CONTENTS

Chapter 1	
What is a Biologic?	
A Brief History of Biologics Regulation in the United States	
Recent Changes in the Government's Approach to Biologics Regulation	
Regulatory Definition of a Biological Product	13
General Comparison of Drug and Biologic Characteristics	15
Product Classification and the FDA's Intercenter Agreements	
The Importance of Product Classification: Impact on Development Strategy	18
The Meaning of "Follow-On" Biologics	
References	22
Chapter 2	
Preclinical Safety Assessment of Therapeutic Proteins and Monoclonal Antibodies	2
Preclinical Development of Biologics	
Biologics-Specific Concepts	
Preclinical Studies to Support the Safety of Biologics	
The Timing of Preclinical Studies Relative to Clinical Trials	
Summary References	
References	
Chapter 3	
The Biological IND	35
FDA Organization and IND Submissions	
Types of IND Submissions	
Before Submitting an IND	
Example Meeting Request Sheet	
The Original IND Submission	
Contents of the IND	40
INDs for Gene Therapies	6
The Submission and Review of the IND	6.
Amendments to the IND	6
Electronic INDs	6
Summary	7
Acknowledgments	7
References	
Chapter /	
Chapter 4	_
The Biological IND Review Process	
The FDA and Regulating Biological Products: Recent History and Agency Structure	
FDA Announces CDER/CBER Consolidation	
A Look at the Structure of CBER and CDER for IND Reviews	
CBER Structure	80
The Office of Tissues and Advanced Therapies (formerly known as Office of Cellular, Tissue and	0.0
Gene Therapies)	82
CDER's Structure for Biological IND Reviews	
The Review Process for INDs	
CBER and the IND Review Process	
CDER and the IND Review Process for Biological Therapeutic Products	
The IND and the 30-Day IND Review Clock	
The Clinical Hold	
IND Status	102

Cl	hapter	: 5
----	--------	-----

Clinical Testing of Biologically Derived Therapeutics	105
Phases of Clinical Drug Development	
References	123
Chapter 6	
The Clinical Evaluation of Preventive Vaccines	125
Federal Regulations Pertaining to Vaccines	126
U.S. FDA Regulations Relevant to the Manufacture,	
Product Quality and Clinical Testing of Vaccines*	
Overview of Clinical Evaluation	127
Phases of Clinical Development	128
Serious Adverse Events (SAEs) During Clinical Development	131
Additional Considerations for Safety Data	139
FDA Advisory Committee Deliberations	140
Postlicensure Studies	140
Postlicensure Surveillance	140
Regulatory Initiatives for Accelerated Vaccine Development During COVID-19 Pandemic	141
Acknowledgments	145
References	145
Chapter 7	
Good Ĉlinical Practices (GCP)	153
Information Sheets: Guidance for Institutional Review Boards	
and Clinical Investigators	
Responsibilities of the Sponsor	162
Responsibilities of Investigators	170
The Institutional Review Board (IRB)	173
Informed Consent	176
References	182
01	
Chapter 8	
The Biological License Application (BLA)	
A Short History of the FDA's Licensing Process for Biologics	
An Introduction to the BLA: Content and Format Requirements and Form 356h	
The Content of the BLA	
CBER and the eBLA Program	
Amending the License Application	
References	233
01	
Chapter 9	
Manufacturing Arrangements For Biological Products	
Biologics Establishment Registration	
Human Cells, Tissues and Cellular and Tissue-Based Products (HCT/Ps) Establishments	
The Biotech Explosion, Industry Consolidation, and Biological Manufacturing	
The FDA Redefines "Manufacturer"	
Sole Manufacturing	
Current Cooperative Manufacturing Arrangements for Licensed Biologics	241
Facility Inspections	252
References	255

Chapter 10

The BLA Nanaged Review Process Within CBER	The Biological License Application (BLA) Review Process	259
The BLA Managed Review Process Within CBER		
Sponsor Rights during the License Application Review Process References		
References		
Post-licensure Requirements		
Post-licensure Requirements	Chantar 11	
Adverse Experience-Related Regulatory Definitions Changes in AE Reporting Requirements Expedited Reporting of Additional Safety Information Jis Expedited Reporting of Additional Safety Information Jis Lot Release Jirch Carrent Good Manufacturing Practice (cGMP) Standards for Biological Products Jis Written Procedures for the investigation should include the following: Jis Written Procedures for the investigation should include: Jis General Reporting Requirements Jis General Reporting Program General Reporting Program Jis General Reporting Program General Reporting Reporting Program Jis General Reporting Requirements Jis General Reporting	Chapter 11	205
Changes in AE Reporting Requirements Expedited Reporting of Additional Safety Information 315 Expedited Reporting of Additional Safety Information 327 Current Good Manufacturing Practice (cGMP) Standards for Biological Products 331 Written Procedures for the investigation should include the following: 338 Written records of the investigation should include: 339 Written Reporting Requirements 339 Phase 4 Study Commitments 335 Phase 4 Study Commitments 336 Phase 4 Study Commitments 337 References 336 Chapter 12 Bioresearch Monitoring Program for Biologics 367 A Brief History of the Bioresearch Monitoring Program 368 An Overview of CBER's Bioresearch Monitoring Program 368 An Overview of CBER's Bioresearch Monitoring Program 377 The Clinical Investigator Compliance Program 377 The Clinical Investigator Compliance Program 377 The Institutional Review Board (IRB) Compliance Program 377 The Nonclinical Laboratory Compliance Program 378 CDER's Bioresearch Monitoring Program 380 CDER's Bioresearch Monitoring Program 381 References 382 Chapter 13 Biologics and the Regulation of Combination Products 383 Defining Biologics, Drugs, and Devices 384 CBER Action Plans 385 Combination Products and Gaining CBER Approval 385 Safe Medical Devices Act (SMDA) of 1990 385 Table. Workload at OCP by Combination Products 386 PDUFA and Various Classes of CBER Regulated Products 387 PDUFA and Various Classes of CBER Regulated Products 388 PDUFA and Various Classes of CBER Regulated Products 389 PDUFA and Various Classes of CBER Regulated Products 380 References 405 Chapter 14 Special Topics in the Development of Biologically Derived Therapeutics 407		
Expedited Reporting of Additional Safety Information	1 0 7	
Lot Release		
Current Good Manufacturing Practice (cGMP) Standards for Biological Products Written Procedures for the investigation should include the following: 338 Written records of the investigation should include: 338 General Reporting Requirements. 335 Phase 4 Study Commitments. 337 References. 336 Chapter 12 Bioresearch Monitoring Program for Biologies. 346 A Brief History of the Bioresearch Monitoring Program. 347 Recent Issues for the FDA's BIMO Program. 348 An Overview of CBER's Bioresearch Monitoring Program. 349 The Clinical Investigator Compliance Program. 347 The Clinical Sponsor/Monitor Compliance Program. 347 The Institutional Review Board (IRB) Compliance Program. 348 CDER's Bioresearch Monitoring Program. 348 CDER's Bioresearch Monitoring Program. 348 References. 348 Chapter 13 Biologics and the Regulation of Combination Products Defining Biologies, Drugs, and Devices. 348 CBER Action Plans Combination Products and Gaining CBER Approval. 348 Safe Medical Devices Act (SMDA) of 1990. 348 Table. RFD Determinations by OCP and Workload Trends: FY 2013 to FY 2018. 349 Table. Workload at OCP by Combination Product Category Number in FY 2018. Combination 340 References. 340 Chapter 14 Special Topics in the Development of Biologically Derived Therapeutics. 405 Chapter 14 Special Topics in the Development of Biologically Derived Therapeutics.		
Written Procedures for the investigation should include the following: Written records of the investigation should include: 338 General Reporting Requirements. 339 Phase 4 Study Commitments. 337 References. 336 Chapter 12 Bioresearch Monitoring Program for Biologics. A Brief History of the Bioresearch Monitoring Program. 346 An Overview of CBER's Bioresearch Monitoring Program. 358 An Overview of CBER's Bioresearch Monitoring Program. 369 The Clinical Investigator Compliance Program. 370 The Clinical Sponsor/Monitor Compliance Program. 371 The Institutional Review Board (IRB) Compliance Program. 372 The Nonclinical Laboratory Compliance Program. 373 The Nonclinical Laboratory Compliance Program. 380 CDER's Bioresearch Monitoring Program. 381 References. 382 Chapter 13 Biologics and the Regulation of Combination Products. 383 Combination Products and Gaining CBER Approval. 384 CBER Action Plans. 385 Combination Products and Gaining CBER Approval. 386 Safe Medical Devices Act (SMDA) of 1990. 387 Table. RFD Determinations by OCP and Workload Trends: FY 2013 to FY 2018. 389 Table. Workload at OCP by Combination Products. 399 Risk-Based Quality and Safety Management throughout the Lifecycle of Combination Products. 405 Chapter 14 Special Topics in the Development of Biologically Derived Therapeutics. 407		
Written records of the investigation should include: General Reporting Requirements. 335 General Reporting Requirements. 335 Phase 4 Study Commitments. 357 References. 366 Chapter 12 Bioresearch Monitoring Program for Biologics. 367 A Brief History of the Bioresearch Monitoring Program. 368 An Overview of CBER's Bioresearch Monitoring Program. 368 An Overview of CBER's Bioresearch Monitoring Program. 379 The Clinical Investigator Compliance Program. 377 The Clinical Investigator Compliance Program. 377 The Institutional Review Board (IRB) Compliance Program. 379 The Nonclinical Laboratory Compliance Program. 380 CDER's Bioresearch Monitoring Program. 381 References. 382 Chapter 13 Biologics and the Regulation of Combination Products. 383 Chapter 13 Biologics and the Regulation of Combination Products. 384 CBER Action Plans. 385 Combination Products and Gaining CBER Approval. 386 Safe Medical Devices Act (SMDA) of 1990. 387 Table. RFD Determinations by OCP and Workload Trends: FY 2013 to FY 2018. 388 PDUFA and Various Classes of CBER-Regulated Products. 389 PDUFA and Various Classes of CBER-Regulated Products. 399 Risk-Based Quality and Safety Management throughout the Lifecycle of Combination Products. 405 Chapter 14 Special Topics in the Development of Biologically Derived Therapeutics. 407		
General Reporting Requirements	ŭ į	
Phase 4 Study Commitments		
Chapter 12 Bioresearch Monitoring Program for Biologics. 367 A Brief History of the Bioresearch Monitoring Program. 368 Recent Issues for the FDA's BIMO Program. 368 An Overview of CBER's Bioresearch Monitoring Program. 374 The Clinical Investigator Compliance Program. 375 The Clinical Sponsor/Monitor Compliance Program. 377 The Institutional Review Board (IRB) Compliance Program. 375 The Nonclinical Laboratory Compliance Program. 380 CDER's Bioresearch Monitoring Program. 380 CDER's Bioresearch Monitoring Program. 381 References. 382 Chapter 13 Biologics and the Regulation of Combination Products 383 Defining Biologics, Drugs, and Devices. 384 CBER Action Plans. 385 Combination Products and Gaining CBER Approval. 385 Combination Products and Gaining CBER Approval. 385 Safe Medical Devices Act (SMDA) of 1990. 385 Table. RFD Determinations by OCP and Workload Tre		
Bioresearch Monitoring Program for Biologics	,	
Bioresearch Monitoring Program for Biologics		
A Brief History of the Bioresearch Monitoring Program Recent Issues for the FDA's BIMO Program 368 An Overview of CBER's Bioresearch Monitoring Program 374 The Clinical Investigator Compliance Program 375 The Clinical Sponsor/Monitor Compliance Program 377 The Institutional Review Board (IRB) Compliance Program 378 The Nonclinical Laboratory Compliance Program 380 CDER's Bioresearch Monitoring Program 381 References 382 Chapter 13 Biologies and the Regulation of Combination Products 383 Defining Biologies, Drugs, and Devices 384 CBER Action Plans 385 Combination Products and Gaining CBER Approval 386 Safe Medical Devices Act (SMDA) of 1990 387 Table. RFD Determinations by OCP and Workload Trends: FY 2013 to FY 2018 398 Table. Workload at OCP by Combination Product Category Number in FY 2018. Combination 398 PDUFA and Various Classes of CBER-Regulated Products 399 Risk-Based Quality and Safety Management throughout the Lifecycle of Combination Products 403 References 405 Chapter 14 Special Topics in the Development of Biologically Derived Therapeutics 407	Chapter 12	2/5
Recent Issues for the FDA's BIMO Program		
An Overview of CBER's Bioresearch Monitoring Program		
The Clinical Investigator Compliance Program	· ·	
The Clinical Sponsor/Monitor Compliance Program	0 0	
The Institutional Review Board (IRB) Compliance Program		
The Nonclinical Laboratory Compliance Program	1	
Chapter 13 Biologics and the Regulation of Combination Products		
Chapter 13 Biologics and the Regulation of Combination Products		
Biologics and the Regulation of Combination Products		
Biologics and the Regulation of Combination Products		
Defining Biologics, Drugs, and Devices		
CBER Action Plans		
Combination Products and Gaining CBER Approval		
Safe Medical Devices Act (SMDA) of 1990		
Table. RFD Determinations by OCP and Workload Trends: FY 2013 to FY 2018	0 11	
Table. Workload at OCP by Combination Product Category Number in FY 2018. Combination		
PDUFA and Various Classes of CBER-Regulated Products	•	
Risk–Based Quality and Safety Management throughout the Lifecycle of Combination Products	,	
Chapter 14 Special Topics in the Development of Biologically Derived Therapeutics		
Special Topics in the Development of Biologically Derived Therapeutics		
Special Topics in the Development of Biologically Derived Therapeutics		
		407
Acterences		
	ACICICIUCS	433

Chapter 15

Biosimilar Products	445
Biosimilar Development, Review, and Approval Processes	446
Interchangeable Products: Definition, Regulatory Review and Approval Process	448
Post-marketing or Post-authorization Surveillance Requirements	451
Nomenclature	453
FDA-Approved Biosimilar Products	454
The Biologics Price Competition and Innovation Act	455
An Abbreviated Approval Pathway for Biological Products	456
References	457
About Barnett International	463
About Cambridge Healthtech Institute	463