CONTENTS

Introduction 1

Jeanne Moldenhauer

References 11

2 Regulatory Basis for FDA Inspections 13

Jeanne Moldenhauer

Responsibilities of the FDA 13
Review of New Products 14
Monitoring Products on the Market 14
Development of Standards and Regulations 15
Research Activities 15
Enforcement Activities 15
The Food, Drug and Cosmetic Act 16
The Bill of Rights 17
Constitutional Challenges to the Authority to Inspect Facilities 17
FDA Responsibilities 19
FDA Inspections 20
FDA Investigators 22
The FDA Investigator’s Role During an Inspection 22
Regulatory Notes 22
Team Inspections 23
FDA’s Inspection Preparation 24
Pre-announcements 24

www.pda.org/bookstore
### Systems-Based Inspections

**Jeanne Moldenhauer**

<table>
<thead>
<tr>
<th>Section</th>
<th>Page</th>
</tr>
</thead>
<tbody>
<tr>
<td>Notice of Inspection</td>
<td>25</td>
</tr>
<tr>
<td>Follow-up Inspections Conducted via Court Order</td>
<td>25</td>
</tr>
<tr>
<td>Inspections when Criminal Acts are Contemplated</td>
<td>26</td>
</tr>
<tr>
<td>Preliminary Questions Asked</td>
<td>26</td>
</tr>
<tr>
<td>Inspectional Approach</td>
<td>26</td>
</tr>
<tr>
<td>Typical Inspection Techniques</td>
<td>27</td>
</tr>
<tr>
<td>Fact-Finding Mission</td>
<td>28</td>
</tr>
<tr>
<td>Sample Collection</td>
<td>29</td>
</tr>
<tr>
<td>Interview Techniques</td>
<td>29</td>
</tr>
<tr>
<td>Reporting Observations</td>
<td>30</td>
</tr>
<tr>
<td>Annotation of the FD-483</td>
<td>31</td>
</tr>
<tr>
<td>Wrap-Up Meetings (Discussions with Management)</td>
<td>31</td>
</tr>
<tr>
<td>Establishment Investigation Report (EIR)</td>
<td>31</td>
</tr>
<tr>
<td>Affidavits</td>
<td>32</td>
</tr>
<tr>
<td>Commonly Used FDA Inspection Forms</td>
<td>32</td>
</tr>
<tr>
<td>Pre-Approval Inspections (PAIs)</td>
<td>33</td>
</tr>
<tr>
<td>Refusing an Inspection</td>
<td>33</td>
</tr>
<tr>
<td>References</td>
<td>34</td>
</tr>
<tr>
<td>3 Systems-Based Inspections for Pharmaceutical Manufacturers</td>
<td>35</td>
</tr>
<tr>
<td>Objectives of Systems-based Drug Inspections</td>
<td>36</td>
</tr>
<tr>
<td>Strategy</td>
<td>37</td>
</tr>
<tr>
<td>Systems for Audit During Inspection</td>
<td>38</td>
</tr>
<tr>
<td>Quality System</td>
<td>38</td>
</tr>
<tr>
<td>Facilities and Equipment System</td>
<td>39</td>
</tr>
<tr>
<td>Materials System</td>
<td>39</td>
</tr>
<tr>
<td>The Production System</td>
<td>39</td>
</tr>
<tr>
<td>The Packaging and Labeling System</td>
<td>39</td>
</tr>
<tr>
<td>The Laboratory Control System</td>
<td>39</td>
</tr>
<tr>
<td>Inspection Options</td>
<td>40</td>
</tr>
<tr>
<td>Full Inspection Option</td>
<td>40</td>
</tr>
<tr>
<td>Abbreviated Inspection Option</td>
<td>40</td>
</tr>
<tr>
<td>Selection of the Systems to be Inspected</td>
<td>40</td>
</tr>
<tr>
<td>Product Classes</td>
<td>41</td>
</tr>
<tr>
<td>Other Types of Inspections</td>
<td>42</td>
</tr>
<tr>
<td>Compliance Inspections</td>
<td>42</td>
</tr>
<tr>
<td>State of Control</td>
<td>42</td>
</tr>
<tr>
<td>Out-of-Control</td>
<td>42</td>
</tr>
<tr>
<td>References</td>
<td>42</td>
</tr>
</tbody>
</table>
4  The Quality System  
David A. Henninger

Introduction  73
The Quality System — Management Responsibility  75
  Introduction  75
  Design Considerations  75
  Inspection of Management Responsibility  76
Quality Systems — Drug Product Reviews  83
  Introduction  83
  System Design Considerations  83
  Inspection Guidance  83
Quality System — Drug Product Complaints  88
  Introduction  88
  System Design Considerations  88
  Inspection Guidance  92
Quality Systems — Discrepancy and Failure Investigations  100
  Introduction  100
  Design Considerations  100
  Inspection Guidance  101
Quality Systems — Change Control  105
  Introduction  105
  Design Considerations  105
  Inspection Guidance  110
Quality Systems — Product Improvement Projects  116
  Introduction  116
  Design Considerations  116
  Inspection Guidance  116
Quality Systems — Reprocess/Rework  119
  Introduction  119
  Design Considerations  119
  Inspection Guidance  119
Quality Systems — Returns and Salvage  124
  Introduction  124
  Design Considerations  124
  Inspection Guidance  125
Quality Systems — Rejects  130
  Introduction  130
  Design Considerations  130
  Inspection Guidance  130
Quality Systems — Stability Testing  134
  Introduction  134
Contents

6 The Materials System 203

Seth Pyers

Areas an Inspection is Expected to Cover 203
Considerations for Assessing Compliance for these Systems 205
Materials System Overview 205
Standard Materials 206
Written and Approved Procedures 206
Training and Qualification of Personnel 207
Identification of Components, Containers and Closures 207
Inventory of Components, Containers and Closures 207
Storage Conditions 207
Quarantine of Materials until Tested and/or Examined 207
Specific Identity Tests for Each Lot of Components 208
Visual Identification Test for Each Lot 208
Validation of Vendor Supplied Test Results 208
Materials are Rejected when Criteria are not Met 208
Determine When and How to Retest Lots of Materials 208
Procedures Ensure First-In-First-Out of Components 208
Surfaces, Containers and Products are Mutually Non-Reactive 209
Change Control 209
Inventory Control Software 209
Part 11 Compliance for Automated Data Handling Systems 210
Record All Finished Products by Lots 211
Document Investigations 211
Utility Provided Materials 212
Water Production Sources 212
Guide to Inspection High Purity Water Systems 213
Systems Design 213
Microbial Limits USP High Purity and WFI Hot, Cold and Ambient 213
Pretreatment 214
Floculation 214
Reverse Osmosis 215
Distillation 216
Biofilms 219
High Purity Water Systems Validation 224
Inspection Strategy 225
Clean Steam Systems 226
Solvents 226
Medical Grade Gases 227
Examples of Significant and/or Trend of Deficiencies 227
Recent Regulatory Findings 228
References 228

7 The Production System 231
Michele Conway and Robert Ferer

Training/Qualification of Personnel 233
Control System for Implementing Changes in Process 234
Adequate Procedure and Practice for Charge-in of Components 236
Formulation/Manufacturing at Not Less Than 100% 237
Identification of Equipment with Contents, and Where Appropriate Phase of Manufacturing and/or Status 238
Validation and Verification of Cleaning/Sterilization/Depyrogenation of Containers and Closures 239
Calculation and Documentation of Actual Yields and Percentage of Theoretical Yields 241
Contemporaneous and Complete Batch Production Documentation 242
Established Time Limits for Completion of Phases of Production 243
Implementation and Documentation of In-Process Controls, Tests, and Examinations (e.g., pH, adequacy of mix, weight variation, clarity) 244
Justification and Consistency of In-Process Specifications and Drug Final Specifications 245
Prevention of Objectionable Microorganisms in Non-Sterile Drug Products 246
Adherence of Preprocessing Procedures (e.g., set-up, line clearance, etc.) 247
Equipment Cleaning and Use Logs 248
Master Production and Control Records/Batch Production and Control Records 249
Process Validation, Including Validation and Security of Computerized or Automated Processes 250
Change Control: The Need for Revalidation Evaluated 252
Documented Investigation into any Unexpected Discrepancy 253
References 254
8 The Packaging and Labeling System 257

Jeanne Moldenhauer

Areas Expected to be Covered in an Inspection 257
Considerations for Assessing Compliance for these Systems 259
Evidence of Written Procedures 259
Training and Qualification of all Affected Personnel 259
Procedure for Acceptance of Packaging and Labeling Materials 259
Effective Change Control System for Implementing Changes in Packaging and Labeling Operations 260
Adequate Storage for Labels and Labeling (both approved and those returned after Issuance) 260
Control of Labels that are Similar in Size, Shape, and Color for Different Products at the Site 261
If Cut Labels are used for Finished Products for Immediate Containers that are Similar in Appearance without Some Type of 100% Electronic or Visual Verification System or Use of Dedicated Lines Verification that Gang Printing of Labels is Not Performed, Unless the Labels are Differentiated by Size, Shape or Color 261
Control Procedures are Established and Followed if Filled Unlabeled Containers are Produced that are Later Labeled under Multiple Private Labels 262
Adequate Packaging Records are Available that Include Specimens of All Labels Used for Each Product and Lot Control Procedures are Established and Followed for Issuance of Labeling, and that there is Appropriate Examination of Issued Labels and Reconciliation of Used Labels 262
Examination of Labeled Finished Product is Conducted Adequate Inspection (proofing) of Incoming Labeling Materials 262
Appropriate Use of Lot Numbers on Labels, and Destruction of Excess Labeling Bearing Lot or Control Numbers 263
Physical and/or Spatial Separation Exists Between Different Labeling and Packaging Lines 263
Monitoring of Printing Devices Associated with Manufacturing Lines is Conducted 279
Line Clearance and Inspection is Performed and Documented 263
Adequate Expiration Dates are Present on the Label
Conformance to Tamper-Evident Packaging (TEP) Requirements, as Required per 21 CFR §211.132 and Compliance Policy Guide No. 7132a.17
Appropriate Validation of Packaging and Labeling Operations is Conducted including Validation and Security of Computerized Processes
Documented Investigations are Performed for any Unexpected Discrepancy
Examples of Significant and/or Trend of Deficiencies

Recent Regulatory Findings
References

9 The Laboratory System
Jeanne Moldenhauer

Areas Expected to be Covered in an Inspection
Evidence of Written Procedures
Training and Qualification of all Affected Personnel
Adequacy of Staffing for Laboratory Operations
Adequacy of Equipment and Facility for Intended Use
Calibration and Maintenance Programs for Analytical Instruments and Equipment
Validation and Security of Computerized or Automated Processes
Reference to Standards, Source, Purity and Assay, and Tests Establish Equivalency to Current Official Reference Standards, as Appropriate
System Suitability Checks on Chromatographic Systems (e.g., GC or HPLC)
Specifications, Standards, and Representative Sampling Plans
Adherence to the Written Methods of Analysis
Validation or Verification of Analytical Methods
Control System for Implementing Changes in Laboratory Operations
Required Testing is Performed on the Correct Samples
Documented Investigation into any Unexpected Discrepancy
Complete Analytical Records from All Tests and Summaries of Results
Quality and Retention of Raw Data (e.g., chromatographs and spectra)
Sterile Process Validation Documentation Packages 330
Key indices 330
Standardization of Documentation 330
Technical Glossary 330
Questions to Ask the FDA 331
Information that Should be Conveyed to the Inspector 331
Practice Tours of the Facility 332
Self-Audit and Know Your Vulnerabilities 332
Prepare for the FDA Areas of Focus 333
Inspectional Guidance Documents 333
Know Your Company’s Policies 334
Documentation 334
Requests for Samples 335
Mock Inspections 336
I Know I Have a Problem. Now What? 336
Simple Rules of Etiquette to Use During an Inspection 337
Handling Difficult Inspectors 338
Learn from the Mistakes of Others 339
Observations for the Quality System 339
Observations for the Laboratory System 340
Observations for the Facilities and Equipment System 340
Observations for the Production System 340
Acknowledgements 341
References 341

12 Managing of Regulatory Inspections 345
Jeanne Moldenhauer

Who May Inspect the Facility? 345
What Requirements Allow the Government Inspection? 336
What is the Purpose of the Audit? 347
Are There Company Policies or Procedures that will Define
What Investigators May Do During the Inspection? 348
What’s Your Job? 349
How Do I Handle Documentation? 351
What Could Go Wrong? 351
Conclusion 351
Acknowledgements 351
## Contents

<table>
<thead>
<tr>
<th>Page</th>
</tr>
</thead>
<tbody>
<tr>
<td>353</td>
</tr>
<tr>
<td>354</td>
</tr>
<tr>
<td>355</td>
</tr>
<tr>
<td>355</td>
</tr>
<tr>
<td>356</td>
</tr>
<tr>
<td>356</td>
</tr>
<tr>
<td>356</td>
</tr>
<tr>
<td>357</td>
</tr>
<tr>
<td>357</td>
</tr>
<tr>
<td>358</td>
</tr>
<tr>
<td>358</td>
</tr>
<tr>
<td>359</td>
</tr>
<tr>
<td>359</td>
</tr>
<tr>
<td>360</td>
</tr>
<tr>
<td>360</td>
</tr>
<tr>
<td>361</td>
</tr>
<tr>
<td>361</td>
</tr>
<tr>
<td>361</td>
</tr>
<tr>
<td>363</td>
</tr>
<tr>
<td>373</td>
</tr>
</tbody>
</table>

### 13 Concluding an Inspection and Handling Inspection Findings

Jeanne Moldenhauer

- The Exit Discussion
- Reporting of Observations, the FDA-483
  - General Principles for FDA-483 Observations
  - Annotation of Observations
  - Impact of these Observations
  - Freedom of Information (FOI)
  - Writing Observations
  - Triggers to Observations
  - Non-reportable Observations
- Determining the Significance of FDA-483 Observations
- Handling Adverse Findings
  - Written Response to the FDA-483
- Dispute Resolution
- Evaluation Compliance with Corrective Action Program
  - Established
- Warning Letters
- On-going Evaluations
- References

### Glossary

#### Author Biographies

#### Index

www.pda.org/bookstore