Contents

Preface  XIX
List of Contributors  XXIII

1 Introduction to Sample Management  1
William P. Janzen and Andy Zaayenga
References  6

2 Generating a High-Quality Compound Collection  9
Philip B. Cox and Anil Vasudevan
2.1 Defining Current Screening Collections  9
2.2 Design Criteria for Enriching a Compound Collection with Drug-Like Compounds  10
2.2.1 Physicochemical Tailoring of a Compound Collection  10
2.2.2 Lipophilicity Design Considerations  11
2.2.3 Other Physicochemical Roadblocks  14
2.2.4 Assessing Risk – from Rule of 5 to Rule of 3/75  18
2.2.5 Tools Enabling Desk Top In Silico Design  19
2.3 Concluding Remarks  20
References  20

3 Assessing Compound Quality  23
Ioana Popa-Burke, Stephen Besley, and Zoe Blaxill
3.1 Introduction  23
3.2 Process Quality and Analytical Quality in Compound Management  24
3.2.1 Process Quality (QA)  25
3.2.2 Analytical Quality (Sample QC)  27
3.3 Identity  28
3.4 Purity/Stability  32
3.4.1 Measuring Purity  32
3.4.2 Determining the Most Appropriate Purity Cut-Off for Solutions  37
3.4.3 Stability of Solutions  38
## Contents

<table>
<thead>
<tr>
<th>Section</th>
<th>Title</th>
<th>Page</th>
</tr>
</thead>
<tbody>
<tr>
<td>3.5</td>
<td>Concentration/Solubility</td>
<td>39</td>
</tr>
<tr>
<td>3.6</td>
<td>Conclusions</td>
<td>41</td>
</tr>
<tr>
<td></td>
<td>Acknowledgments</td>
<td>41</td>
</tr>
<tr>
<td></td>
<td>References</td>
<td>42</td>
</tr>
<tr>
<td></td>
<td>Further Reading</td>
<td>44</td>
</tr>
<tr>
<td>4</td>
<td>Delivering and Maintaining Quality within Compound Management</td>
<td>45</td>
</tr>
<tr>
<td></td>
<td>Isabel Charles</td>
<td></td>
</tr>
<tr>
<td>4.1</td>
<td>Introduction</td>
<td>45</td>
</tr>
<tr>
<td>4.2</td>
<td>What is Quality from a Compound Management Perspective?</td>
<td>46</td>
</tr>
<tr>
<td>4.3</td>
<td>Storage and Delivery of Samples in Solution</td>
<td>47</td>
</tr>
<tr>
<td>4.4</td>
<td>Intercepting Low Purity</td>
<td>49</td>
</tr>
<tr>
<td>4.5</td>
<td>Storage and Delivery of Solids</td>
<td>51</td>
</tr>
<tr>
<td>4.6</td>
<td>Automation Quality Control and Reliability</td>
<td>52</td>
</tr>
<tr>
<td>4.7</td>
<td>High-Quality Data Management</td>
<td>54</td>
</tr>
<tr>
<td>4.8</td>
<td>Conclusion</td>
<td>55</td>
</tr>
<tr>
<td></td>
<td>Acknowledgments</td>
<td>56</td>
</tr>
<tr>
<td></td>
<td>References</td>
<td>56</td>
</tr>
<tr>
<td>5</td>
<td>Obtaining and Maintaining High-Quality Tissue Samples: Scientific and Technical Considerations to Promote Evidence-Based Biobanking Practice (EBBP)</td>
<td>59</td>
</tr>
<tr>
<td></td>
<td>Lisa B. Miranda</td>
<td></td>
</tr>
<tr>
<td>5.1</td>
<td>Introduction</td>
<td>59</td>
</tr>
<tr>
<td>5.1.1</td>
<td>Current Issues and Impediments to Benchmark Level Biospecimen Research</td>
<td>59</td>
</tr>
<tr>
<td>5.1.2</td>
<td>The Role of the Research Protocol in Preserving Biospecimen Quality</td>
<td>60</td>
</tr>
<tr>
<td>5.1.3</td>
<td>Rationale for Best Practice Integration into Sample Management Procedures and Protocols</td>
<td>61</td>
</tr>
<tr>
<td>5.2</td>
<td>The Path toward Integration of Evidence-based Biobanking Practice</td>
<td>62</td>
</tr>
<tr>
<td>5.2.1</td>
<td>Conceptual Foundations of Evidence-based Biobanking Practice</td>
<td>62</td>
</tr>
<tr>
<td>5.2.2</td>
<td>The Pre- and Post-Acquisition Analytic Variable Relationship to EBBP</td>
<td>63</td>
</tr>
<tr>
<td>5.2.3</td>
<td>The Biospecimen Lifecycle Concept: a Framework to Aid EBBP Protocol Design</td>
<td>64</td>
</tr>
<tr>
<td>5.3</td>
<td>Integrating Evidence-based Biobanking Practice into Sample Protocols</td>
<td>66</td>
</tr>
<tr>
<td>5.3.1</td>
<td>Protocol Planning for EBBP-based Sample Management</td>
<td>66</td>
</tr>
<tr>
<td>5.3.2</td>
<td>Crucial Scientific and Technical Considerations for EBBP Protocol Design</td>
<td>68</td>
</tr>
<tr>
<td>5.3.3</td>
<td>Utilizing Publication Reporting Guidelines to Guide EBBP Protocol Design</td>
<td>73</td>
</tr>
</tbody>
</table>
5.4 Final Thoughts and Recommendations  74
5.4.1 Proposed Staging System to Qualify EBBP Related Data  74
5.4.2 Revisiting Crucial Considerations Related to Implementation of EBBP  77
5.4.3 Strategies to Optimize Real-Time Implementation of EBBP  78

References  79

6 Thinking Lean in Compound Management Laboratories  83

Michael Allen

6.1 The Emergence of ‘Lean Thinking’  83
6.2 The Application of ‘Lean Thinking’  83
6.3 Lean Thinking in Drug Discovery  86
6.4 A Lean Laboratory Toolbox  87
6.4.1 Defining Value  87
6.4.2 Understanding the Current Process – Process Mapping  88
6.4.3 Identifying Waste  88
6.4.4 Standardized Work, Future State Mapping, and Continuous Improvement  89
6.4.5 Batch Size Reduction, Changeover Time Reduction, and Workload Smoothing  90
6.4.6 5S and Kanban  92
6.4.7 Lean Layouts and Flow  95
6.4.8 Total Productive Maintenance  96
6.4.9 Theory of Constraints (TOC)  99
6.4.10 The Visual Workplace  100
6.4.11 Engaging Staff  100
6.5 Streamlining Compound Processing – An Example  101
6.6 Summary  103
References  105

7 Application of Supply Management Principles in Sample Management  107

Paul A. Gosnell

7.1 Introduction  107
7.2 Common Pitfalls of Sample Management  107
7.2.1 One Size Does Not Fit All  108
7.3 Sample Management and Supply Chain Concepts  108
7.3.1 Goods and Services – Classification and Strategy  109
7.4 Implementing the Sample Management Strategy  111
7.5 Sample Management Organization  111
7.6 Sample Management Informatics  113
7.7 Avoid Monolithic Silos of Excellence  114
7.8 Position and Synchronize Inventory  115
7.9 Expand the Sample Management Boundary  117
7.10 Measuring and Assessing Effectiveness and Quality  118
8 Solid Sample Weighing and Distribution 121
Michael Gray and Snehal Bhatt
8.1 The Practicalities and Technology of Weighing Solid Compounds 121
8.1.1 Introduction 121
8.1.2 Manual Weighing 122
8.1.3 Automated Weighing 123
8.1.4 Volatile Solvent Transfer 125
8.1.5 Sample Weighing – Summary and Conclusions 126
8.2 Logistical Challenges of Transportation of Small Molecules 127
8.2.1 Introduction to Transportation 127
8.2.2 Complexity of Logistics and Compliance Challenges of Supply Chain 129
8.2.3 Regulations and Procedures for Shipping Hazardous Materials, Hazardous Material in Small, Limited Quantity, with Dry Ice 131
8.2.3.1 Domestic Regulations 131
8.2.3.2 General Shipping Procedures and Associated Regulations 132
8.2.3.3 International Regulations 134
8.2.4 Cold Supply Chain Challenges 136
8.2.5 Collaboration with Subject Experts 137
8.2.5.1 Process Development and Standardization 138
8.2.6 Software Solutions 140
8.2.7 Conclusion 141
References 142

9 Managing a Global Biological Resource of Cells and Cellular Derivatives 143
Frank P. Simione and Raymond H. Cypess
9.1 Introduction 143
9.2 Diversity of Collections 144
9.3 Sourcing and Acquisition 148
9.4 Authentication and Characterization 149
9.4.1 Viability 151
9.4.2 Cellular Morphology 151
9.4.3 Microbial Contamination 151
9.4.4 Mycoplasma Detection 151
9.4.5 Virus Testing 151
9.4.6 Short Tandem Repeat (STR) Profiling 152
9.4.7 Isoenzyme Analysis 152
9.4.8 Cox 1 and CO1 152
9.4.9 Karyotyping 152
9.4.10 Immunophenotyping and Immunochemistry 153
<table>
<thead>
<tr>
<th>Section</th>
<th>Title</th>
<th>Page</th>
</tr>
</thead>
<tbody>
<tr>
<td>9.4.11</td>
<td>Pico Green and PI</td>
<td>153</td>
</tr>
<tr>
<td>9.5</td>
<td>Cryopreservation, Storage, and Production</td>
<td>153</td>
</tr>
<tr>
<td>9.6</td>
<td>Data Management</td>
<td>154</td>
</tr>
<tr>
<td>9.7</td>
<td>Quality and Standards</td>
<td>155</td>
</tr>
<tr>
<td>9.8</td>
<td>Order Fulfillment and Distribution</td>
<td>157</td>
</tr>
<tr>
<td>9.9</td>
<td>Offsite Biorepository Management</td>
<td>158</td>
</tr>
<tr>
<td>9.10</td>
<td>Regulatory and Legal Compliance</td>
<td>159</td>
</tr>
<tr>
<td>9.11</td>
<td>Ownership and Intellectual Property Management</td>
<td>160</td>
</tr>
<tr>
<td>9.12</td>
<td>Collaborations</td>
<td>161</td>
</tr>
<tr>
<td>9.13</td>
<td>Conclusion</td>
<td>162</td>
</tr>
<tr>
<td></td>
<td>References</td>
<td>163</td>
</tr>
</tbody>
</table>

10 Development of Automation in Sample Management 165

Gregory J. Wendel

10.1 Introduction 165
10.2 Historical Background 165
10.3 Automation of Sample Management Today 167
10.4 System Building Blocks 169
10.4.1 Storage Systems 169
10.4.2 Liquid Handling 169
10.4.3 Accessories 170
10.4.4 Plate Handling, Integration 170
10.4.5 Data Management 171
10.5 Storage Systems 171
10.5.1 Features 171
10.5.1.1 Size 171
10.5.1.2 Format 172
10.5.1.3 Temperature 172
10.5.1.4 Environment 172
10.5.1.5 Internal Manipulation 172
10.5.1.6 Robotic Interface 172
10.5.2 Example Hardware 173
10.6 Liquid Handler 175
10.6.1 Features 175
10.6.1.1 Deck Size 176
10.6.1.2 Head Format 176
10.6.1.3 Head Volume Range 176
10.6.1.4 Individual Channels 176
10.6.1.5 Gripper 177
10.6.1.6 Tip Loading 177
10.6.1.7 Barcode Reader 177
10.6.1.8 Tube/Vial Gripping 177
10.6.1.9 Integration Options 177
10.6.1.10 On-Deck Accessories 177
10.6.2 Example Hardware 178
10.7 Accessories 180
  10.7.1 Common Devices 180
  10.7.1.1 Plate Seal/Unseal 180
  10.7.1.2 Plate Label 181
  10.7.1.3 Tube Sorting 181
  10.7.1.4 Centrifuge 182
  10.7.1.5 Mixing 182
  10.7.1.6 Bulk Reagent Addition 183
  10.7.1.7 Tube Inspection 184
10.8 Plate Handling, Integration 184
10.9 Case Study: Evolution of a Compound Management Group 186
  10.9.1 Background 186
  10.9.2 Starting Condition 187
  10.9.3 Roadmap to Evolution 188
  10.9.4 Current Holdings Integrity 188
  10.9.5 Automated Solutions 189
    10.9.5.1 Storage Format 190
    10.9.5.2 Storage Systems 190
    10.9.5.3 Liquid Handling 190
    10.9.5.4 Accessories 191
    10.9.5.5 System Integration 191
    10.9.6.1 Integrated vs Walk-Up 192
    10.9.6.2 Integrated vs Walk-Up 192
    10.9.6.3 Compound Registration 195
  10.10 Results 196
11 Applications of Acoustic Technology 199
  Eric Tang, Colin Bath, and Sue Holland-Crimmin
  11.1 Introduction 199
  11.2 Compound-Handling Challenges in Drug Discovery 201
  11.3 Acoustic Drop Ejection – Performance, Quality Assurance, and
      Platform Validation 203
    11.3.1 Precision 203
    11.3.2 Quality Assurance – Non-Invasive DMSO Hydration Monitor 203
    11.3.3 Platform Validation 205
  11.4 Acoustic-Assisted Compound Solubilization and Mixing 206
    11.4.1 Sonication 207
    11.4.2 Ultrasonic Mixing 207
  11.5 Acoustic Applications in Drug Discovery 209
    11.5.1 HTS and Assay-Ready Plates – Compound Reformatting and Generic
        Dose Response Studies 209
    11.5.2 Compound Dosing in Cell-Based Screening Applications 211
13 Information Technology Systems for Sample Management 243
Brian Brooks

13.1 Sample Registration 243
13.1.1 Why the Need for Registration? 243
13.1.2 Assigning and Using Identifiers at Different Levels 245
13.1.3 Preparation Numbering 246
13.1.4 Sample Numbering 246
13.1.5 Methods for Naming Compounds 246
13.1.6 Some History to Compound Registration 247
13.1.7 Business Rules for Compound Registration 247
13.1.7.1 Number Format 248
13.1.7.2 Compound Number Prefix 248
13.1.7.3 Purity 248
13.1.7.4 Salts 249
13.1.7.5 Stereochemistry 249
13.1.7.6 Enantiomers and Racemic Mixtures 250
13.1.7.7 Standardization of Charge Form 250
13.1.7.8 Tautomerism 250
13.1.7.9 Radioactivity 250
13.1.7.10 Project Codes, Site Codes, Country Codes 251
13.1.7.11 Larger Molecules – of Known Structure 251
13.1.7.12 Larger Molecules – of Unknown Structure 252
13.1.7.13 Combinatorial Mixtures 252
13.1.7.14 Inorganic Compounds 252
13.1.7.15 Development Compounds, Outside Publications, Generic, and Trade Names 252
13.1.8 The Role of the Chemical Registrar 253
13.2 Intellectual Property and Laboratory Notebooks 253
13.3 Some Observations on Information Technology 254
13.4 Biological Data Management 255
13.4.1 The Corporate Biological Screening Database (CBSD) 255
13.4.2 Data Entry Tools 257
13.4.3 Database Querying 258
13.4.4 Special Data Types 261
13.4.5 Database Designs 261

Dedication and Acknowledgments 263

14 Key Features of a Compound Management System 265
Clive Battle

14.1 Why Do We Need Compound Management Information Technology Systems? 265
14.2 Compound Management Software 266
14.2.1 Inventory Management 266
14.2.1.1 Data Storage 267
14.2.1.2 Inventory Tracking 267
<table>
<thead>
<tr>
<th>Section</th>
<th>Page</th>
</tr>
</thead>
<tbody>
<tr>
<td>14.2.1.3 Inventory Browsing</td>
<td>267</td>
</tr>
<tr>
<td>14.2.1.4 Importing Inventory Items</td>
<td>267</td>
</tr>
<tr>
<td>14.2.1.5 Editing Inventory Items</td>
<td>267</td>
</tr>
<tr>
<td>14.2.1.6 Organizing the Inventory</td>
<td>267</td>
</tr>
<tr>
<td>14.2.2 Ordering</td>
<td>268</td>
</tr>
<tr>
<td>14.2.2.1 Web-Based Ordering</td>
<td>268</td>
</tr>
<tr>
<td>14.2.2.2 Sample Naming</td>
<td>268</td>
</tr>
<tr>
<td>14.2.2.3 Definition of an Order</td>
<td>268</td>
</tr>
<tr>
<td>14.2.2.4 Order Validation</td>
<td>268</td>
</tr>
<tr>
<td>14.2.2.5 Order Approval</td>
<td>269</td>
</tr>
<tr>
<td>14.2.2.6 Restrictions</td>
<td>269</td>
</tr>
<tr>
<td>14.2.2.7 Queries</td>
<td>269</td>
</tr>
<tr>
<td>14.2.2.8 Order Status Notifications</td>
<td>269</td>
</tr>
<tr>
<td>14.2.3 Workflow Management</td>
<td>269</td>
</tr>
<tr>
<td>14.2.3.1 Workflow Steps</td>
<td>269</td>
</tr>
<tr>
<td>14.2.4 Fulfillment</td>
<td>270</td>
</tr>
<tr>
<td>14.2.4.1 Offline Instrument Integration</td>
<td>270</td>
</tr>
<tr>
<td>14.2.4.2 Online Instrument Integration</td>
<td>270</td>
</tr>
<tr>
<td>14.2.4.3 Offline vs Online</td>
<td>271</td>
</tr>
<tr>
<td>14.2.4.4 Despatch</td>
<td>271</td>
</tr>
<tr>
<td>14.2.4.5 Reports and Metrics</td>
<td>271</td>
</tr>
<tr>
<td>14.2.5 Interfaces with External Systems</td>
<td>271</td>
</tr>
<tr>
<td>14.2.5.1 Chemical Registration System</td>
<td>271</td>
</tr>
<tr>
<td>14.2.5.2 External Ordering System</td>
<td>272</td>
</tr>
<tr>
<td>14.2.5.3 Results Analysis</td>
<td>272</td>
</tr>
<tr>
<td>14.3 Benefits of Commercially Available Compound Management Systems</td>
<td>272</td>
</tr>
<tr>
<td>References</td>
<td>273</td>
</tr>
</tbody>
</table>

15 What Does an HTS File of the Future Look Like? 275

François Bertelli

15.1 Introduction 275

15.2 History of Compounds Collection for HTS 276

15.3 Impact of High-Throughput Chemistry on Corporate Files 277

15.4 Chemical Library Management 278

15.5 The Concept of Drug-Likeness and the Lipinski Rules 279

15.5.1 Drug-Like 280

15.5.2 Lead-Like 282

15.6 Quality versus Quantity 283

15.7 The Emergence of the Subsets: Fragment, G-Protein-Coupled Receptor (GPCR), Ion Channel, Kinase, Protein–Protein Interaction, Chemogenomics, Library Of Pharmacologically Active Compounds (LOPAC), Central Nervous System (CNS), and Diversity 285

15.7.1 ‘Cherry Picking’ from Virtual Space 286

15.7.2 Diverse Subsets 287
15.7.3 Creation of the Global Diversity Representative Subset (GDRS) 288
15.7.4 Plate-Based Diversity Set (PBDS) 290
15.8 Re-designing the Corporate File for the Future 291
15.8.1 Pooling Compounds Moving Forward 291
15.8.2 Re-designing the Future File 296
15.9 Future Routes for Hit Identification 299
References 301

16 New Enabling Technology 305
Neil Hardy, Ji Yi Khoo, Shoufeng Yang, Holger Eickhoff, Joe Olechno, and Richard Ellson
16.1 Introduction 305
16.2 A Drop-On-Demand Printer for Dry Powder Dispensing 307
16.2.1 Dispensing Device Setup 308
16.2.2 Effect of Powder Dispensing Parameters on Micro-feeding 309
16.3 Piezo Dispense Pens: Integrated Storage and Dispensing Devices and their Potential in Secondary Screening and Diagnostic Manufacturing 312
16.3.1 An Introduction to Piezo Dispensers 312
16.3.2 PDP Mode of Operation and Its Advantages 313
16.3.3 PDPs in the High-Throughput Screening Environment 317
16.3.4 The Instrument to Operate PDPs in a Pharmaceutical Laboratory: sciSWIFTER 319
16.3.5 PDPs for the Sterile and Contamination-Free Production of In Vitro Diagnostics 321
16.3.6 Summary and Outlook 322
16.4 Future Directions in Acoustic Droplet Ejection Technology 323
16.4.1 Introduction 323
16.4.2 Stretching the Boundaries of Current ADE Uses 323
16.4.2.1 High-Viscosity Fluids 324
16.4.2.2 Low-Surface-Tension Fluids 326
16.4.2.3 Layered, Bi-Phasic Fluids 329
16.4.2.4 Combinatorial Chemistry 331
16.4.2.5 Particle Formation 332
16.4.2.6 Precision Coating 332
16.4.2.7 Touchless Transfer of Dangerous Materials 333
16.4.2.8 Assay Miniaturization 334
16.4.2.9 Transfection via Sonoporation 336
16.4.2.10 Expanded Reporting Capabilities 336
16.4.2.11 Transfer of Droplets of Different Volume – Smaller Droplets 337
16.4.2.12 Transfer of Droplets of Different Volume – Larger Droplets 338
16.4.3 Expanded Auditing Capabilities 338
16.4.3.1 Auditing for Volume 339
16.4.3.2 Auditing for Restoration 340
16.4.3.3 Auditing for Solute Information 341
16.4.3.4 Auditing Bi-Phasic Solutions 342
16.4.3.5 Auditing for Sample Quality 342
16.4.3.6 Frequency-Domain Analysis 343
16.4.4 New Software Advances 344
16.4.4.1 Improved Meniscus Scan 344
16.4.5 ADE Summary 344
16.5 Closing Remarks 347
References 347

17 The Impact of Future Technologies within Biobanking 351
Manuel M. Morente, Laura Cereceda, and María J. Artiga
17.1 Introduction 351
17.2 The Role of Biobanks in Biomedical Research 351
17.2.1 Biobanking Activity Is Based on Commitments 351
17.2.2 Scientific Commitment: Biobanks Must Be Open to Updating and Redefinition According to the Ever-Changing Scientific Requirements 352
17.2.3 Personalized Medicine on the Horizon: Biobanks for Better Health 353
17.3 The Increasing Complexity of Biobanking 354
17.3.1 Biobanks versus Sample Collections 354
17.3.2 Biobank Diversity 355
17.3.3 Biobanking, a Young Discipline 356
17.4.1 IT Solutions and Challenges 357
17.4.2 Storage Mechanization 359
17.4.3 Virtual Microscopy 360
17.4.4 Nanotechnology and Quality Control 360
17.4.5 Tissue Microarrays 361
17.4.6 New Fixatives 362
17.4.7 Robotized RNA/DNA/Protein Extraction 363
17.5 The Future of Biobanking Does Not Depend on Technological Developments Alone 363
17.6 Conclusions 364
Acknowledgments 364
References 364

18 Outsourcing Sample Management 367
Sylviane Boucharens and Amelia Wall Warner
18.1 Outsourcing in the Pharmaceutical Industry 367
18.1.1 Economic and Organizational Advantage of Outsourcing 368
18.1.2 Sourcing the Right Partner 368
18.1.3 Compound Inventory – Cost of Ownership 369
18.1.4 Areas of Outsourcing in Compound Management 371