VALIDATION OF
ACTIVE
PHARMACEUTICAL
INGREDIENTS

Second Edition

Ira R. Berry
Daniel Harpaz
Editors
<table>
<thead>
<tr>
<th>CONTENTS</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>PREFACE 2001</strong></td>
</tr>
<tr>
<td><strong>AUTHOR BIOGRAPHIES</strong></td>
</tr>
<tr>
<td><strong>1. INTRODUCTION</strong></td>
</tr>
<tr>
<td>Daniel Harpaz</td>
</tr>
<tr>
<td>GMP Concepts</td>
</tr>
<tr>
<td>Regulatory</td>
</tr>
<tr>
<td>FDA Site Inspections</td>
</tr>
<tr>
<td>References</td>
</tr>
<tr>
<td><strong>2. THE LEGAL FRAMEWORK FOR THE REGULATION OF ACTIVE PHARMACEUTICAL INGREDIENTS</strong></td>
</tr>
<tr>
<td>David F. Weeda, Arthur Y. Tsien, Neil F. O’Flaherty, and Robert A. Hahn</td>
</tr>
<tr>
<td>The Regulatory Status of APIs</td>
</tr>
<tr>
<td>APIs and BPCs</td>
</tr>
<tr>
<td>APIs as “Drugs”</td>
</tr>
<tr>
<td>APIs as “New Drugs” or “New Animal Drugs”</td>
</tr>
<tr>
<td>API Adulteration</td>
</tr>
<tr>
<td>cGMP Noncompliance</td>
</tr>
<tr>
<td>Validation as Part of cGMPs</td>
</tr>
<tr>
<td>Other Forms of Adulteration</td>
</tr>
<tr>
<td>API Misbranding</td>
</tr>
</tbody>
</table>
API Inspections 21
  History of API Inspections 21
  Reasonable Inspections Under Section 374(a) 22
  Scope of FDA Inspectional Authority over APIs 23
  Inspection Priorities: Active Drug Substances Versus Excipients 25
  Foreign Versus Domestic Plant Inspection 26
  Other Inspection Issues 30

Enforcement Tools Against APIs 32
  Administrative Tools 32
  Judicial Tools 34
  FDA Import/Export Authority over APIs 37

Drug Master Files for APIs 42
  DMF Types 42
  DMF Holder Obligations 43
  Status of DMFs as Records 44

Conclusion 45
Notes 45
References 52

3. THE LEGAL BASIS FOR VALIDATION 55

Irving L. Wiesen

Current Good Manufacturing Practices 55
  The 1962 Food and Drug Amendments 56
  Challenges to the cGMPs 59
  FDA’s Analysis of cGMPs 59
Judicial Analysis of cGMPs 61
  “Open-Endedness” of the cGMP Framework 63
  Failure to Comply with cGMPs Constitutes Product Adulteration 65

Active Pharmaceutical Ingredient Standards 66
Validation 67
  FDA’s Validation Guideline of 1987 69
  Validation of Active Pharmaceutical Ingredients 70
  The Barr Laboratories Decision 70

Conclusion 76
Notes 76
References 81

4. DRUG MASTER FILES 83

Arthur B. Shaw

Regulatory Basis for DMFs 84
  Guideline 84
Relationship Between Holder and Applicant 84
Filing and Referencing a DMF 85
Review of a DMF 87
Contents

Approval of DMFs 89
Types of DMFs 89
Manufacturing Performed at More Than One Site 91
Intermediates 93
Rereview of DMFs for APIs 93
Changing the Manufacturing Procedure in a DMF 95
Summary 96

5. THE FDA's PERSPECTIVES ON ACTIVE PHARMACEUTICAL INGREDIENT MANUFACTURING, cGMP CONTROLS, AND VALIDATION 97

Edwin Rivera Martinez

Development of the FDA's API GMP Draft Guidance 98
“What to Do” Versus “How to Do” in the FDA's API Guidance 100
cGMP Deficiencies Uncovered by the FDA's Inspections Abroad 101
Scope of the FDA's Draft API Guidance 105
Application of cGMPs to API Processes 106
Defining and Identifying the Starting Material 107
API Process Validation 110
Defining and Identifying Critical Process Steps 113
Defining Critical Process Parameters 115
Types of Process Validation 116
Equipment Cleaning and Validation 118
Process Water 120
Review of Batch Production and Control Records 123
Reprocessing and Reworking 123
Impurity Testing and Impurity Profiles 124
Initiatives to Develop an Internationally Harmonized GMP Guidance for APIs 127
Conclusions 129
References 130

6. DOMESTIC AND FOREIGN API MANUFACTURING FACILITY AUDITS AND FINDINGS 133

Peter D. Smith

Quality Assurance Functions and Systems 133
Standard Operating Procedures 134
Batch Release Procedure 136
Deviation and Failure Investigations, Reports 136
7. **VALIDATION OF APIs: A CASE STUDY**

*Nirmal Khanna*

The FDA and the History of Validation 164
What Is Validation? 164
A Successful Validation Program 165
API Validation—A Case Study 166
Manufacturing Operations 166
Quality Assurance Systems 167
Validation Program 168
Retrospective Reviews 169
  *Master Plan* 169
Retrospective Review Effort 170
Concurrent/Prospective Validations 172
  *Master Plan* 174
  *Validation Protocols* 175
  *Summary Report* 175
Cleaning Operations 176
  *Cleaning Validation—Concurrent or Prospective Validation* 178
Computer Control Systems 179
  *Concurrent Validation* 179
9. IMPURITIES IN DRUG SUBSTANCES AND DRUG PRODUCTS 271

Stephen R. Byrn and Joseph G. Stowell

Quality 272

A Typical USP Monograph 272

USP Descriptions of Impurities 273

Foreign Substances 273
Toxic Impurities 273
Ordinary Impurities 273
Other Impurities 274
Signal Impurities 274
Organic Volatile Impurities 274
Concomitant Components 275

ICH Documents on Impurities 275

Specifications 276
Qualification of Impurities 276
Analytical Procedures for Degradation Products or Drug-Excipient Reaction Products 278
Specification Limits for Degradation Products or Drug-Excipient Reaction Products 279
Impurities in Drug Products in Abbreviated New Drug Applications (ANDAs) 279

Validation 280

Impurity Issues Related to Manufacturing, Processing, or Holding Drug Substances (APIs) 282

Enantiomers as Impurities 285
Polymorphs as Unwanted Components 285
BACPAC 287

Summary and Conclusion 289

References 290

10. INVESTIGATING PROCESS DEVIATIONS 293

Frank J. Golden

Process Deviations 294
Regulatory Considerations 295

Process Deviation Principles 297
Problem Description 297
Classification of Deviation 297
Contents

Examination of Data Available 298
Review Procedures Utilized 298
Materials Used 298
Suitability of Facilities 298
Suitability of Equipment 299
Employee Training 299
Extent of Deviation 300
Validation Impact 300
Equivalency 300
Testing Required 300
Regulatory Impact 301
Results of Investigation 301
Corrective Action 301
Preventive Actions 301
Conclusions 302
Documentation 302
Signatures and Approvals 302
Periodic Review 302
Investigating Quality Problems 302
Process Deviation Examples 304
Example 1 304
Example 2 305
Example 3 307
References 308

11. TECHNOLOGY TRANSFER:
ACTIVE PHARMACEUTICAL INGREDIENTS 309

B. J. Evanoff and K. L. Hofmann, Jr.

Preliminary Considerations 310
The Role of Marketing 310
Defining the Process 311

Categories of Technology Transfer 312
New Chemical Entities 312
Changes to Established Processes 312

Process Development Report 313
Organization for Technology Transfer 317
Technology Transfer Team 317
Intracompany Project 318
External Technology Transfer Project 319

Considerations for Plant Scale-Up 319
Raw Materials 320
Plant Equipment and Utilities 320
Process Control Parameters 321
Process Equipment 322
Cleaning Validation 323
Process Validation 323
Analytical Methods 324
12. POSTAPPROVAL CHANGES TO BULK DRUG SUBSTANCES

Eric Sheinin, Eric Duffy,
Kasturi Srinivasachar, and John Smith

BACPAC I
Scope 331
Filing Mechanism 332
Assessment of Change 333
Manufacturing Site, Manufacturing Scale, and Equipment Changes 335
Specification Changes 336
Process Changes 336

BACPAC II
Scope 338
Principles of Equivalence 338
Filing Mechanisms 339
Types of Changes 339
Summary 339

Conclusion 340

13. VENDOR QUALIFICATION AND CERTIFICATION

Ira R. Berry

Definition of Terms 344
Purpose of Vendor Qualification and Certification 345
Qualification/Certification Procedure Overview 346
How to Qualify a Vendor 347
Certifying a Vendor 351
Monitoring a Vendor 352
Vendor Audits

Philosophy of Pharmaceutical GMP Compliance 354
Documentation 354
Quality Assurance Program 355
Standard Operating Procedures Manual 355
Change Control Procedure 356
Personnel Training 356
Out-of-Specification Data Handling/Failure Investigation 356
Written Master Production and Control Records with
In-Process Controls 357
14. QUALITY ASSURANCE SYSTEMS

Fred C. Radford

Definition and Decision 375
FDA Requirements Are Central 380
The Inspection Focus 381
Beyond the Manufacturing Instruction 383
Tangent Considerations 385
Plan, Do, Study, Act 388
References 395

15. CLEANING FOR ACTIVE PHARMACEUTICAL INGREDIENT MANUFACTURING FACILITIES

William E. Hall

Regulatory Requirements 397
Multiple Use Versus Dedicated Equipment 399
The Unique Nature of APIs 401
Multiple Levels Approach to Cleaning 402
Level 1 Cleaning 402
Level 2 Cleaning 402
Level 3 Cleaning 402
Validation of Active Pharmaceutical Ingredients

Level 4 Cleaning 403
Philosophy of Cleaning 403

Nature of Contaminants 404
Product Groupings and Selection of a Worst Case 405
Cleaning Techniques 406
Sampling 407

Analytical Methods 409
Visual Examination 411
Analytical Techniques for Biotechnology Cleaning Validation 412
High Performance Liquid Chromatography 412
Microbial and Endotoxin Testing 413
Total Organic Carbon Analysis 413

Limits and Acceptance Criteria 414
Calculation of Limit Based on Smallest Therapeutic Dose 416
Calculation of Limit Based on Toxicity 417

Cleaning Validation Documentation 420
Protocols 421
Final Validation Report 425

Emerging Trends in Cleaning in the Pharmaceutical Industry 425

References 427

16. VALIDATION OF STERILE APIs 429

Robert V. Kasubick

Regulatory Aspects 431
Validation Protocol Format 431
General Manufacturing Process Description 432

Facility 432
Room Classification 434
Airflow Patterns and Pressure Differentials 435
Personnel Flow 437
Material Flow 439

Support Systems 439
Water Systems 442
Air Systems 442
Equipment Sterilization 444
Clean Steam System 445
Filtration Systems 445
Heat Exchangers 447
Vacuum Systems 447

Manufacturing Process Validation 447
Validation Maintenance 449

References 449
17. **VALIDATION OF BIOTECHNOLOGY ACTIVE PHARMACEUTICAL INGREDIENTS** 451

*Rob Murphy and Robert J. Seely*

- Master Planning 452
- Equipment Qualification 453
  - Installation Qualification 453
  - Operational Qualification 454
  - Performance Qualification 454
- Cleaning Validation 454
- Equipment Sterilization 456
- Process Validation 457
  - Timing 458
  - Process Variables 459
  - Impurity Profile 462
  - Additional Studies 463
  - The Final Package 463
  - Process Monitoring 464
  - Change Control 466
  - Revalidation 468

References 469

Appendix 17.1: Process Validation Protocol PV-08 471

18. **MICROBIOLOGICAL ATTRIBUTES OF ACTIVE PHARMACEUTICAL INGREDIENTS** 475

*Karen Zink McCullough and John Shirtz*

- Preliminary Issues 478
  - Standard Operating Procedures 478
- Microbiological Quality of Water 479
  - Validation/Qualification and Maintenance of the Water Purification, Storage, and Distribution System 482
- Bioburden 484
- API Processing 486
- Facility and Equipment Considerations for the Production of Sterile APIs 488
- Use of Isolator Systems to Minimize Human Contact with Sterile APIs 493
  - Containment 493
- Monitoring the Environment in API Manufacturing Facilities 494
  - Monitoring of Classified and Critical Areas: Manufacturing and Support for Products and APIs Produced Aseptically 495
  - Monitoring of Unclassified Areas: Nonsterile Dosage Forms and APIs 496
  - Site Selection and Frequency of Testing 496
Contents

Validation Master Plan 563
Cleaning Validation 563
Explosion Suppression Validation 566
Validation Documentation 566
Recommended Reading 569
References 570

INDEX 573