

Contents

Foreword	xv
Preface	xvii
Acknowledgment	xxv
Author	xxvii
Chapter 1 Testing for Heavy Metals: An ACS Perspective	1
Introduction	1
What Is a Reagent Chemical?	2
Historical Perspective	2
Eleventh Edition	3
Heavy Metals Test	3
Sulfide Colorimetric and Precipitation Procedure	4
Which Plasma-Based Spectrochemical Technique Is the Best One to Use?	5
Optimum Technique Based on Detection Limits, Sensitivity, and Linear Dynamic Range	6
Approaches to Reducing Interferences	7
Calibration	8
Instrumentation	8
Measurement Procedure and Data Integrity	9
Final Thoughts	9
Acknowledgments	10
References	10
Chapter 2 Elemental Impurities in Pharmaceuticals: An Overview	11
Background	11
Beginnings of Change	13
Development of New Limits and Procedure General Chapters	14
General Chapter <232>, “Elemental Impurities—Limits”: Overview	16
Application of Limits and Risk Assessment of Excipients and Drug Substances	17
Speciation	17
Elemental Impurity Classes	18
Exposure and Route of Administration	19
Options for Demonstrating Compliance	20
Drug Product Option	21
Summation Option	21
Individual Component Option	21
Justification for Levels Higher than the PDE	22
Risk Assessment and Regulatory Considerations	23
General Chapter <233>, “Elemental Impurities—Procedures”: Overview	24

USP <233> Compendial Procedures 1 and 2	24
Sample Preparation.....	25
USP <233> J-Value Parameter.....	25
Alternative Procedure Validation: USP <233> Requirements	26
Limit Procedures: Detectability	26
Acceptance Criteria: Noninstrumental Procedures.....	27
Acceptance Criteria: Instrumental Procedures	27
Limit Procedures: Precision (Repeatability) and Specificity	27
Quantitative Testing Validation Requirements.....	27
Final Thoughts	28
References	29
Chapter 3 An Overview of ICP: Mass Spectrometry	31
Principles of Operation	31
Chapter 4 Principles of Ion Formation.....	35
Ion Formation.....	35
Natural Isotopes	37
Chapter 5 Sample Introduction	41
Aerosol Generation.....	41
Droplet Selection	43
Nebulizers	44
Concentric Design	45
Cross-Flow Design	45
Microflow Design	47
Spray Chambers	48
Double-Pass Spray Chamber	49
Cyclonic Spray Chamber.....	49
Aerosol Dilution	51
Final Thoughts	52
References	52
Chapter 6 Plasma Source	53
Plasma Torch	54
Formation of an ICP Discharge.....	57
Function of the RF Generator	57
Ionization of the Sample.....	59
References	60
Chapter 7 Interface Region	61
Capacitive Coupling	63
Ion Kinetic Energy	65
Benefits of a Well-Designed Interface.....	66

	Final Thoughts	67
	References	67
Chapter 8	Ion-Focusing System	69
	Role of the Ion Optics.....	69
	Dynamics of Ion Flow	71
	Commercial Ion Optic Designs	73
	References	77
Chapter 9	Mass Analyzers: Quadrupole Technology	79
	Quadrupole Technology	80
	Basic Principles of Operation.....	80
	Quadrupole Performance Criteria.....	82
	Resolution	83
	Abundance Sensitivity	84
	Benefit of Good Abundance Sensitivity	86
	References	87
Chapter 10	Mass Analyzers: Double-Focusing Magnetic Sector Technology	89
	Magnetic Sector Mass Spectroscopy: A Historical Perspective	89
	Use of Magnetic Sector Technology for ICP-MS.....	90
	Principles of Operation of Magnetic Sector Technology	91
	Resolving Power	92
	Other Benefits of Magnetic Sector Instruments.....	95
	Simultaneous Measurement Approach Using One Detector.....	95
	Final Thoughts	97
	References	97
Chapter 11	Mass Analyzers: Time-of-Flight Technology	99
	Basic Principles of TOF Technology.....	99
	Commercial Designs	100
	Differences Between Orthogonal and On-Axis TOF.....	103
	Benefits of TOF Technology for ICP-MS.....	104
	Rapid Transient Peak Analysis	104
	Improved Precision.....	105
	Rapid Data Acquisition.....	105
	High-Speed MultiElemental Imaging	106
	Final Thoughts	107
	References	107
Chapter 12	Mass Analyzers: Collision/Reaction Cell and Interface Technology	109
	Basic Principles of Collision/Reaction Cells	110
	Different Collision/Reaction Cell Approaches	111

75	Collisional Mechanisms Using Nonreactive Gases and	
77	Kinetic Energy Discrimination	112
79	Reaction Mechanisms with Highly Reactive Gases and	
81	Discrimination by Selective Bandpass Mass Filtering.....	116
83	Dynamic Reaction Cell	116
85	Low-Mass-Cutoff Collision/Reaction Cell	120
87	Triple-Quadrupole Collision/Reaction Cell	123
89	M/S Mode.....	124
91	MS/MS Mode.....	124
93	On-Mass MS/MS Mode	124
95	Mass-Shift MS/MS Mode	125
97	Integrated Collision/Reaction Cell.....	127
99	Using Reaction Mechanisms in a Collision Cell.....	129
101	Universal Cell.....	132
103	Detection Limit Comparison.....	133
105	Final Thoughts	134
107	References	135
109	Chapter 13 Ion Detectors	137
111	Channel Electron Multiplier.....	137
113	Faraday Cup	139
115	Discrete Dynode Electron Multiplier.....	139
117	Extending the Dynamic Range	140
119	Filtering the Ion Beam.....	140
121	Using Two Detectors	140
123	Using Two Scans with One Detector.....	141
125	Using One Scan with One Detector	142
127	Extending the Dynamic Range Using Pulse-Only Mode	144
129	Simultaneous Array Detectors	145
131	References	146
133	Chapter 14 Peak Measurement Protocol.....	147
135	Measurement Variables.....	147
137	Measurement Protocol.....	148
139	Optimization of Measurement Protocol.....	152
141	Multielement Data Quality Objectives.....	153
143	Data Quality Objectives for Single-Particle Icp-MS Studies	158
145	Final Thoughts	159
147	References	160
149	Chapter 15 Methods of Quantitation	161
151	Quantitative Analysis	161
153	External Standardization.....	162
155	Standard Additions.....	163
157	Addition Calibration.....	164

208	Semiquantitative Analysis.....	165
209	Isotope Dilution.....	166
210	Isotope Ratios.....	169
212	Internal Standardization.....	169
212	References.....	170
Chapter 16	Review of ICP-MS Interferences.....	173
	Spectral Interferences.....	173
212	Oxides, Hydroxides, Hydrides, and Doubly Charged Species	174
216	Isobaric Interferences.....	175
216	Ways to Compensate for Spectral Interferences.....	176
217	Mathematical Correction Equations.....	176
217	Cool and Cold Plasma Technology.....	178
218	Collision/Reaction Cells.....	180
218	High-Resolution Mass Analyzers.....	181
219	Matrix Interferences.....	182
220	Compensation Using Internal Standardization.....	182
	Space Charge-Induced Matrix Interferences.....	183
221	References.....	184
Chapter 17	Routine Maintenance.....	185
222	Sample Introduction System.....	186
223	Peristaltic Pump Tubing.....	186
224	Nebulizers.....	187
225	Spray Chamber.....	189
226	Plasma Torch.....	190
228	Interface Region.....	191
230	Ion Optics.....	193
232	Roughing Pumps.....	194
232	Air Filters.....	194
233	Other Components to Be Periodically Checked.....	195
238	Detector.....	195
241	Turbomolecular Pumps.....	195
243	Mass Analyzer and Collision/Reaction Cell.....	196
243	Final Thoughts.....	196
244	Reference.....	197
Chapter 18	Collecting and Preparing the Sample for Analysis.....	199
248	Collecting the Sample.....	199
	Preparing the Sample.....	200
	Grinding the Sample.....	201
251	Cryogenic Grinding.....	201
254	Sample Dissolution Methods.....	202
254	Choice of Reagents and Standards.....	204
254	Vessels, Containers, and Sample Preparation Equipment.....	205

162	The Environment.....	208
166	The Analyst.....	209
169	Instrument and Methodology.....	210
169	Final Thoughts.....	212
170	References.....	212
Chapter 19	Sample Digestion Techniques for Pharmaceutical Samples.....	215
173	Sample Preparation Procedures as Described in USP	
174	Chapter <233>.....	215
175	Sample Preparation Guidance.....	216
176	Why Dissolve Samples?.....	216
176	Microwave Digestion Considerations.....	217
178	Why Microwave Digestion?.....	217
180	Choice of Acids.....	218
181	Microwave Technology.....	218
182	Sampling Procedures for Mercury.....	219
182	References.....	220
Chapter 20	Performance and Productivity Enhancement Techniques.....	221
182	Performance-Enhancing Techniques.....	222
186	Laser Ablation.....	222
186	Commercial Laser Ablation Systems for ICP-MS.....	223
187	Excimer Lasers.....	224
189	Benefits of Laser Ablation for ICP-MS.....	225
190	Optimum Laser Design Based on the Application Requirements.....	226
191	193 nm Laser Technology.....	228
191	Flow Injection Analysis.....	230
192	Electrothermal Vaporization.....	233
194	Chilled Spray Chambers and Desolvation Devices.....	237
194	Water-Cooled and Peltier-Cooled Spray Chambers.....	237
195	Ultrasonic Nebulizers.....	238
195	Specialized Microflow Nebulizers with Desolvation	
195	Techniques.....	241
196	Direct Injection Nebulizers.....	243
196	Productivity-Enhancing Techniques.....	243
197	Faster Analysis Times.....	244
199	Automated In-Line Autodilution and Autocalibration.....	247
199	Automated Sample Identification and Tracking.....	248
199	References.....	248
Chapter 21	Coupling ICP-MS with Chromatographic Separation	
201	Techniques for Speciation Studies.....	251
202	HPLC Coupled with ICP-MS.....	254
204	Chromatographic Separation Requirements.....	254

Ion Exchange Chromatography	256
Reverse-Phase Ion Pair Chromatography	257
Column Material	258
Isocratic or Gradient Elution	258
Sample Introduction Requirements	259
Optimization of ICP-MS Parameters	261
Compatibility with Organic Solvents	261
Collision/Reaction Cell or Interface Capability	262
Optimization of Peak Measurement Protocol	263
Full Software Control and Integration	265
Final Thoughts	266
References	266
Chapter 22 Fundamental Principles, Method Development, and Operational Requirements of ICP-OES	269
Basic Definitions	269
Principles of Emission	270
Atomic and Ionic Emission	270
Instrumentation	271
Sample Introduction	272
Aerosol Generation	273
Nebulizers	275
Spray Chambers	277
Torches	279
Spectrometers	281
Fore-Optics	281
Optical Designs	282
Detectors	284
Historical Perspective	284
Photomultiplier Tubes	286
Photodiode Arrays	287
Charge Transfer Devices	287
Charge-Coupled Devices	288
Charge Injection Devices	290
Analytical Performance	293
Dependence on Environmental Operating Conditions	294
Exhaust Requirements	294
Electrical Requirements	294
Temperature and Pressure Requirements	295
Maintenance	295
Dependence on Plasma Operating Conditions	296
RF Power	297
Plasma Gases	298
Pump Settings	299
Plasma Viewing Height	300

Precision and Accuracy	301
Detection Limits	302
Limit of Quantitation	303
Background Equivalent Concentration	303
Sensitivity	303
Method Development Considerations	304
Analytical Wavelength Considerations	304
Interferences	306
Physical Interferences	307
Chemical Interferences	307
Spectral Interferences	309
Data Acquisition	311
Method Validation	311
Final Thoughts	312
References	312
Chapter 23 What Atomic Spectroscopic Technique is Right for Your Lab?	321
Flame Atomic Absorption	322
Electrothermal Atomization	323
HGAA	323
Radial ICP-OES	324
Axial ICP-OES	324
ICP-MS	325
Comparison Highlights	325
Pharmaceutical Application Demands	327
Suitability of Technique	328
Relationship Between Loq And J-Value	330
Final Thoughts	333
References	333
Chapter 24 Do You Know What It Costs to Run Your Atomic Spectroscopy Instrumentation?	335
Gases	335
FAA	335
Air-C ₂ H ₂	336
ETA	336
ICP-OES and ICP-MS	336
Electricity	337
FAA	337
ETA	337
ICP-OES and ICP-MS	337
Consumables	338
FAA	338
ETA	338
ICP-OES	338

ICP-MS	339
Cost Per Sample	339
FAA	339
ETA	340
ICP-OES	340
ICP-MS	340
Final Thoughts	341
Chapter 25 The Risk Assessment Approach.....	343
Benefits of using a Risk Assessment Approach	343
Essential Reading	344
Performing the Risk Assessment	344
Water	347
Manufacturing Equipment	348
Container Closure System.....	348
Drug Substance	348
Excipients	349
Risk Assessment Frequency	349
Case Study.....	349
Drug Substance.....	350
Drug Product	351
Test Data on a New Product	352
Screening Method	352
Documentation	352
References	353
Chapter 26 Regulatory Inspection Readiness.....	355
Quality System	355
People	355
Facilities	356
Equipment	356
User Requirements Specification	356
Functional Requirements Specification.....	356
Design Specification.....	357
Supplier Assessment.....	357
Validation Plan	357
IQ/OQ and PQ.....	358
System Administration.....	359
Preventative Maintenance and Calibration	359
Training	359
Change Control Management.....	359
Periodic Review.....	359
Data Management	360
21 CFR Part 11	360
Data Integrity.....	360

.....	Data Backup and Recovery	360
.....	Computer System Validation.....	361
.....	Decommissioning.....	361
.....	References	361
Chapter 27	How to Select an ICP Mass Spectrometer: The Most Important Analytical Considerations	363
.....	Evaluation Objectives.....	364
.....	Analytical Performance	364
.....	Detection Capability.....	365
.....	Precision	370
.....	Isotope Ratio Precision.....	371
.....	Accuracy.....	373
.....	Dynamic Range.....	374
.....	Interference Reduction	377
.....	Reducing Spectral Interferences.....	377
.....	Resolution Improvement.....	378
.....	Higher Abundance Sensitivity Specifications	379
.....	Use of Cool Plasma Technology.....	379
.....	Using Collision/Reaction Cell and Interface Technology	382
.....	Reduction of Matrix-Induced Interferences	384
.....	Sample Throughput	387
.....	Transient Signal Capability	389
.....	Single-Particle ICP-MS Transient Signals	389
.....	Usability Aspects.....	392
.....	Ease of Use	392
.....	Routine Maintenance.....	393
.....	Compatibility with Alternative Sampling Accessories	395
.....	Installation of Instrument.....	395
.....	Technical Support.....	395
.....	Training	396
.....	Reliability Issues	396
.....	Service Support	397
.....	Financial Considerations.....	398
.....	The Evaluation Process: A Summary	399
.....	References	400
Chapter 28	Plasma Spectrochemistry Glossary of Terms	401
.....	Inductively Coupled Plasma Mass Spectrometry Glossary	401
.....	Inductively Coupled Plasma Optical Emission Spectrometry Glossary.....	443
Chapter 29	Useful Contact Information.....	449
Index.....		465