
TABLE OF CONTENTS

PREFACE.....	V
ACKNOWLEDGMENTS.....	XV
IN MEMORIAM	XIX
TABLE OF CASES.....	LXV
Chapter 1. History and Context.....	1
A. Global Precedents	1
Peter Barton Hutt, <i>Government Regulation of the Integrity of the Food Supply</i>	1
B. The Development of FDA as an Institution	3
Peter Barton Hutt, <i>A Historical Introduction</i>	3
Richard A. Merrill, <i>The Architecture of Government Regulation of Medical Products</i>	5
C. The Development of American Food and Drug Legislation	6
1. State and Local Laws in the 19th Century	6
2. National Developments Leading up to 1906	7
3. The 1906 Pure Food and Drugs Act	9
Lauffer Hayes & Frank Ruff, <i>The Administration of the Federal Food and Drugs Act</i>	9
1917 Report of the USDA Bureau of Chemistry	10
Note	11
4. The Federal Food, Drug, and Cosmetic Act of 1938	11
1933 Report of the Food and Drug Administration	11
5. The Growth of the FD&C Act: Amendments Since 1938	12
6. Other Laws Enforced by FDA	15
D. FDA's Mission	16
Agriculture, Rural Development, Food and Drug Administration, and Related Agencies Appropriations Bill, 2022	16
Fact Sheet: FDA at a Glance	18
Note	20
E. FDA's Structure and Organization	20
1. Legal Basis for the Agency	20
2. The FDA Commissioner.....	20
3. The FDA Chief Counsel	21
4. FDA's Place Within the Federal Government.....	21
Peter Barton Hutt, <i>Balanced Government Regulation of Consumer Products</i>	23
5. FDA's Size and Internal Organization	24
F. FDA's Relationship with Other Agencies	26
G. FDA's Relationship with Regulated Industry	28
Review Panel on New Drug Regulation, Final Report	28
Final Report of the National Committee to Review Procedures for Approval of New Drugs for Cancer and Aids	29
Note	30

H.	FDA Records: The Freedom of Information Act.....	30
	Peter Barton Hutt, <i>Public Information and Public Participation in the Food and Drug Administration</i>	31
	Notes	32
I.	FDA Resources	33
	Note.....	34
J.	The Regulatory Environment	34
 Chapter 2. Administrative Law and Procedure at FDA		37
A.	Introduction.....	37
B.	Rulemaking	38
	1. Rulemaking Under the APA.....	38
	2. Evolution of Rulemaking at FDA.....	39
	a. Early Innovations.....	39
	b. The Statutory Framework	40
	c. Judicial Acknowledgment of FDA's Rulemaking Authority.....	42
	Abbott Laboratories v. Gardner	42
	Notes	45
	National Association of Pharmaceutical Manufacturers v. Food and Drug Administration	46
	Notes	51
	3. Rulemaking Procedures.....	52
	a. APA Notice-and-Comment Requirements	52
	United States v. Nova Scotia Food Products Corp.....	53
	Notes	56
	b. HHS Oversight of FDA Rulemaking	56
	c. OMB Oversight of FDA Rulemaking	57
	d. Direct Final Rules and Interim Final Rules.....	59
	4. Formal Rulemaking	60
	a. When Is a Formal Hearing Required?	60
	Dyestuffs and Chemicals, Inc. v. Flemming	60
	Notes	62
	b. Formal Hearing Procedures	63
	c. Alternative Hearings	64
	Notice of Proposed Rulemaking: Administrative Practices and Procedures	64
C.	Guidance.....	66
	1. Exceptions to APA Rulemaking	66
	2. The Rise of Guidance at FDA	67
	3. Litigation over Guidance	69
	Professionals and Patients for Customized Care v. Shalala	69
	Notes	75
	4. Good Guidance Practices	76
D.	Judicial Review	78
	1. Introduction.....	78
	Note.....	79
	2. Standards of Review	79

3.	Deference to FDA Decisions	80
	Note.....	82
4.	Judicial Review of Agency Inaction	82
	a. Enforcement Discretion	82
	b. Unreasonable Delay	83
	Center for Food Safety v. Hamburg	83
	Notes	87
5.	Barriers to Judicial Review	89
	a. Justiciability	89
	Notes	89
	b. Primary Jurisdiction	90
	Notes	91
	c. Exhaustion of Remedies.....	93
E.	Public Information	93
1.	Statutory Obligations	93
	a. The Freedom of Information Act (FOIA)	93
	Notes	95
	i. Implementing FOIA: Procedures, Costs, and Backlogs	96
	Pharmaceutical Manufacturers Association v. Weinberger	96
	Note	99
	Judicial Watch, Inc. v. Food & Drug Administration	99
	ii. Trade Secrets and Confidential Commercial Information	104
	Notes.....	105
	iii. The Scope of Exemption 4 of FOIA.....	108
	Public Citizen Health Research Group v. Food & Drug Administration	108
	Note	112
	iv. Non-FOIA Disclosure of Clinical Trial Information....	112
	Notes.....	114
	b. The Shelby Amendment.....	114
	c. The Information Quality Act	115
	Notes	116
2.	Modern Dissemination of Information.....	117
F.	Advisory Committees	118
1.	FDA's Reliance on Advisory Committees	119
	Food and Drug Administration Advisory Committees	119
	Notes	122
2.	Statutory Requirements for Advisory Committees.....	122
	Consumers Union of United States, Inc. v. Department of HEW	122
	National Nutritional Foods Ass'n v. Califano	126
	Notes	129
	Public Citizen v. National Advisory Committee	130

Robert Steinbrook, M.D., <i>Financial Conflicts of Interest and the Food and Drug Administration's Advisory Committees</i>	133
Notes	135
Chapter 3. FDA Jurisdiction: A Matter of Definitions	139
A. Introduction.....	139
Food, Drugs, and Cosmetics	139
United States v. An Article of Drug . . . Bacto-Unidisk.....	140
Notes	142
B. Food.....	143
United States v. Tuente Livestock.....	143
Notes	148
Nutrilab, Inc. v. Schweiker	149
Notes	152
C. Drugs and Devices	154
1. Inclusion in Official Compendia.....	155
2. Establishing “Intended Use”	156
National Nutritional Foods Ass’n v. Mathews	158
Notes	161
United States v. Travia	162
3. Diagnostic Products	164
United States v. 25 Cases, More or Less, of an Article of Device . . . “Sensor Pad for Breast Self-Examination”	164
Notes	166
D. The Food-Drug Spectrum Adjusted: Health Claims and Dietary Supplements.....	167
Letter from Felicia B. Satchell, Director, FDA CFSAN Office of Nutritional Products, Labeling and Dietary Supplements, Division of Standards and Labeling Regulations, to Jason S. Crush	170
Notes	172
Warning Letter from Donald D. Ashley, Director, Office of Compliance, CDER- FDA to Edward Chaney, Cannafyl.....	176
Notes	178
E. Cosmetics.....	179
Notes	180
F. The Cosmetic-Drug Spectrum.....	181
1. Cosmetic Claims Versus Drug Claims.....	181
United States v. An Article . . . Sudden Change	181
Notes	184
Letter From John M. Taylor, FDA Associate Commissioner for Regulatory Affairs, to Various Attorneys Representing the Cosmetic Industry.....	185
Notes	186
2. The “Active Ingredient” Approach	189
Notes	191

G.	Exploring the Outer Limits of the Drug and Device Definitions	193
1.	Cosmetic Devices.....	193
	Letter From Rep. Henry A. Waxman to Tommy Thompson, Secretary of Health and Human Services	194
	Notes	195
2.	Common Sense Limits?.....	196
	Notes	198
	Letter From Daniel E. Troy, FDA Chief Counsel, to Jeffrey N. Gibbs	199
	Note.....	202
	Whether the Food and Drug Administration Has Jurisdiction over Articles Intended for Use in Lawful Executions	203
	Notes	210
3.	First Amendment Limits	212
	United States v. 23 . . . Articles.....	212
	United States v. Undetermined Quantities of Article of Device.....	213
H.	Human Biological Products	216
	David M. Dudzinski, <i>Reflections on Historical, Scientific, and Legal Issues Relevant to Designing Approval Pathways for Generic Versions of Recombinant Protein-Based Therapeutics and Monoclonal Antibodies</i>	217
	Notes	219
I.	Tobacco Products.....	220
	Deeming Tobacco Products To Be Subject to the Federal Food, Drug, and Cosmetic Act, as Amended by the Family Smoking Prevention and Tobacco Control Act (Final Rule).....	222
	Notes	225
J.	“Label,” “Labeling,” and “Advertising”	225
1.	Introduction	225
	Note.....	226
2.	Labeling	226
	Kordel v. United States	226
	Note.....	228
	United States v. 24 Bottles “Sterling Vinegar & Honey,” etc.	228
	Notes	230
3.	Advertising	231
4.	The Internet.....	232
	Letter From Margaret M. Dotzel, Assoc. Comm. for Policy, FDA, to Daniel J. Popeo and Paul D. Kamenar, Washington Legal Foundation	232
	Notes	233
	Chapter 4. Enforcement and the Geographic Range of FDA Power.....	235
A.	Introduction to Enforcement	235
1.	Section 301: Prohibited Acts.....	235
2.	Tools of Enforcement	236
	Note.....	237

3.	FDA Enforcement Statistics.....	237
	Notes	238
4.	FDA Enforcement Policy	239
	Remarks by Margaret A. Hamburg, Commissioner of Food and Drugs, “Effective Enforcement and Benefits to Public Health”	239
	Notes	240
B.	Enforcement Jurisdiction	241
1.	“Introduction into Interstate Commerce”	242
	United States v. Sanders	243
	Notes	244
2.	“Held for Sale After Shipment in Interstate Commerce”	245
	United States v. Kaplan	246
	Notes	250
3.	Components Shipped in Interstate Commerce	253
	Baker v. United States	254
	Notes	256
4.	Devices and Tobacco Products.....	257
5.	Biologics.....	258
	United States v. Calise	258
	Notes	259
C.	Enforcement Consistency, Selectivity, and Discretion.....	261
1.	Administrative Consistency and Selective Enforcement	261
	United States v. Undetermined Quantities of an Article of Drug Labeled as Exachol.....	261
	Notes	263
2.	Enforcement Discretion	265
	Heckler v. Chaney.....	265
	Notes	269
D.	Factory Inspection	272
1.	Introduction.....	272
	FDA Investigations Operations Manual, Chapter 5 (“Establishments Inspection”)	273
	Notes	275
2.	Constitutional Limitations	276
	United States v. Jamieson-McKames Pharmaceuticals, Inc.....	276
	Notes	280
3.	Scope of Inspections	281
a.	Records.....	281
	Notes	282
b.	Samples.....	285
	Triangle Candy Co. v. United States	285
	Notes	286
c.	Photographs.....	287
	Frederick H. Branding & James M. Ellis, <i>Underdeveloped: FDA’s Authority to Take Photographs During an FDA Establishment Inspection Under Section 704</i>	287
	Notes	289

4.	The USDA Inspection Regime.....	290
E.	Seizure	292
1.	Introduction	292
	Peter Barton Hutt, <i>Philosophy of Regulation Under the Federal Food, Drug and Cosmetic Act</i>	292
	Note	293
2.	The Seizure Process	293
	United States of America v. Argent Chemical Laboratories, Inc.....	293
	Notes	297
3.	Pre-Condemnation Release	298
	United States v. Undetermined Quantities of Drugs	298
	Notes	301
4.	Multiple Seizures	301
	Ewing v. Mytinger & Casselberry, Inc.	302
	Notes	304
5.	Proof Required for Condemnation.....	305
	United States v. 43 1/2 Gross Rubber Prophylactics Labeled in Part “Xcello’s Prophylactics”	305
	Notes	306
6.	Final Condemnation Decrees and Salvaging	307
	United States v. 1,638 Cases of Adulterated Alcoholic Beverages.....	307
	Notes	310
7.	Administrative Detention	310
F.	Injunctions.....	311
1.	Introduction	311
	Notes	312
2.	Preliminary Injunctions.....	313
	United States v. Nutri-cology, Inc.....	313
3.	Permanent Injunctions	315
	United States v. Laerdal Manufacturing Corp.	315
	Notes	318
4.	Consent Decrees, Restitution, and Disgorgement	319
	Department of Justice Press Release	319
	William W. Vodra & Arthur N. Levine, <i>Anchors Away: The Food and Drug Administration’s Use of Disgorgement Abandons Legal Moorings</i>	321
	Notes	324
G.	Recalls.....	325
1.	Voluntary Recalls	325
	Enforcement Policy, Practices and Procedures: Recall Policy and Procedures	326
	Notes	329
2.	Mandatory Recalls	330
	Notes	332
H.	Criminal Liability	334
1.	Introduction	334
	Sam D. Fine, <i>The Philosophy of Enforcement</i>	334

Notes	335
2. Standard of Liability.....	336
a. Criminal Liability of Responsible Corporate Officials.....	336
United States v. Park.....	338
United States v. DeCoster	344
Notes	347
b. The Defense of Impossibility	350
3. The Guaranty Clause.....	351
Notes	351
I. Debarment and Exclusion	352
1. Debarment.....	352
Bae v. Shalala.....	353
Notes	357
2. Exclusion	357
Friedman v. Sebelius	357
Notes	362
J. Civil Money Penalties.....	363
Notes	364
K. Informal Compliance Correspondence.....	365
FDA Regulatory Procedures Manual, Chapter 4 (“Advisory Actions”).....	365
Notes	368
L. Publicity.....	370
Hoxsey Cancer Clinic v. Folsom.....	370
Notes	371
M. Regulation of Foreign Commerce.....	373
1. Introduction	373
a. International Offices and Arrangements.....	373
b. International Trade Agreements	374
2. Importation into the United States	376
a. FDA’s General Authority over Importation.....	376
Sugarman v. Forbragd	376
Notes	377
Cook v. FDA.....	378
Notes	384
b. Reconditioning, Destroying, or Reexporting Goods	
Refused Admission	386
Carl Borchsenius Co. v. Gardner	387
c. Refusal of Admission Compared to Seizure.....	389
United States v. Food, 2,998 Cases.....	389
Notes	393
3. Importation of Food	394
Notes	396
4. Importation of Prescription Drugs.....	397
a. Commercial Importation.....	397
Warning Letter From David J. Horowitz, Dir., CDER	
Office of Compliance, to Harry Lee Jones,	
Store Manager, Rx Depot, Inc.	397

United States of America v. Rx Depot, Inc.	400
Notes	403
b. Importation for Personal Use	404
c. Importation Pursuant to Waiver	404
State of Vermont v. Leavitt	404
Notes	406
5. Exportation Pursuant to Section 801(e)(1)	408
a. General.....	408
United States v. Kanasco, Ltd.	409
Notes	411
b. Exportation of Unapproved New Drugs and Unlicensed Biologics	412
United States v. An Article of Drug . . .	
Ethionamide-INH	412
Notes	413
c. Exportation of Unapproved New Animal Drugs	414
d. Exportation of Unapproved Devices.....	415
6. Exportation of Unapproved Medical Products Pursuant to Section 802.....	416
Guidance for Industry: Exports Under the FDA Export Reform and Enhancement Act of 1996	416
Notes	421
7. Import for Export	422
FDA Regulatory Procedures Manual, Chapter 9 (“Import Operation and Actions”).....	422
N. The Relationship Between FDA and the States	424
1. The Elusive Goal of Uniformity of State Laws.....	424
Melvin Hinich & Richard Staelin, <i>Regulation of the U.S. Food Industry</i>	426
2. Introduction to Federal Preemption	428
a. Basics of the Doctrine	428
b. Historical Background	429
3. Field Preemption.....	431
Hillsborough County v. Automated Medical Laboratories, Inc.....	431
Notes	434
4. Conflict Preemption	436
a. Impossibility Preemption.....	436
Grocery Manufacturers of America v. Gerace	436
Notes	438
b. Obstacle Preemption	439
Florida Lime & Avocado Growers, Inc. v. Paul	439
Jones v. Rath Packing Co.	442
Notes	446
5. Express Preemption	448
a. Devices	449
Notes	450
b. Food Labeling	451
Notes	453

c. Nonprescription Drugs and Cosmetics	453
Note	454
d. Tobacco Products	454
Chapter 5. Food	457
A. Subcategories of Food	457
1. Food Regulated Primarily by Agencies Other than FDA	457
a. Meat, Poultry, and Eggs	458
b. Alcoholic Beverages.....	460
c. Water and Ice	461
2. Dietary Supplements	461
Warning Letter From Michael W. Roosevelt, Acting Director, CFSAN Office of Compliance, to Terry Harris, HBB, LLC dba Baked World.....	462
Notes	463
3. Other FDA-Regulated Foods with Special Requirements	466
a. Infant Foods.....	466
b. Medical Foods	466
c. Hypoallergenic Foods	467
d. Diet Foods	468
B. Historical Overview of FDA Regulation of Food Identity, Quality, and Labeling.....	468
C. What's in a Name? Regulation of Food Identity and Quality	475
1. Food Standards of Identity.....	476
a. Strong Standards of Identity: The Filled Milk Act	477
United States v. Carolene Products Co.....	477
Notes	479
Milnot Co. v. Richardson	480
Notes	482
b. The Formation and Zenith of the FD&C Act Food Standards Regime	482
Federal Security Administrator v. Quaker Oats Co.	484
Notes	487
Richard A. Merrill & Earl M. Collier, <i>"Like Mother Used to Make": An Analysis of FDA Food Standards of Identity</i>	488
Notes	489
62 Cases of Jam v. U.S.....	492
Notes	493
c. The Declining Significance of Food Standards.....	494
i. "Safe and Suitable Ingredients"	494
ii. Redefining "Imitation"	495
iii. Rise and Fall of "Alternative"/"Substitute" Nomenclature	495
iv. New Understanding of "Purports to Be"	496
v. The Abandonment of Food Standards as a Primary Vehicle for Fortification and Vitamin/Mineral Supplement Policy	498

2.	The Modern Food-Naming Regime	500
a.	The Persistence of Food Standards.....	500
	Food Standards; General Principles and Food Standards Modernization: Proposed Rule.....	501
	Notes	502
	Notes	504
	<i>Gitson v. Trader Joe's Co.</i>	506
	Notes	508
b.	Regulation of Common or Usual Food Names for Nonstandardized Foods	509
	Common or Usual Names for Nonstandardized Foods.....	510
	21 C.F.R. Part 102—Common or Usual Name for Nonstandardized Foods.....	511
	<i>American Frozen Food Institute v. Mathews</i>	513
	Notes	515
	<i>POM Wonderful LLC v. Coca-Cola Co.</i>	517
	Notes	521
c.	Limited Use of “Imitation”	521
	Imitation Foods, Application of Term “Imitation”: Proposed Rulemaking	522
	Notes	523
	<i>Federation of Homemakers v. Schmidt</i>	524
	Notes	525
d.	The Use of Nutrient Descriptors (“Nutrient Content Claims”) in Food Names	525
	21 C.F.R. § 130.10. Requirements for Foods Named by Use of a Nutrient Content Claim and a Standardized Term.....	526
	Notes	528
3.	Economic Adulteration	529
	<i>United States v. 88 Cases . . . Bireley's Orange Beverage</i>	529
	Notes	531
D.	Regulation of Food Labeling.....	532
1.	“False or Misleading in Any Particular”.....	532
	<i>United States v. Ninety-Five Barrels of . . . Apple Cider Vinegar</i>	533
	<i>United States v. 432 Cartons . . . Candy Lollipops</i>	535
	Notes	536
	<i>United States v. Farinella</i>	537
	Notes	540
2.	Mandatory Information and Disclosures.....	543
a.	Prominence and Conspicuousness	544
	21 C.F.R. Part 101—Food Labeling	544
b.	Net Quantity of Contents.....	545
	Note	546
c.	Ingredient Labeling.....	546
	Notes	547

FDA Response to Petition From Corn Refiners Association to Authorize “Corn Sugar” as an Alternate Common or Usual Name for High Fructose Corn Syrup (HFCS)	550
Notes	552
d. Allergen Disclosure	553
e. Mandatory Warning Statements	555
Food, Drug and Cosmetic Products, Warning Statements (Final Rule)	555
Notes	556
f. Nutrition Facts	559
Notes	560
g. Mandatory Country of Origin Labeling	566
3. Voluntary Claims	567
a. Introduction	567
Lewis A. Grossman, <i>Food, Drugs, and Droods: A Historical Consideration of Definitions and Categories in American Food and Drug Law</i>	567
b. Categories of Claims Related to Health.....	571
c. Nutrient Descriptors (“Nutrient Content Claims”).....	572
21 C.F.R. § 101.62. Nutrient Content Claims for Fat, Fatty Acid, and Cholesterol	573
Notes	574
d. “Healthy” Claims	576
Guidance: Use of the Term “Healthy” in the Labeling of Human Food Products.....	577
Notes	579
e. NLEA Disease Prevention Claims (“Unqualified Health Claims”).....	579
Food Labeling; General Requirements for Health Claims for Food (Final Rule)	582
Notes	584
f. Structure/Function Claims	590
Regulations on Statements Made for Dietary Supplements Concerning the Effect of the Product on the Structure or Function of the Body (Proposed Rule).....	592
21 CFR § 101.93. Certain Types of Statements for Dietary Supplements	595
Notes	596
Dachauer v. NBTY, Inc.	600
g. Other Common Voluntary Food Claims	604
i. “Natural”	604
Scholder v. Riviana Foods.....	604
Notes.....	607

ii. "Fresh"	608
iii. "Organic"	609
Notes	610
h. FTC Regulation of Food Advertising	612
Note	614
4. The First Amendment and Food Labeling	614
a. Introduction	614
b. Disease Prevention Claims Based on Credible Scientific Evidence ("Qualified Health Claims")	615
Pearson v. Shalala	616
Whitaker v. Thompson	620
Fleminger v. HHS	624
Notes	627
c. The First Amendment and Mandatory Information in Food Labeling	628
American Meat Institute v. USDA	629
Note	632
5. Labeling of Genetically Modified Foods	632
Food and Drug Administration, Statement of Policy: Foods Derived From New Plant Varieties	633
Alliance for Bio-Integrity v. Shalala	634
Agricultural Marketing Service, National Bioengineered Food Disclosure Standard (Final Rule)	637
Note	640
International Dairy Foods Association v. Amestoy	640
Notes	644
E. Food Sanitation and Aesthetic Adulteration	646
1. "Filthy, Putrid, or Decomposed Substance"	647
United States v. 1,500 Cases More or Less, Tomato Paste	647
Notes	650
Natural or Unavoidable Defects in Food for Human Use That Present No Health Hazard: Public Availability of Information (Proposed Rule)	651
Notes	652
<i>Melvin J. Hinich & Richard Staelin, Regulation of the U.S. Food Industry</i>	654
Notes	655
United States v. 1,200 Cans . . . Pasteurized Whole Eggs, etc.	656
Note	659
2. "Prepared Under Insanitary Conditions . . . Whereby It May Have Become Contaminated with Filth"	659
Berger v. United States	660
Notes	662
3. "Otherwise Unfit for Food"	663
United States v. 298 Cases . . . Ski Slide Brand Asparagus	663
Notes	664

F.	The Presence of Poisonous or Deleterious Substances	666
1.	Introduction to FDA's Regulation of the Safety of Food Constituents	666
2.	Nonadded Substances and the "Ordinarily Injurious" Standard	670
	United States v. 1232 Cases American Beauty Brand Oysters	670
	Notes	672
3.	Added Substances and the "May Render Injurious" Standard	673
	United States v. Lexington Mill & Elevator Co.	674
	Notes	676
	United States v. Anderson Seafoods, Inc.	677
	Notes	680
	Continental Seafoods v. Schweiker	681
	Notes	684
4.	Tolerances and Action Levels for Unavoidable Poisonous or Deleterious Substances	687
a.	Section 406 Tolerances	687
b.	Action Levels: Legal Basis and Procedure	689
	Poisonous or Deleterious Substances in Food: Notice of Proposed Rulemaking	689
	Note	691
	Young v. Community Nutrition Institute	692
	Note	695
c.	Action Levels: The Example of Mercury	696
	Action Level for Mercury in Fish and Shellfish: Notice of Proposed Rulemaking	696
	Notes	697
d.	The Question of Blending	699
	Note	699
G.	Regulation of Food Production and the Problem of Pathogenic Microorganisms	700
1.	Introduction	700
	Enhancing Food Safety: The Role of the Food and Drug Administration	702
	Note	704
	Background on the FDA Food Safety Modernization Act	704
	Notes	707
2.	Good Manufacturing Process (GMP) Regulations	710
	United States v. Nova Scotia Food Products Corp.	712
	Notes	714
3.	Mandatory Pasteurization	716
	Requirements Affecting Raw Milk for Human Consumption in Interstate Commerce: Final Rule	716
	Notes	721
4.	Emergency Permit Control	722
	Notes	723

5.	Hazard Analysis and Critical Control Points (HACCP)	724
	Food and Drug Administration Development of Hazard	
	Analysis Critical Control Points for the Food Industry:	
	Advanced Notice of Proposed Rulemaking	724
	Notes	730
H.	Intentional Functional Ingredients	732
1.	Introduction	732
	Investigation of the Use of Chemicals in Foods and	
	Cosmetics	732
	Food Additives Amendment of 1958	733
	Note	735
2.	Food Additive Approval	735
	21 C.F.R. § 172.867. Olestra.....	737
	Marion Nestle, <i>The Selling of Olestra</i>	738
	Henry I. Miller, <i>Who Is Trying to Kill Olestra? and Why?</i>	741
	Notes	742
	Notes: Specific Additives	745
3.	The Meaning of “Food Additive”	747
	United States v. An Article of Food . . . FoodScience Labs.....	749
	United States v. Two Plastic Drums . . . Black Currant Oil	751
	Notes	752
	National Nutritional Foods Ass'n v. Kennedy.....	753
	Notes	755
4.	The Deterioration of the Food Additive Approval Process	755
	Peter Barton Hutt, <i>Regulation of Food Additives in the United States</i>	755
	Note	757
5.	Procedures for Establishing Generally Recognized as Safe	
	(GRAS) Status	757
	a. FDA GRAS Lists.....	757
	b. Voluntary GRAS Notice	758
	c. Self-Determination (Independent Conclusion) of GRAS	
	Status	759
	Ctr. for Food Safety v. Becerra	761
	Notes	765
6.	Substantive Criteria for GRAS Status	766
	Substances Generally Recognized as Safe.....	766
	Notes	769
	United States v. An Article of Food . . . Coco Rico, Inc.....	771
	Notes	772
	Fmali Herb, Inc. v. Heckler	773
	Notes	775
	Agency Response Letter GRAS Notice No. 000737, From	
	Dennis M. Keefe, Director, CFSAN Office of Food	
	Additive Safety to Gary Yingling	775
	Note	777

Warning Letter from Joann M. Givens, Acting Director, CFSAN Office of Compliance, to Jaisen Freeman et al., Phusion Projects, LLC	777
Note	779
7. Loss of GRAS Status	780
Final Determination Regarding Partially Hydrogenated Oils	780
Notes	784
8. The GRAS Presumption for Genetically Modified Ingredients	784
FDA Statement of Policy: Foods Derived From New Plant Varieties	785
Notes	789
Alliance for Bio-Integrity v. Shalala	789
Notes	790
9. Prior Sanctioned Substances	792
Proposal Regarding Regulation of Prior-Sanctioned Food Ingredients	792
Notes	793
10. Food Packaging and Processing Substances	795
Natick Paperboard Corp. v. Weinberger	797
Monsanto Co. v. Kennedy	799
Notes	803
11. Color Additive Regulation	806
a. Historical Background	806
b. The Color Additives Amendment	807
Notes	808
Kalsec, Inc., Citizen Petition Requesting FDA to Enforce Ban on Carbon Monoxide Gas in Fresh Meat Packaging	810
Notes	814
FD&C Yellow No. 5: Labeling in Food and Drugs for Human Use	815
Notes	816
12. Dietary Ingredients in Dietary Supplements	817
Notes	818
Nutraceutical Corporation v. Von Eschenbach	820
Notes	823
13. Animal Drug Residues	824
14. Pesticide Residues	825
Notes	826
Notes	828
Chapter 6. Human Drugs.....	831
A. Historical Background	831
1. Drug Regulation Before the 1938 FD&C Act	831
Note	832

2. Drug Regulation Under the 1938 FD&C Act and 1962 Amendments.....	832
Note	834
3. Regulation of Drug Efficacy: History and Policy	834
American School of Magnetic Healing v. McAnnulty	835
Research Laboratories, Inc. v. United States.....	839
Rutherford v. United States	842
Notes	844
Abigail Alliance v. Von Eschenbach.....	846
Note	853
B. The Concept of a “New Drug”	853
1. GRAS/GRAE Status	854
Weinberger v. Hynson, Westcott & Dunning, Inc.....	854
Notes	858
2. The “Grandfather” Clauses	859
3. Jurisdiction to Determine New Drug Status.....	860
Weinberger v. Bentex Pharmaceuticals, Inc.	860
Note	862
C. Drug Development and FDA Approval of New Drugs.....	863
Richard Merrill, <i>The Architecture of Government Regulation of Medical Products</i>	863
Notes	865
1. Drug Discovery and Nonclinical Testing	865
Amy M. Avila et al., <i>An FDA/CDER perspective on nonclinical testing strategies: Classical toxicology approaches and new approach methodologies (NAMs)</i>	866
Notes	868
2. Clinical Testing	870
Notes	871
a. The Investigational New Drug Application (IND)	871
i. The IND Requirement.....	871
Notes.....	873
ii. Human Subject Protection	874
Note	875
(a) Informed Consent	875
21 C.F.R. § 50.25. Elements of Informed Consent.....	876
Notes.....	877
(b) Institutional Review Board Review.....	879
Notes	880
iii. Clinical Testing Outside the United States.....	881
Note	882
b. The Clinical Program	883
i. The Testing Sequence	883
Guidance for Industry, Investigators, and Reviewers: Exploratory IND Studies.....	884
Notes.....	886
ii. Protocol Amendments	887

iii.	Clinical Trial Design	887
(a)	The “Adequate and Well-Controlled” Investigation	887
	21 C.F.R. § 314.126. Adequate and Well- Controlled Studies	887
	Notes.....	889
(b)	Clinical Endpoints and Surrogate Endpoints	891
	James Bilstad, M.D., “Surrogate Endpoints”	892
	Notes.....	894
iv.	Subpopulations	895
(a)	Children.....	896
	Note	899
(b)	The Elderly.....	899
(c)	Subjects with Childbearing Potential	900
(d)	Racial and Ethnic Diversity.....	901
	Notes.....	901
v.	Meetings with FDA and Special Protocol Assessments.....	902
(a)	Meetings	902
	Guidance for Industry and Review Staff: Best Practices for Communication Between IND Sponsors and FDA During Drug Development.....	902
	Draft Guidance for Industry: Formal Meetings Between the FDA and Sponsors or Applicants of PDUFA Products	903
	Notes.....	905
(b)	Special Protocol Assessment	906
	Guidance for Industry: Special Protocol Assessment.....	907
	Note	909
vi.	Data Monitoring Committees	909
	Guidance for Clinical Trial Sponsors: Establishment and Operation of Clinical Trial Data Monitoring Committees	910
	Notes.....	911
c.	FDA Oversight.....	911
i.	Reporting and Recordkeeping.....	911
ii.	The Clinical Hold.....	911
	Notes.....	912
iii.	Investigator Non-Compliance and Fraud	913
	Notes.....	914
iv.	Inspections	914
v.	Good Manufacturing Practice	915
	Note	916
vi.	Clinical Trial Registration and Results Reporting	916
3.	The New Drug Application	918
a.	Preparation and Submission of the NDA	918

i.	Content of the NDA	918
	New Drug Application (NDA)	918
	Notes.....	920
ii.	User Fees	922
	Congressional Research Service, FDA Human Medical Product User Fee Programs.....	923
	Notes.....	926
iii.	The Filing Decision.....	926
	Notes.....	926
b.	FDA's Review Process	927
i.	Deadline for Decision	927
ii.	Agency Review Process	928
	Notes.....	930
iii.	Advisory Committee Review.....	930
	Peter Barton Hutt, <i>The Regulation of Drug Products by the United States Food and Drug Administration</i>	931
	Note	931
c.	The Approval Decision	932
i.	The Safety Standard	932
	Testimony of FDA Commissioner George Lerrick	932
	Michael A. Friedman et al., <i>The safety of newly approved medicines: do recent market removals mean there is a problem?</i>	934
	Managing the Risks from Medical Product Use: Report to the FDA Commissioner from the Task Force on Risk Management	934
	Scott Gottlieb, M.D., <i>The Price of Too Much Caution</i>	935
	Notes.....	936
ii.	The Effectiveness Standard	938
	Notes.....	941
iii.	Balancing Benefit and Risk	944
	Testimony of FDA Commissioner George Lerrick	944
	Kathleen Miller, PhD & Janet Woodcock, MD, <i>Value Assessment in the Regulatory Context</i>	945
	Notes.....	947
iv.	Labeling Review	949
	House of Representatives.....	949
v.	Final Approval or Denial	951
	Ubiotica Corp. v. FDA	952
	Notes.....	953
4.	The Impact of the 1962 Amendments.....	956
	Richard Merrill, <i>The Architecture of Government Regulation of Medical Products</i>	956
a.	Impact on Innovation	957
	Statement of Sam Peltzman	957
	Notes	960

b.	The Risk, Duration, and Cost of New Drug Research and Development	960
i.	The Risk	960
ii.	The Duration	961
iii.	The Cost	963
D.	Variations on, and Exceptions to, the Standard Drug Development and Approval Process	964
1.	Expediting Development and Approval of Drugs for Serious Conditions	964
a.	Fast Track	965
i.	The FDA Regulations (“Subpart E”)	965
	Investigational New Drug, Antibiotic, and Biological Drug Product Regulations: Procedures for Drugs Intended to Treat Life-Threatening and Severely Debilitating Illnesses	965
ii.	The Statute	966
	Notes	967
b.	Breakthrough Therapy	967
	Notes	968
c.	Accelerated Approval	968
	Note	969
i.	Approval Based on a Surrogate Endpoint	969
	Findings; Sense of Congress	970
	Julia A. Beaver, MD, et al., <i>A 25-Year Experience of US Food and Drug Administration Accelerated Approval of Malignant Hematology and Oncology Drugs and Biologics: A Review</i>	972
	Notes	974
ii.	Approval Conditioned on Restricted Distribution	975
d.	Priority Review	976
	CDER Manual of Policies and Procedures 6020.3 Rev.2	
	Review Designation Policy: Priority (P) and Standard (S)	976
	Notes	978
e.	Limited Population Pathway for Antibacterial and Antifungal Drugs	979
2.	Use of Investigational New Drugs for Therapy	980
a.	Introduction	980
	Notes	982
b.	Types of Expanded Access Programs	986
i.	Individual Patient IND or Protocol	986
	Notes	986
ii.	Emergency Use IND or Protocol	987
iii.	Intermediate-Size Patient Population IND or Protocol	987
	Note	988
iv.	Treatment IND or Protocol	988
	Notes	989
v.	Promoting and Charging for Expanded Access	990

c.	The Right-to-Try Laws.....	991
	Note	993
3.	Emergency Use Authorization	993
	Notes	994
4.	Unapproved Prescription Drugs.....	995
a.	Pre-1962 DESI Drugs.....	995
i.	Marketing of Drugs Under the 1938 FD&C Act.....	995
	Note	996
ii.	The 1962 Drug Amendments and the NAS Review	996
iii.	The Commencement of NDA-Withdrawal Proceedings	998
iv.	Manufacturers Challenge DESI in Court	999
v.	Finding a Path Forward for “Me-Too” Drugs	1000
vi.	The Elusive Goal of DESI Completion	1003
	Notes.....	1004
b.	Non-DESI Unapproved Prescription Drugs	1004
	Notes	1008
5.	Traditional Exceptions to the NDA Requirement.....	1010
a.	Homeopathic Drugs.....	1010
	Note	1012
b.	Traditional Chinese Medicine	1012
6.	The Practice of Pharmacy.....	1012
	FDA’s Oversight of NECC and Ameridose: A History of Missed Opportunities	1013
	Guidance: Pharmacy Compounding of Human Drug Products Under Section 503A of the Federal Food, Drug, and Cosmetic Act.....	1016
	Notes	1019
7.	Other Special Situations.....	1020
a.	Radiopharmaceutical Drugs	1020
	Guidance: Compounding and Repackaging of Radiopharmaceuticals by Outsourcing Facilities.....	1020
	Syncor International Corporation v. Shalala	1023
	Notes	1026
b.	Botanical Drugs.....	1027
c.	Medical Gas	1027
d.	Insulin and Antibiotic Drugs (Historically)	1027
	Note	1028
e.	Importation of Unapproved New Drugs	1028
	Coverage of Personal Importations	1030
	Notes	1032
8.	Modernizing the Drug Development and Approval Process	1034
	Advancing Regulatory Science at FDA: Focus Areas of Regulatory Science	1034
	Paving the Way for Personalized Medicine: FDA’s Role in a New Era of Medical Product Development.....	1037
	Notes	1038

E.	Prescription Status and Other Restrictions on Distribution	1039
1.	Limitation to Prescription Sale	1039
a.	Legal Basis.....	1039
	Peter Temin, <i>The Origin of Compulsory Drug Prescriptions</i>	1040
	United States v. El-O-Pathic Pharmacy	1041
	Notes	1044
b.	Authority to Prescribe and the Requirement of a Valid Prescription	1045
	Notes	1047
2.	Scheduled Prescription Drugs.....	1047
a.	Cannabis and Its Derivatives	1048
	Note	1050
b.	The Opioid Crisis.....	1051
	Notes	1052
3.	The (Non)Regulation of the Practice of Medicine	1053
a.	Development of FDA's Practice of Medicine Policy.....	1054
	New Drugs Used for Nonapproved Purposes (Methotrexate for Psoriasis)	1055
	Legal Status of Approved Labeling for Prescription Drugs; Prescribing for Uses Unapproved by the Food and Drug Administration: Notice of Proposed Rule Making	1056
	Notes	1058
	United States v. Evers	1062
	Note	1066
4.	Use and Distribution Restrictions Imposed by FDA	1066
a.	Before 2007	1066
	American Pharmaceutical Association v. Weinberger.....	1066
	Notes	1069
	Speech by Scott Gottlieb, M.D., Before the American Medical Association	1071
b.	Risk Evaluation and Mitigation Strategies (REMS)	1072
	Risk Evaluation and Mitigation Strategy (REMS) Document	1074
	Notes	1075
F.	Physician Labeling and Patient Labeling for Prescription Drugs....	1076
1.	Physician Labeling (Prescribing Information)	1076
a.	Purpose and Content.....	1076
	Notes	1079
b.	Safety-Related Language.....	1081
	Bradley v. Weinberger	1083
	Notes	1085
	Labeling: Failure to Reveal Material Facts.....	1086
	Notes	1087
c.	Drug Names.....	1089
i.	The Nonproprietary Name.....	1089
	Administered Prices—Drugs	1090
	Notes.....	1091

ii.	Proprietary Names	1092
	Notes.....	1092
2.	Patient Labeling for Prescription Drugs	1093
a.	Mandatory Patient Labeling: Patient Package Inserts (PPIs).....	1094
	Statement of Policy Concerning Oral Contraceptive Labeling Directed to Users	1094
	Note	1097
	Pharmaceutical Manufacturers Association v. FDA.....	1097
	Notes	1100
b.	The Rise of Voluntary Patient Labeling	1100
	Prescription Drug Products: Patient Labeling Requirements.....	1101
	Prescription Drug Products: Revocation of Patient Package Insert Requirements.....	1102
	Notes	1104
c.	Modern Mandatory Patient Labeling: Medication Guides	1104
	Note	1105
G.	After NDA Approval	1106
1.	Establishment Registration and Drug Product Listing	1106
	Notes	1106
2.	Adverse Event Reporting and Other Postmarket Monitoring	1107
	Notes	1108
3.	Supplemental NDAs (sNDAs)	1109
4.	Postmarket Testing	1110
	Guidance for Industry: Postmarketing Studies and Clinical Trials—Implementation of Section 505(o)(3) of the Federal Food, Drug, and Cosmetic Act	1112
	Note	1113
5.	Safety-Related Labeling Changes	1113
	Notes	1114
6.	Good Manufacturing Practices (GMPs)	1115
a.	Background	1115
	United States v. An Article of Drug . . . White Quadrisect	1115
	Human and Veterinary Drugs: Current Good Manufacturing Practice in Manufacture, Processing, Packing, or Holding	1117
	Notes	1119
b.	Enforcement.....	1120
	United States v. Barr Laboratories, Inc.	1121
c.	Modernization.....	1123
	Pharmaceutical CGMPs for the 21st Century: A Risk- Based Approach	1123
	Notes	1125

7.	Voluntary Withdrawal from the Market	1126
	Statement of Sandra L. Kweder, Deputy Director, CDER	
	Office of New Drugs	1127
	Bernadine Healy, M.D., <i>What Is a ‘Safe’ Drug?</i>	1128
	Notes	1129
8.	Withdrawal of NDA Approval	1130
	Weinberger v. Hynson, Westcott & Dunning, Inc.	1130
	Notes	1133
9.	Summary Ban Based on an “Imminent Hazard”	1134
	Forsham v. Califano.....	1135
	Notes	1139
H.	Communicating About Prescription Drugs	1141
1.	Introduction.....	1141
2.	Advertising and Promotion to Healthcare Professionals	1142
a.	Advertising to Healthcare Professionals	1142
	21 C.F.R. § 202.1. Prescription-Drug Advertisements....	1142
	Notes	1145
b.	Labeling	1147
	Note	1148
3.	Direct-to-Consumer Promotion	1149
a.	Print Advertising to Consumers.....	1149
	Direct-to-Consumer Advertising of Prescription Drugs;	
	Withdrawal of Moratorium	1149
	Notes	1150
b.	Broadcast Advertising.....	1150
	Draft Guidance for Industry: Consumer-Directed	
	Broadcast Advertisements	1151
	Guidance for Industry: Consumer-Directed Broadcast	
	Advertisements.....	1152
	Notes	1153
	Warning Letter From Thomas Abrams, Dir., DDMAC to	
	Reinhard Franzen, Pres. & CEO, Bayer HealthCare	
	Pharmaceuticals, Inc.....	1154
c.	General Issues Relating to Promotion to Consumers	1158
	Keeping Watch Over Direct-to-Consumer Ads.....	1158
	Notes	1159
4.	Communications About Off-Label Uses	1161
a.	Off-Label Promotion in Labeling.....	1163
b.	Off-Label Promotion in Advertising.....	1164
c.	Off-Label Promotion in Oral Statements and FDA’s	
	“Squeeze Play”	1164
i.	The “Squeeze Play” in the OTC Context.....	1165
	U.S. v. Articles of Drug . . . Foods Plus	1165
	Notes.....	1168
ii.	The “Squeeze Play” in the Prescription Context	1169
	Memorandum of Law in Support of Motion for	
	Preliminary Injunction.....	1170

d.	The Government's Use of Other Statutes to Enforce the Prohibition Against Off-Label Promotion	1171
	United States ex rel. Franklin v. Parke-Davis	1172
	Notes	1175
e.	Permitted Communication About Unapproved Uses.....	1176
i.	Scientific Exchange and Disclosures Required by Law	1177
ii.	Responses to Unsolicited Requests for Information	1177
	Draft Guidance for Industry: Responding to Unsolicited Requests for Off-Label Information About Prescription Drugs and Medical Devices.....	1178
	Note	1180
iii.	Distribution of Scientific Literature About Unapproved Uses.....	1181
	Washington Legal Foundation v. Henney	1182
	Note	1186
	Revised Draft Guidance for Industry: Distributing Scientific and Medical Publications on Unapproved New Uses—Recommended Practice.....	1188
	Note	1192
iv.	The Full Extent of First Amendment Protection	1192
	United States v. Caronia	1192
	Amarin Pharma, Inc. v. U.S. Food and Drug Administration.....	1200
	Notes.....	1203
5.	Preapproval Promotion	1206
6.	Other Regulators	1207
	FDA and SEC Work to Enhance Public's Protection From False and Misleading Statements	1207
7.	Relationships with Healthcare Professionals	1207
	Notes	1209
I.	Over-the-Counter Drugs.....	1210
1.	Distinguishing Between Prescription and OTC Drugs.....	1210
	United States v. Article of Drug . . . “Decholin”	1210
	Note	1213
	Peter Barton Hutt, <i>A Legal Framework for Future Decisions on Transferring Drugs From Prescription to Nonprescription Status</i>	1214
	Notes	1216
2.	Switches from Prescription to Nonprescription Status	1217
	Notes	1220
	Tummino v. Hamburg	1222
	Notes	1229
3.	The OTC Drug Review	1230
a.	Rationale for and Procedures of the Original OTC Drug Review	1230

	Over-the-Counter Drugs: Proposal Establishing Rule	
	Making Procedures for Classification	1231
	Elizabeth Guo, Richard Kingham, & David Spangler, <i>An Unofficial Legislative History of Over-the-Counter Monograph Reform</i>	1232
	Notes	1235
b.	Modernization of the OTC Drug Review	1239
	Over-the-Counter Drug Monograph System—Past, Present, and Future; Public Hearing	1239
	Note	1241
4.	OTC Drug Labeling and Advertising	1242
a.	OTC Drug Review Restrictions	1242
	Labeling of Drug Products for Over-the-Counter Human Use	1242
	Notes	1243
b.	OTC “Drug Facts”	1244
	Over-the-Counter Human Drugs; Proposed Labeling Requirements.....	1244
c.	OTC Drug Label Warnings.....	1246
	Notes	1247
d.	FTC Regulation of OTC Drug Advertising	1247
	Notes	1249
5.	OTC Drug Product Packaging	1249
	Tamper-Resistant Packaging Requirements for Certain Over-the-Counter Human Drug and Cosmetic Products	1250
	Notes	1251
J.	Generic Drugs	1253
1.	Generic Drugs Before the Hatch-Waxman Amendments (1984)	1253
	a. Copies of Pre-1962 Drugs	1253
	Hoffmann-LaRoche, Inc. v. Weinberger.....	1254
	Note	1256
	b. Copies of Post-1962 Drugs	1256
	Note	1258
	United States v. Generix Drug Corp.....	1258
2.	The Drug Price Competition and Patent Term Restoration Act (Hatch-Waxman Amendments) of 1984	1261
	a. Enactment of the Hatch-Waxman Framework	1261
	Notes	1263
	b. Abbreviated Applications.....	1264
	Notes	1264
	i. The ANDA.....	1265
	Note	1266
	(a) Sameness.....	1266
	Serono Laboratories, Inc. v. Shalala	1266
	Notes.....	1270
	(b) Bioequivalence	1272
	Notes	1273

ii.	The 505(b)(2) Application.....	1274
	Notes.....	1275
c.	Timing of Approval.....	1275
i.	Patent Term Restoration	1276
	Notes.....	1277
ii.	Patent Litigation	1279
	Notes.....	1281
iii.	Statutory Exclusivity	1284
	Notes.....	1284
3.	The Orange Book and the Multisource Marketplace.....	1289
	Note.....	1291
K.	Innovation and Access Issues.....	1292
1.	Additional Incentives for Innovation	1293
a.	Orphan Drug Exclusivity.....	1293
	Genentech, Inc. v. Bowen.....	1294
	Notes	1299
	Marlene E. Haffner, <i>Adopting Orphan Drugs—Two Dozen Years of Treating Rare Diseases</i>	1301
	Notes	1303
b.	Pediatric Exclusivity	1304
	Notes	1305
c.	Antibiotic Exclusivity	1306
	(FDA) Report to Congress: Generating Antibiotic Incentives Now	1306
	Notes	1308
d.	Tropical Diseases, Rare Pediatric Diseases, and Medical Countermeasure Priority Review Vouchers	1308
	Notes	1309
2.	Addressing Affordability.....	1309
a.	Concerns About Drug Prices.....	1309
	Notes	1313
b.	Encouraging Development and Uptake of Generic Drugs.....	1314
	FDA Tackles Drug Competition to Improve Patient Access	1315
	Guidance for Industry: Competitive Generic Therapies....	1316
	Note	1317
c.	Recent Controversies	1317
	FTC v. Actavis, Inc.....	1318
	Note	1324
	New York ex rel. Schneiderman v. Actavis PLC	1325
	Notes	1331
3.	Protecting the Supply of Drugs	1333
a.	Drug Shortages.....	1333
	Drug Shortages: Root Causes and Potential Solutions: A Report by the Drug Shortages Task Force.....	1333
	Note	1337

b.	Supply Chain Security: Counterfeit and Diverted Drugs.....	1337
	Notes	1340
L.	FDA Regulation and State Tort Law	1342
1.	Failure to Warn: Learned Intermediary Doctrine and Exceptions.....	1342
	MacDonald v. Ortho Pharmaceutical Corporation	1343
	Notes	1348
2.	Federal Preemption	1348
	Wyeth v. Levine.....	1348
	Note.....	1361
	PLIVA, Inc. v. Mensing.....	1361
	Notes	1371
Chapter 7. Food and Drugs for Animals.....		1375
A.	Introduction.....	1375
	Notes	1375
B.	Animal Food and Feed.....	1375
	Notes	1376
1.	Pet Food	1377
	United States v. Sally Miller, Stephen S. Miller, and ChemNutra, Inc.....	1377
	Notes	1379
2.	Livestock Feed and the Mad Cow Disease Crisis	1381
	Substances Prohibited From Use in Animal Food or Feed	1382
	Notes	1384
C.	Animal Drugs	1386
1.	New Animal Drug Approval	1386
	Animal Drug Amendments.....	1386
	Eugene I. Lambert, <i>The Reformation of Animal Drug Law: The Impact of 1996</i>	1388
	Notes	1391
2.	The Effectiveness Standard.....	1393
3.	The Safety Standard	1394
	Notes	1395
4.	Prescription Status and Veterinary Feed Directives.....	1396
a.	Prescription Animal Drugs	1396
b.	Veterinary Feed Directive Drugs	1397
	Note	1398
5.	Extra-Label Use of Animal Drugs and Use of Human Drugs in Animals	1398
a.	Extra-Label Use of Animal Drugs in Animals	1398
	Takhar v. Kessler	1399
	United States v. Scenic View Dairy, L.L.C.....	1401
	Notes	1404
b.	Extra-Label Use of Human Drugs in Animals	1405
6.	Animal Drugs for Minor Use and Minor Species	1406
	FDA, Minor Use/Minor Species.....	1406
a.	Conditional Approval	1407

b.	Indexing	1407
c.	Designation	1408
d.	Noneforcement Discretion for Extra-Label/Unapproved Use.....	1408
7.	Animal Drug Compounding.....	1409
	United States v. Franck's Lab, Inc.....	1409
	Notes	1411
8.	The Safety of Antibiotics Used in Livestock Production	1412
	Harold C. Hopkins, <i>Keeping the Kick in Antibiotics</i>	1412
	Antibiotic and Sulfonamide Drugs in the Feed of Animals.....	1413
	Natural Resources Defense Council, Inc. v. Food and Drug Administration	1416
	Guidance for Industry: The Judicious Use of Medically Important Antimicrobial Drugs in Food-Producing Animals	1421
	Notes	1423
	Natural Resources Defense Council v. Food and Drug Administration	1424
	Withdrawal of Approval of the New Animal Drug Application for Enrofloxacin in Poultry: Final Decision of the Commissioner	1426
	Notes	1432
9.	Bioengineered Animals.....	1432
	CVM Draft Guidance for Industry No. 187, Regulation of Intentionally Altered Genomic DNA in Animals	1433
	Notes	1435
	Institute for Fisheries Resources v. FDA	1437
10.	Xenotransplantation	1438
	Roni Caryn Raybin, <i>Breakthrough on Pig Organs in Transplants</i>	1439
Chapter 8. Biological Products		1441
A.	Historical Background	1441
1.	Early Biologics Regulation	1441
	Notes	1443
2.	FDA Acquires Responsibility for Biologics	1443
	Note	1446
3.	The Biologics Review (Pre-1972 Biologics)	1446
	Biological Products: Procedures for Review of Safety, Effectiveness, and Labeling	1447
	Reclassification Procedures to Determine That Licensed Biological Products are Safe, Effective, and Not Misbranded Under Prescribed, Recommended, or Suggested Conditions of Use; Proposed Revision	1449
	Notes	1451
	Licensing; Reclassification Procedures To Determine That Licensed Biological Products Are Safe, Effective, and Not Misbranded Under Prescribed, Recommended or Suggested Conditions of Use	1452

Notes	1454
4. The Modern Era	1455
Reinventing Regulation of Drugs Made From Biotechnology ...	1457
Elimination of Establishment License Application for Specified Biotechnology and Specified Synthetic Biological Products.....	1457
Biological Products Regulated Under Section 351 of the Public Health Service Act; Implementation of Biologics License; Elimination of Establishment License and Product License	1459
Transfer of Therapeutic Products to the Center for Drug Evaluation and Research (CDER).....	1460
Notes	1461
B. Therapeutic Biologics Regulated by CDER.....	1463
1. The Biologics License Application.....	1463
Note.....	1465
2. The Biosimilar Application.....	1466
a. Development and Approval of a Biosimilar Biological Product.....	1468
Guidance for Industry: Scientific Considerations in Demonstrating Biosimilarity to a Reference Product	1468
Notes	1472
b. Demonstrating Interchangeability.....	1473
Guidance for Industry: Considerations in Demonstrating Interchangeability With a Reference Product	1474
Notes	1475
c. Naming and Labeling of Biological Products, Including Biosimilar Biologics.....	1475
i. Naming.....	1475
Guidance for Industry: Nonproprietary Naming of Biological Products	1476
Note	1478
ii. Labeling	1478
Notes.....	1479
d. Exclusivity and Patents	1479
i. Exclusivity Provisions	1480
Notes.....	1481
ii. Patent Litigation	1482
Sandoz v. Amgen	1483
Notes.....	1487
C. Vaccines	1489
Notes	1490
1. Premarket Development and Licensure	1490
Notes	1491
2. Postmarket Regulation	1493
Note	1494

3.	The Fragility of the U.S. Vaccine Supply	1494
	Paul Offit, <i>The Cutter Incident: How America's First Polio Vaccine Led to the Growing Vaccine Crisis</i>	1494
	Gottsdanker v. Cutter Laboratories.....	1496
	Reyes v. Wyeth Laboratories.....	1499
	Note.....	1504
	Berkovitz v. United States	1505
	Note.....	1509
	Institute of Medicine, <i>Financing Vaccines in the 21st Century: Assuring Access and Availability</i>	1510
4.	Policy Solutions	1512
	Michael Greenberger, <i>The 800 Pound Gorilla Sleeps: The Federal Government's Lackadaisical Liability and Compensation Policies in the Context of Pre-Event Vaccine Immunization Programs</i>	1512
	Notes	1516
	Note.....	1517
D.	Blood and Blood Products.....	1518
1.	History of FDA Jurisdiction	1518
2.	The Regulatory Mechanism.....	1520
	Notes	1521
3.	Protecting the Safety of the Blood Supply.....	1523
	Adequacy of the National Blood Supply: Report to Congress.....	1523
	Note.....	1526
a.	The Five Layers of Blood Safety.....	1526
	Keeping Blood Transfusions Safe: FDA's Multi-Layered Protections for Donated Blood	1526
b.	Testing Blood and Screening Donors	1528
	Snyder v. American Association of Blood Banks.....	1528
	R.F. and R.F. v. Abbott Laboratories	1535
	Note	1539
	Guidance: Revised Recommendations for Reducing the Risk of Human Immunodeficiency Virus Transmission by Blood and Blood Products	1539
	Notes	1543
E.	Regenerative Medicine	1544
1.	Whole Organ Transplants	1544
	Statement by the Food and Drug Administration Concerning Its Legal Authority to Regulate Human Organ Transplants and to Prohibit Their Sale	1545
	Note	1547
2.	Human Cell-Based and Tissue-Based Products: Part 1271	1547
a.	Historical Background	1547
	Richard A. Merrill, <i>Human Tissues and Reproductive Cloning: New Technologies Challenge FDA</i>	1548
	Note	1553

b.	Regulation Under Part 1271	1553
	Human Cells, Tissues, and Cellular and Tissue-Based Products; Establishment Registration and Listing....	1554
	Notes	1555
c.	Identifying Products Regulated Only Under Part 1271	1556
	Guidance: Regulatory Considerations for Human Cells, Tissues, and Cellular and Tissue-Based Products: Minimal Manipulation and Homologous Use	1556
	Notes	1559
3.	Cellular and Gene Therapy Products Subject to Licensure	1560
a.	Stem Cell Therapies.....	1560
	Peter W. Marks, Celia M. Witten, and Robert M. Califf, <i>Clarifying Stem- Cell Therapy's Benefits and Risks</i>	1561
	United States v. Regenerative Sciences, LLC	1563
	Note	1568
b.	(Somatic) Cell Therapy Products	1568
	Note	1569
c.	Gene Therapy Products	1569
	Francis Collins and Scott Gottlieb, <i>The Next Phase of Human Gene-Therapy Oversight</i>	1569
	Note	1572
	Note	1574
d.	Xenotransplantation Products	1574
	Guidance: Source Animal, Product, Preclinical, and Clinical Issues Concerning the Use of Xenotransplantation Products in Humans	1574
4.	(Human) Reproductive Cloning.....	1577
	Richard A. Merrill, <i>Human Tissues and Reproductive Cloning: New Technologies Challenge FDA</i>	1577
	FDA's Jurisdiction Over Human Cloning Activities.....	1580
	Richard A. Merrill, <i>Human Tissues and Reproductive Cloning: New Technologies Challenge FDA</i>	1582
	Notes	1583
5.	The Regenerative Medicine Framework.....	1584
F.	Other Biological Products.....	1585
Chapter 9. Medical Devices		1587
A.	Introduction.....	1587
	Wallace F. Janssen, <i>The Gadgeteers</i>	1587
	Note.....	1588
B.	Regulation of Devices Under the FD&C Act Before 1976	1588
1.	The 1938 Framework	1589
	Medical Device Legislation—1975	1589
2.	Diapulse Litigation	1590
3.	Scientology's E-Meter	1591
	Founding Church of Scientology v. United States	1591
	Notes	1593
4.	Distinguishing Drugs from Devices Before 1976	1595

C. The Medical Device Amendments of 1976.....	1597
1. The Need for Legislation	1597
Medical Device Amendments of 1976	1597
Study Group on Medical Devices, Medical Devices: A Legislative Plan	1598
Notes	1598
2. Overview of the Modern Regime	1599
3. Defining “Device”	1600
a. The Line Between a “Drug” and a “Device”	1600
<i>Genus Medical Technologies LLC v. Food and Drug Administration</i>	1602
Note	1610
b. Drug-Device Combinations.....	1610
<i>PREVOR v. Food and Drug Administration</i>	1611
Notes	1616
c. Diagnostic Devices	1617
D. Classification of Devices into Class I, Class II, or Class III.....	1618
1. Classification Procedures	1618
Medical Devices: Classification Procedures	1618
Note	1619
2. The Classification Regulations.....	1619
21 C.F.R. Part 872—Dental Devices	1620
Notes	1621
E. Changeover Issues: Regulating Pre-1976 Devices Under the 1976 Amendments	1621
1. Equitable Treatment of Old and New Devices	1621
2. Reviewing Preamendment Class III Devices	1622
3. “Transitional” Devices Previously Regulated as Drugs.....	1624
F. Regulation of Market Entry	1625
1. Premarket Notification via the 510(k) Process	1627
a. Background	1627
b. “Substantial Equivalence”	1627
c. “Piggybacking”	1628
d. Exemptions from the 510(k) Requirement	1629
e. Revoking a 510(k) Clearance	1630
<i>Ivy Sports Medicine, LLC v. Burwell</i>	1630
Notes	1637
f. Modified 510(k) Pathways	1638
Notes	1638
g. Reprocessed Single-Use Devices	1642
2. Investigational Devices.....	1643
a. General Requirements	1643
b. Feasibility Studies.....	1644
c. “Research Use Only” Exemption for Diagnostic Devices	1645
Notes	1645
d. Emergency Investigational Use	1646
<i>Cristine Russell, Temporary Heart Implanted: Tucson Operation Lacked FDA Approval</i>	1647

Information Sheet Guidance For IRBs, Clinical Investigators, and Sponsors: Frequently Asked Questions About Medical Devices	1648
e. Emergency Use Authorizations.....	1649
Guidance for Developers and FDA Staff: Policy for Coronavirus Disease-2019 Tests During the Public Health Emergency (Revised).....	1650
Notes	1653
3. Premarket Approval (PMA) Applications.....	1654
a. Comparing PMAs and NDAs.....	1654
Notes	1656
b. Advisory Committee Review.....	1657
c. FDA Action on PMAs	1658
Notes	1659
d. Efforts to Quicken PMA Reviews.....	1660
Notes	1661
e. Postapproval PMA Requirements.....	1662
4. Shortcuts and Exemptions	1663
a. Breakthrough Devices.....	1663
Note	1664
b. In Vitro Diagnostics	1664
c. Humanitarian Device Exemptions.....	1669
Note	1670
d. Custom Devices	1670
Note	1671
5. Reclassification and De Novo Classification	1671
Lake v. FDA.....	1673
Notes	1675
G. Postmarket Regulation of Devices	1676
1. General Controls Applicable to All Devices	1676
a. Adulteration and Misbranding.....	1676
United States v. An Article . . Acu-dot.....	1677
Medical Devices; Labeling for Menstrual Tampons; Ranges of Absorbency; Reproposed Rule	1680
Note	1681
b. Establishment Registration and Product Listing	1682
c. Adverse Event Reporting.....	1682
d. Good Manufacturing Practice (Quality Systems Regulation)	1684
Medical Devices; Current Good Manufacturing Practice (CGMP) Regulations; Proposed Revisions; Request for Comments	1685
Notes	1686
e. Restricted Devices	1688
i. Introduction	1688
ii. Hearing Aids	1689
American Speech and Hearing Ass'n v. Califano	1690
Note	1691
iii. In Vitro Diagnostic Devices	1691

iv.	Cigarettes	1693
	Coyne Beahm, Inc. v. United States Food & Drug	
	Administration.....	1694
	Notes.....	1696
f.	Banned Devices	1696
	Judge Rotenberg Educational Center, Inc. v. FDA	1697
	Note	1705
g.	Administrative Detention	1705
h.	Notification and Repair, Replacement, or Refund	1705
	In re Procter & Gamble Co.: Consent Agreement	1706
	Notes	1706
i.	Postmarket Surveillance.....	1708
j.	Device Tracking.....	1709
k.	Mandatory Recalls.....	1710
l.	Reports of Removals and Corrections	1710
m.	Civil Penalties	1711
2.	Special Controls for Class II Devices	1712
a.	Performance Standards	1712
	i. Introduction	1712
	ii. Voluntary Medical Device Standards.....	1713
b.	Other Special Controls.....	1715
H.	Digital Health Devices	1715
1.	History	1717
	Nathan Cortez, <i>Analog Agency in a Digital World</i>	1717
	Notes	1723
2.	Current Framework	1724
a.	The Scope of FDA Jurisdiction over Software	1724
	Guidance for Industry and FDA Staff: Policy for Device	
	Software Functions and Mobile Medical	
	Applications	1725
	Notes	1730
b.	Regulatory Expectations for Software	1731
3.	The Digital Health Action Plan.....	1733
a.	Pre-Market to Post-Market Evidence Gathering	1734
b.	From Product-Level to Firm-Level Oversight	1735
c.	Third-Party Reviews	1736
	Notes	1736
I.	Radiation Control.....	1737
1.	Performance Standards	1737
	Electronic Products; Performance Standard for Diagnostic	
	X-Ray Systems and Their Major Components	
	(Final Rule)	1738
	Notes	1739
	Sunlamp Products; Performance Standard	1741
	Notes	1742
2.	Enforcement of Radiation Standards.....	1743
3.	Collection and Dissemination of Information	1744
4.	Other Federal Radiation Control Programs	1745

J. Preemption of State Law	1746
1. Preemption Under the 1976 Medical Device Amendments	1746
Exemptions From Federal Preemption of State and Local Device Requirements	1747
Notes	1748
2. Medtronic v. Lohr	1748
Medtronic, Inc. v. Lohr	1749
Notes	1756
3. Riegel v. Medtronic	1757
Riegel v. Medtronic, Inc.	1757
Notes	1760
Chapter 10. Cosmetics.....	1763
A. Historical and Statutory Background	1763
Peter Barton Hutt, <i>A History of Government Regulation of Adulteration and Misbranding of Cosmetics</i>	1763
Personal Care Products Council, Driving the Economy, Shaping the Future.....	1764
Senate Report No. 361	1765
Notes	1766
George P. Larrick, <i>Some Current Problems in the Regulation of Cosmetics Under the Federal Food, Drug, and Cosmetic Act</i>	1766
Investigation of the Use of Chemicals in Foods and Cosmetics.....	1767
S. L. Mayham, <i>Chemicals in Cosmetics</i>	1769
U.S. General Accounting Office, Lack of Authority Hampers Attempts to Increase Cosmetic Safety	1770
Statement of the Cosmetic, Toiletry and Fragrance Association, Inc.....	1772
Notes	1774
B. Definition of “Cosmetic”	1775
C. Adulterated Cosmetics	1775
United States v. An Article of Cosmetic . . . “Beacon Castile Shampoo”	1775
Notes	1777
Aerosol Drug and Cosmetic Products Containing Zirconium	1779
Notes	1780
Nitrosamine-Contaminated Cosmetics; Call for Industry Action; Request for Data	1782
Notes	1782
D. Coal-Tar Hair Dyes	1787
Toilet Goods Association v. Finch	1787
Notes	1789
E. The Scope of the Color Additive Amendments.....	1790
F. Misbranded Cosmetics.....	1790
1. Label Warnings	1790
Preservation of Cosmetics Coming in Contact With the Eye: Intent to Propose Regulations and Request for Information	1790
Notes	1791

Food, Drug, and Cosmetic Products: Warning Statements.....	1792
Notes	1795
2. Misleading Labeling.....	1796
Almay, Inc. v. Califano.....	1796
Note.....	1798
Peter Barton Hutt, <i>The Legal Distinction in the United States Between a Cosmetic and a Drug</i>	1799
Notes	1800
G. Cosmetic Ingredient Labeling	1801
Cosmetic Ingredient Labeling	1801
Notes	1802
H. Voluntary Self-Regulation of Cosmetics	1804
Voluntary Registration of Cosmetic Product Establishments;	
Voluntary Filing of Cosmetic Product Ingredient and Cosmetic Raw Material Composition Statements	1805
Voluntary Filing of Cosmetic Product Experiences	1805
Notes	1806
Robert L. Elder, <i>The Cosmetic Ingredient Review—A Safety Evaluation Program</i>	1808
Statement of Robert L. Elder, SC.D.	1810
Wilma F. Bergfeld et al., <i>Safety of Ingredients Used in Cosmetics</i>	1811
Letter From Ronald G. Chesemore, Associate Commissioner for Regulatory Affairs, FDA, to Consumer Federation of America	1812
Note.....	1813
Letter From Robert E. Brackett, Director, FDA Center for Food Safety and Applied Nutrition, to CTFA.....	1813
Notes	1814
I. The Present and Future of Cosmetics Regulation	1815
Peter Barton Hutt, “Examining the Current State of Cosmetics”....	1815
J. The Draft Modernization of Cosmetics Regulation Act of 2022	1817
Chapter 11. Tobacco Products	1819
A. Introduction.....	1819
B. Efforts to Regulate Tobacco Products Under the FD&C Act	
Before 2009.....	1820
Food and Drug Administration v. Brown & Williamson Tobacco Corp.....	1822
C. The Family Smoking Prevention and Tobacco Control Act	1827
1. The Line Between Tobacco Products and Drugs and Devices	1828
Sottera, Inc. v. FDA	1829
21 C.F.R. § 1100.5. Exclusion from Tobacco Regulation	1833
Notes	1834
2. “Deemed” Products.....	1835
Nicopure Labs, LLC v. FDA	1837
Notes	1839

3.	Comprehensive Plan for Tobacco and Nicotine Regulation	1842
	Speech by Scott Gottlieb, M.D., "Protecting American	
	Families: Comprehensive Approach to Nicotine and	
	Tobacco"	1843
	Notes	1845
D.	Tobacco Product Review	1847
1.	Substantial Equivalence (SE) Reports	1848
	Content and Format of Substantial Equivalence Reports	
	(Final Rule)	1849
	Notes	1851
2.	Exemptions from Demonstrating Substantial Equivalence	
	(SE)	1852
3.	Premarket Tobacco Product Applications (PMTAs)	1853
	21 C.F.R. § 1114.7. Required Content and Format	1854
	Notes	1855
4.	Modified Risk Tobacco Product (MRTP) Application.....	1856
a.	Products Subject to MRTP Application Requirements	1856
	Letter From Lawrence R. Deyton, Dir., Center for	
	Tobacco Products, to Tobacco Manufacturers on	
	Tobacco Products Labeled or Advertised With the	
	Descriptors "Light," "Low," "Mild," or Similar	
	Descriptors	1857
	Notes	1858
b.	FDA Review of MRTP Applications	1858
	Scientific Standards for Studies on Modified Risk	
	Tobacco Products	1860
	Notes	1861
E.	Tobacco Product Restrictions	1862
	Cigar Ass'n of Am. v. United States Food & Drug Admin.	1863
F.	Tobacco Product Standards.....	1865
	Letter from May D. Nelson, Director, Office of Regulations, CTP,	
	FDA to D. Douglas Blanke, Public Health Law Center	1866
	Notes	1869
G.	Graphic Warnings for Cigarettes.....	1870
	Discount Tobacco City & Lottery, Inc. v. United States	1871
	Notes	1873
	R.J. Reynolds Tobacco Co. v. Food & Drug Administration.....	1874
	Tobacco Products: Required Warnings for Cigarette Packages and	
	Advertisements (Final Rule)	1879
	Note.....	1882
	Chapter 12. Regulation of Carcinogens.....	1883
A.	Historical Background.....	1883
B.	Early FDA Policy	1884
	Arnold Lehman et al., <i>Procedures for the Appraisal of the Toxicity</i>	
	<i>of Chemicals in Foods</i>	1884
	Notes	1884
C.	Evolution of Legislative Policy.....	1885
1.	The Food Additive Delaney Clause.....	1885

2.	The Color Additive Delaney Clause	1887
3.	The Animal Drug Delaney Clause and the “DES Proviso”.....	1889
	Diethylstilbestrol: Withdrawal of Approval of New Animal Drug Application	1890
	Notes	1891
D.	FDA Embraces Quantitative Risk Assessment	1891
1.	Applied to Animal Drugs (the “DES Proviso”)	1892
	Chemical Compounds in Food-Producing Animals; Criteria and Procedures for Evaluating Assays for Carcinogenic Residues in Edible Products of Animals	1894
	Notes	1900
	Sponsored Compounds in Food-Producing Animals; Criteria and Procedures for Evaluating the Safety of Carcinogenic Residues	1901
	Notes	1902
2.	Applied to Contaminants of Food.....	1903
	Aflatoxins in Shelled Peanuts and Peanut Products Used as Human Foods: Proposed Tolerance	1903
	Notes	1903
3.	Applied to “Constituents” of Additives	1905
	Policy for Regulating Carcinogenic Chemicals in Food and Color Additives: Advance Notice of Proposed Rulemaking.....	1905
	Scott v. Food and Drug Administration.....	1907
	Notes	1908
4.	Applied to Direct Additives	1909
a.	Artificial Sweeteners in Food	1909
	Notes	1910
b.	Color Additive in Hair Dye	1911
	Lead Acetate; Listing as a Color Additive in Cosmetics That Color the Hair on the Scalp	1911
	Notes	1912
c.	Color Additive (Orange No. 17) in Externally Applied Drugs and Cosmetics.....	1913
	Listing of D&C Orange No. 17 for Use in Externally Applied Drugs and Cosmetics.....	1913
	Correction of Listing of D&C Orange No. 17 for Use in Externally Applied Drugs and Cosmetics	1914
	Public Citizen v. Young	1914
	Notes	1917
5.	Applied to Natural Food	1918
6.	Summary of Applications to Food	1920
7.	Applied to Drugs	1921
8.	Administrative Review and Decision on Carcinogens and Risk Assessment.....	1922
E.	Deciding Whether an Additive “Induces Cancer”	1922
1.	Carcinogenicity Thresholds	1922
	Selenium in Animal Feed; Proposed Food Additive Regulation	1923

Notes	1924
2. FDA Scientific Assessment.....	1925
Notes	1930
F. Resolving the “Delaney Paradox” for Food Pesticides	1931
Les v. Reilly	1932
James Smart, <i>All the Stars in the Heavens Were in the Right Places: The Passage of the Food Quality Protection Act of 1996</i>	1934
Allison D. Carpenter, <i>Impact of the Food Quality Protection Act of 1996</i>	1935
Notes	1936
G. Other Efforts to Identify or Regulate Carcinogens.....	1937
1. IARC and NTP	1937
2. Other Federal Agency Cancer Regulation.....	1938
a. The Environmental Protection Agency	1938
b. The Occupational Safety and Health Administration	1939
c. The Consumer Product Safety Commission	1940
3. Government-Wide Policies	1941
H. The Limits of Regulating Carcinogens	1942
1. Reduction or Elimination of Cancer Would Have a Small Impact on Human Lifespan.....	1942
Peter Barton Hutt, <i>Food and Drug Law: A Strong and Continuing Tradition</i>	1942
Notes	1943
2. California Proposition 65	1945
3. The First Amendment Limitations on Cancer Warnings.....	1946
National Association of Wheat Growers v. Zeise	1946
INDEX	1951