral Delivery of Genetic Material	234	
			sions and Future Perspectives	236	
		owledgm	•	237	
	Refer	_		237	
14			d Systems for Ocular Delivery of Biopharmaceuticals Rishi Paliwal, and Shivani Rai Paliwal	243	
	14.1	Introdu	ction	243	
			Delivery of Biopharmaceuticals	244	
			n: A Suitable Biomaterial for Ocular Therapeutics	244	
			n-Based Systems for Ocular Delivery of Biomacromolecules	245	
			Chitosan Solutions as Permeation Enhancers	245	
			Chitosan-Based Nanoemulsions	246	
		14.4.3	Chitosan Micro- and Nanoparticles	247	
			Chitosan-Coated Delivery Systems	248	
			Chitosan Complexed with Other Biomaterials	248	
	14.5		ogical and Compatibility Aspects of Chitosan-Based Ocular Systems	249	
	14.6	Conclus	sions and Future Perspectives	250	
	Refer	ences		250	
15	Chemi	cal Mod	ification of Chitosan for Delivery of DNA and siRNA	255	
	You-Kyoung Kim, Hu-Lin Jiang, Ding-Ding Guo, Yun-Jaie Choi, Myung-Haing Cho,				
	Toshih	iro Akaik	e, and Chong-Su Cho		
	15.1	Introdu	ction	255	
	15.2	Hydrop	hilic Modification	256	
	15.3	Hydrop	hobic Modification	257	
	15.4	Specific	c Ligand Modification	259	
		15.4.1	Galactose Ligand	259	
		15.4.2	Mannose Ligand	261	
		15.4.3	Folate Ligand	263	
	15.5	pH-Sen	sitive Modification	264	
		15.5.1	Imidazole	264	
		15.5.2	PEI	267	
		15.5.3	Spermine	269	

			Contents	xi
		15.5.4 PAMAM Dendron		269
	15.6	Conclusions and Future Perspectives		269
		owledgment		269
	Refer			269
Par	t Three	Advanced Application of Chitosan and Derivatives for Biopharmaceutical	s	275
16	Target	-Specific Chitosan-Based Nanoparticle Systems for Nucleic Acid Delivery		277
10		ool Jain and Mansoor Amiji		
	16.1	Introduction		277
		16.1.1 Nanotechnology in Vaccine and Drug Delivery		277
		16.1.2 Chitosan: A Versatile Biopolymer		278
		16.1.3 Chitosan for Delivery of Nucleic Acid Vaccines and Therapies		279
		16.1.4 Passive versus Active Systemic Targeted Delivery		280
	16.2	1 , ,		283
		16.2.1 Chitosan-Based Nanodelivery Systems for DNA Vaccines		283
		16.2.2 Chitosan-Based Nanodelivery Systems for Nucleic Acid Therapy		285
	16.3	Illustrative Examples of DNA Vaccine Delivery		286
		16.3.1 Mucosal Vaccination		286
	16.4	16.3.2 Systemic Vaccination		287
	16.4 16.5	Illustrative Examples of Nucleic Acid Delivery Systems for		288
		Anti-Inflammatory Therapy		291
		Conclusions and Future Perspectives		294
	Refer	ences		295
17		onal PEGylated Chitosan Systems for Biopharmaceuticals		301
	Hee-Je	ong Cho, Goen Kim, Hyeok-Seung Kwon, and Yu-Kyoung Oh		
	17.1	Introduction		301
		17.1.1 Physicochemical Properties of PEGylated Chitosan		302
		17.1.2 Biological Properties of PEGylated Chitosan		303
	17.2	PEGylated Chitosan for the Delivery of Proteins and Peptides		304
		17.2.1 Protein Delivery		304
		17.2.2 Peptide Delivery		307
	17.3	PEGylated Chitosan for Delivery of Nucleic Acids		308
		17.3.1 Plasmid DNA Delivery		308
	15.4	17.3.2 Oligonucleotide Delivery		310
	17.4	PEGylated Chitosan for Delivery of Other Macromolecular Biopharmaceuticals		311
	17.5	PEGylated Chitosan Used for Cellular Scaffolds		313
	17.6	Conclusions and Future Perspectives		313
	Refer	ences		314
18		i-Sensitive Chitosan-Based Systems for Biopharmaceuticals g Zhai, Jinfang Yuan, and Qingyu Gao		319
	-			0.1.5
	18.1	Introduction		319
	18.2	pH-Sensitive Chitosan-Based Systems		319

xii Contents

18.3	Thermosens	sitive Chitosan-Based Systems	321
			323
		· · · · · · · · · · · · · · · · · · ·	325
	•	· · · · · · · · · · · · · · · · · · ·	325
			326
			326
			327
			327
		s and I deale I elspeed ves	328
Chitos	n Conolym	ors for Rionharmocauticals	333
			333
			333
17.1			334
			336
			336
10.2			337
19.2	_		331
	-	•	337
			347
19 3	-		347
17.5	_	· · ·	350
			353
19.4		1	357
17			357
			357
		·	362
19.5			363
			363
			366
			367
			368
19.6		· ·	368
		•	369
Applic	ation of Chi	itosan for Anticancer Biopharmaceutical Delivery	381
20.1	Introduction	n	381
20.2	Chitosan an	nd Cancer: Intrinsic Antitumor Activity of the Polymer Itself	382
		· · · · · · · · · · · · · · · · · · ·	
			382
			383
20.3		<u> •</u>	383
		•	383
			384
		itosans as Absorption Enhancers	384
	18.6 18.7 18.8 18.9 18.10 Refere Chitosa Ramon 19.1 19.2 19.3 19.4 19.5 Applica Claudio 20.1 20.2	18.4 pH-Sensitiv 18.5 pH- and Io 18.6 Photo-Sens 18.7 Electrical-S 18.8 Magnetic-S 18.9 Chemical S 18.10 Conclusion References Chitosan Copolym Ramon Novoa-Carl 19.1 Introduction 19.1.1 Ge 19.1.2 Ch 19.1.3 Th 19.2 Chitosan-g- 19.2.1 Sy Po 19.2.2 Ap 19.3 Chitosan-g- 19.3.1 Sy 19.3.2 Ap 19.4 Other Copol 19.4.1 Ch 19.4.2 Gr 19.4.2 Gr 19.4.3 Ch 19.5 Copolymer 19.5.1 Ch 19.5.2 Ch 19.5.3 Ble 19.5.4 Ch 19.5.3 Ble 19.5.4 Ch 19.6 Conclusion References Application of Chi Claudia Philippi, B 20.1 Introduction 20.2 Chitosan ar 20.2.1 Eff 20.3.1 Ch 20.3.2 Na	18.4 pH-Sensitive and Thermosensitive Chitosan-Based Systems 18.5 pH- and Ionic-Sensitive Chitosan-Based Systems 18.6 Photo-Sensitive Chitosan-Based Systems 18.7 Electrical-Sensitive Chitosan-Based Systems 18.8 Magnetic-Sensitive Chitosan-Based Systems 18.9 Chemical Substance-Sensitive Chitosan-Based Systems 18.10 Conclusions and Future Perspectives References Chitosan Copolymers for Biopharmaceuticals Ramon Novoa-Carballal, Ricardo Riguera, and Eduardo Fernandez-Megia 19.1 Introduction 19.1.1 General Copolymerization Methods 19.1.2 Chitosan Copolymers for Biopharmaceuticals 19.1.3 The Integrity of the Chitosan Chain in Chitosan Copolymers 19.2 Chitosan-g-Poly(Ethylene Glycol) 19.2.1 Synthetic Procedures towards the Preparation of Chitosan-g-Poly(Ethylene Glycol) 19.2.2 Applications of Chitosan-g-Poly(Ethylene Glycol) with Biopharmaceuticals 19.3 Chitosan-g-Polyethylenimine 19.3.1 Synthetic Strategies toward the Preparation of Chitosan-g-Polyethylenimine 19.3.2 Applications to Gene Therapy 19.4 Other Copolymers of Chitosan 19.4.1 Chitosan-g-Polyeptide 19.4.2 Grafting of Chitosan to Thermoresponsive Polymers 19.4.3 Chitosan-g-Polyesters 19.5.1 Chitosan-g-Polyesters 19.5.2 Chitosan-g-Polyesters 19.5.2 Chitosan-g-Polyesters 19.5.3 Block Copolymers of Chitosan 19.5.4 Chitosan-g-Polyesters 19.5.5 Block Copolymers of Chitosan 19.5.4 Chitosan-g-Polyesters 19.5.5 Conclusions and Future Perspectives References Application of Chitosan for Anticancer Biopharmaceutical Delivery Claudia Philippi, Brigitta Loretz, Ulrich F. Schaefer, and Claus-Michael Lehr 20.1 Introduction 20.2 Effects of Chitosan, Low-Molecular Weight Chitosan, and Chitooliposaccharides 20.2.1 Effects of Chitosan Nanoparticles 20.3.2 Chitosan Formulations Developed for Classic Anticancer Drugs 20.3.1 Chemically Modified Chitosans or Chitosan-Drug Conjugates 20.3.2 Nanoparticulate Carrier Systems

			Contents	xiii
	20.4	Biopharmaceuticals Delivered by Chitosan Preparations		384
		20.4.1 Nucleic Acid–Based Therapeutics		385
		20.4.2 Peptide-Based Actives for Cancer Treatment		387
	20.5	Active Targeting Strategies and Multifunctional Chitosan Formulations		388
		20.5.1 Active Targeting Strategies		388
		20.5.2 Multifunctional Chitosan Nanoparticles		389
		Conclusions and Future Perspectives		389
	Refer	ences		390
21		an-Based Biopharmaceutical Scaffolds in Tissue Engineering		
		egenerative Medicine		393
	Tao Jio	ing, Meng Deng, Wafa I. Abdel- Fattah, and Cato T. Laurencin		
		Introduction		393
	21.2	Fabrication of Chitosan-Based Biopharmaceuticals Scaffolds		395
		21.2.1 Techniques for Fabricating Chitosan-Based Scaffolds		395
		21.2.2 Functionalization of Chitosan-Based Scaffolds via Biopharmaceuticals		402
	21.3	Applications of Chitosan-Based Biopharmaceutical Scaffolds		
		in Tissue Engineering and Regenerative Medicine		403
		21.3.1 Regeneration of Soft Tissue		404
	24.4	21.3.2 Regeneration of Hard Tissue		410
		Future Trends: Regenerative Engineering		416
		Conclusions and Future Perspectives		417
		owledgments		417
	Refer	ences		418
22		l-Healing Properties of Chitosan and Its Use in Wound Dressing		
	-	armaceuticals		429
	Tyler C	G. St. Denis, Tianhong Dai, Ying-Ying Huang, and Michael R. Hamblin		
		Introduction		429
	22.2	Brief Review of Wound Repair		430
		22.2.1 Inflammatory Phase		430
		22.2.2 Proliferative Phase		431
	22.2	22.2.3 Remodeling Phase		432
	22.3	Wound-Healing Effects of Chitosan		433
		22.3.1 In Vitro Studies		433
		22.3.2 In Vivo Studies		435
	22.4	22.3.3 Clinical Studies		438
	22.4	Chitosan for Wound Therapeutics Delivery 22.4.1 Antimicrobials		440
				440
		22.4.2 Combination with Photodynamic Therapy22.4.3 Growth Factors		442 443
		22.4.4 Delivery of Other Drugs		443
	22.5	Conclusions and Future Perspectives		444
		owledgments		447
	Refer			447
				,

Part Four		Regulatory Status, Toxicological Issues, and Clinical Perspectives		
23		icological Properties of Chitosan and Derivatives for Biopharmaceutical Applications mas J. Kean and Maya Thanou		
	23.1	Introduction	453	
	23.2	In Vitro Toxicity of Chitosan and Derivatives	454	
		23.2.1 <i>In Vitro</i> Toxicity of Chitosan	454	
		23.2.2 <i>In Vitro</i> Toxicity of Chitosan Derivatives	455	
		23.2.3 In Vitro Toxicity of Chitosan Formulations	455	
		23.2.4 Antibacterial, Antifungal, and Antiparasitic Activities of Chitosan		
		and Chitosan Derivatives	457	
	23.3	In Vivo Toxicity of Chitosan and Derivatives	457	
		23.3.1 In Vivo Toxicity of Chitosan	457	
		23.3.2 <i>In Vivo</i> Toxicity of Chitosan Derivatives	458	
		23.3.3 In Vivo Toxicity of Chitosan Formulations	458	
	23.4	Conclusions and Future Perspectives	459	
	Refer	ences	459	
24		atory Status of Chitosan and Derivatives	463	
	Міснає	el Dornish, David S. Kaplan, and Sambasiva R. Arepalli		
		Introduction	463	
		Source	464	
		Characterization	464	
	24.4	Purity	465	
		24.4.1 Impurities	465	
		24.4.2 Heavy Metals	465	
		24.4.3 Protein	465	
		24.4.4 Microbiological Bioburden	466	
		24.4.5 Bacterial Endotoxin	466	
	24.5	Applications of Advanced Uses of Chitosan	466	
		24.5.1 Tissue Engineering	466	
		24.5.2 Gene Delivery with Chitosan	467	
		24.5.3 Nasal Drug and Vaccine Delivery	467	
	24.6	Regulatory Considerations for Chitosan and Chitosan Derivatives in the		
		European Union, and Medical Devices or Combination Products with		
		Medical Device (CDRH) Lead	468	
	2.4.	24.6.1 The US Food and Drug Administration	468	
	24.7	Regulatory Pathways	469	
	24.8	Chitosan Medical Products: US Regulatory Review Processes for Medical	4.60	
	240	Devices or Combination Products with CDRH Lead	469	
	24.9	Chitosan Wound Dressings	470	
	2442	24.9.1 Hemostasis and Antimicrobial Activities	470	
	24.10	The European Regulatory System: The European Medicines Agency (EMA)		
		and European Directorate for the Quality of Medicines (EDQM)	474	
		24.10.1 Pharmaceuticals – Europe	474	
		24.10.2 Medical Devices – Europe	475	

		Contents	XV
	24 11	Further Regulatory Considerations	475
	2	24.11.1 Generally Recognized as Safe (GRAS)	476
		24.11.2 Pharmacopoeia Monographs	476
		24.11.3 Standards Development Organizations	476
	24 12	2 Conclusions and Future Perspectives	477
		owledgments	478
		Disclaimer	478
		rences	478
	Keici	Circes	470
25		ability and Intellectual Property Issues Related to Chitosan-Based	
	_	armaceutical Products	483
	Mafala	la Videira and Rogério Gaspar	
		Introduction	483
	25.2	Setting the Scene: The Role of Chitosan as a Pharmaceutical Excipient	484
		25.2.1 Current Achievements in Chitosan Use	484
		25.2.2 Chitosan-Based Ocular Therapy	486
		25.2.3 Tissue Engineering and Wound Management	487
		25.2.4 Drug Delivery Systems: Emerging Targeting Solutions	488
		25.2.5 Recent Trends in Using Chitosan	494
	25.3	Addressing the Drivers for Scientific Progress on Chitosan: Innovation and Inventability	495
		25.3.1 Is There a Next Generation of Chitosan?	495
	25.4	Conclusions and Future Perspectives	496
	Refer	rences	497
26	Qualit	y Control and Good Manufacturing Practice (GMP) for Chitosan-Based	
20		armaceutical Products	503
	_	n Richter, Maika Gulich, and Katja Richter	303
	Torsier	i Richier, Maika Gutich, ana Katja Richier	
	List c	of Abbreviations	503
	26.1	Introduction	504
	26.2	Regulatory Requirements for Production	505
		26.2.1 Medical Devices	505
		26.2.2 Excipients	506
		26.2.3 APIs/Pharmaceuticals	507
	26.3	Manufacturing GMP: Fundamental Considerations	508
	26.4	Requirements for Rooms, Personnel, and Equipment	511
	26.5	Qualification and Validation	511
		26.5.1 Qualification	511
		26.5.2 Process Validation	513
	26.6	Quality Control	513
		26.6.1 Specific Features of Chitosan Quality Control	516
	26.7	Monitoring and Maintenance of a GMP System	519
		26.7.1 Vendor and Customer Audits	519
		26.7.2 Public Authority Inspections	521
	26.8	Conclusions and Future Perspectives	522
	Refer	rences	522

xvi Contents

27	Preclinical and Clinical Use of Chitosan and Derivatives for Biopharmaceuticals:			
	From Preclinical Research to the Bedside David A. Zaharoff, Michael Heffernan, Jonathan Fallon, and John W. Greiner			525
	27.1	Introduction		
	27.2	Chitosan as a Parenteral (Subcutaneous) Vaccine Platform		526
		27.2.1	Enhancement of Humoral and Cell-Mediated Immune Responses	526
		27.2.2	Enhancement of the Immunoadjuvant Properties of GM-CSF	527
	27.3	Chitosan as an Immunotherapeutic Platform		530
		27.3.1	Intratumoral Immunotherapy with Chitosan–IL-12	530
		27.3.2	Intravesical Immunotherapy of Superficial Bladder Carcinoma	
			with Chitosan–IL-12	535
	27.4 Conclusions and Future Perspectives		537	
	References			539
Index				543