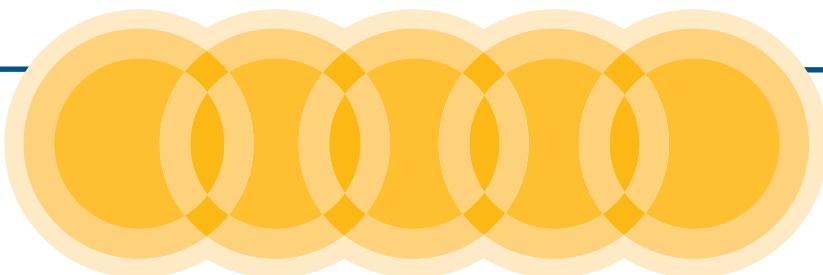


ENVIRONMENTAL MONITORING

A COMPREHENSIVE HANDBOOK

VOLUME 4



Jeanne Moldenhauer
Editor

CONTENTS

About the Authors

I	DESIGNING AND VALIDATING A CONTAMINATION CONTROL PROGRAM	I
	<i>Sandra A. Lowery and Maureen Mueller</i>	
Introduction		1
Contamination Control		2
Sources of Contamination		3
Extraneous Contamination: Microbial		4
Extraneous Contamination: Particulate		4
Extraneous Contamination: Chemical		4
The Human Factor		5
Trafficking		5
Surface Disinfection		5
Controlled Environments and Facility Design		6
Qualification of Classified Areas		9
Barrier Systems		10
Process Barrier		10
Equipment/Material/Personnel Barriers		10
Disinfection Program		11
Disinfectant Qualification Studies		14
Sterilization and Maintenance of Sterility		14

Operator Training and Qualification	17
Aseptic Technique	17
Interventions	18
Proper Cleanroom Behavior	18
Working in Unidirectional Airflow	19
cGMPs of Contamination Control	20
Aseptic Operator Qualification Curriculum	20
Controlled Area and Aseptic Gowning	22
Controlled Area Gowning	22
Aseptic Gowning	22
Aseptic Gowning Qualification	23
Process Simulation Studies (Media Fills)	25
Introduction	25
Sterile Bulk Process Simulations	26
Principles of Challenge: Aseptic Filling and/or Bulk Processing	27
Study Design	27
Use of a Matrix Approach	28
Frequency of Challenge	29
Choice of Media	30
Oxygen Availability	31
Fill Volume	31
Personnel Intervention	32
Duration and Yield	34
Worse-Case Conditions ("Standard" and "Defined")	36
Documentation	37
Unit Inspection	39
Unit Incubation Requirements	40
Unit Accountability and Reconciliation	41
Acceptance Criteria	41
Investigations	42
Lyophilization Simulation	45
Additional Measurement Programs: Environmental and Personnel Monitoring	45
Sterility Testing	48
Bioburden and Endotoxin Burden Program	49
Data Trending and Analysis	51
Correlation of Assessments/Annual Product Reviews	51
Conclusion	52
References	52
Additional Reading	53
About the Authors	54
2 REAL-TIME TRENDING OF ENVIRONMENTAL MONITORING DATA	55
<i>Austin Kuo, Terrence Shelley and Thomas Burns</i>	
Introduction	55
Trending Expectations	56
Challenging the Traditional Approach to Trending	57

Developing Real-Time Approaches to Trending	59
Time Frames for Trending	59
Elements of a Real-Time Trending Program	59
Incidents	60
Alert Trends	60
Percent Positive Trends	61
Microflora Trends	63
Summary	63
Applying New Concepts	63
The Information Technology (IT) Solution	65
Additional Considerations for IT Tool User Requirements	66
Examples of Real-Time Trend Analysis using an IT Tool	66
Scenario	66
Incidents	66
Alert Trend	68
Percent Positive Trend	69
Microflora Trend	71
References	72
About the Authors	72
3 THE USE OF RISK MANAGEMENT IN ENVIRONMENTAL MONITORING	73
<i>Karen Ginsbury</i>	
Points to Address — FDA Aseptic Processing Guide	76
Points to Address — EU Annex I	77
Case Study #1 — Informal Risk Assessment for an Aseptic Processing Operation	79
Case Study #2 — HACCP Analysis for an Aseptic Processing Operation	81
Case Study #3 — FMEA Analysis for a Non-Sterile Process	85
References	94
About the Author	94
4 LEAN MICROBIOLOGY LABORATORIES	95
<i>Jeanne Moldenhauer</i>	
Introduction	95
Background	95
Issues Common in Conventional Testing Laboratories	96
Key Principles for Implementing Lean Concepts into the Laboratory	97
Designing a Lean Laboratory	101
Development of the Laboratory Design	102
The Lean Work Cell	103
The Lean Laboratory Toolbox and Building Blocks	104
What is 6S?	104
Standardized Work	105
Waste Walks	108
Visual Management Tools	108

Metrics	108
Pulse Surveys	110
Training	110
Building Blocks	110
Quick Changeover/Set-up Reduction	110
Value Stream Analysis	111
Pull/Kanban Systems	111
Workplace Organization	112
Total Productive Maintenance (TPM)	112
Cellular Operations	112
Implementation of the Lean Laboratories	112
Management Infrastructure	112
Mindsets and Capabilities	113
Operating Systems	114
Oversight	114
Implementation Strategy	114
Conclusion	115
References	116
About the Author	117
5 OBSERVATIONS IN SUPPORT OF LEAN MICROBIAL IDENTIFICATION	119
<i>David Shelep</i>	
Introduction	119
Laboratory Issues	120
Current Patterns and Lean Ideas	120
Abbreviated Identifications	123
Laboratory Consolidation Within a Corporate Entity	123
Reduce Capital Equipment	125
Send Testing to Outside Laboratory	125
Reducing Overall Testing	126
Specific Challenges and Opportunities to Evaluate Savings	127
Conclusions	131
References	132
About the Author	132
6 DEALING WITH CONTAMINATION: WHAT IS THE RISK TO THE PRODUCT?	133
<i>Jeanne Moldenhauer</i>	
Introduction	133
Investigation Expectations	134
Risk Assessments	134
Other Concerns with Contamination Events	138
The Production of Toxins	138
Closely Related Organisms	138
How Much Contamination is Too Much	138

Inability to Identify the Contaminant	139
Changes to Bergey's Manual	139
The Problem of "Ones"	140
Conclusion	140
References	140
About the Author	141
7 COLLECTION EFFICIENCY OF MICROBIOLOGICAL IMPACTION AIR SAMPLERS	143
<i>Bengt Ljungqvist and Berit Reinmüller</i>	
Introduction	144
Physical Efficiency	144
Biological Efficiency	147
Design Guidelines	148
Air Sampling	149
Evaluation of Sampling Locations	149
Summary	151
References	151
About the Authors	152
8 MICROBIOLOGICAL EXCURSIONS IN ENVIRONMENTAL MONITORING: A RISK-BASED APPROACH IN STERILE PRODUCTION	
<i>Hanna Filipek</i>	
Introduction	
Regulatory Expectations	
Requirements	
Regulatory Findings	
Microbiological Excursion in Environmental Monitoring (MEE)	
Definition	
Requirements	
Actions	
Meaning of MEEM	
Risk Management Program	
Risk Initiation	
Risk Assessment	
Risk identification	
Risk analysis	
Risk evaluation	
Risk Control	
Risk reduction	
Risk acceptance	
Risk Communication	
Risk Review	
FMEA in Batch Release in the Case of MEE	
Basic Information	

- Application of FMEA
 - Severity
 - Occurrence
 - Detection
- Limitations of Environmental Methods
- Limitations of Sterility Testing Method
- Effective Environmental Program
- Example of FMEA Application
- Summary and Conclusions
- References
- About the Author

9 OVERVIEW OF RECENT WARNING LETTERS FOR ENVIRONMENTAL MONITORING

Jeanne Moldenhauer

- Introduction
- Water Monitoring Observations
- Microbial Contamination
 - Out-of-Limits Events for Environmental Monitoring
 - Failure to Identify Contaminating Organisms Found
 - Failure to Establish an Adequate Environmental Monitoring Program
 - Failure to Adequately Control the Environment
 - Microbial Data Excursions
 - Lack of Appropriate Training
 - Failure to Follow Established Procedures
 - Failure to Use Appropriate Aseptic Technique
 - Failure to Perform Sufficient or Appropriate Testing
 - Failure to Properly Document
- Lessons to Learn from these Observations
- Conclusion
- References
- About the Author

10 LONG-TERM MICROBIOLOGICAL AIR MONITORING

Claudia Scherwing, Jasmin Grigat and Karl Pflanz

- Introduction
- Requirements
- Gelatin Filter Method
- Study
- Test Parameters
 - Test Sterility of the Laminar Flow Hood Conditions
 - Experiment 1 — Recovery on Long-Term Air-Stressed Membranes
 - Experiment 2 — Recovery after Long-Term Air-Stressed Microorganisms
 - Composition of the Microbiological Population
 - Visual Comparison of the Microbiological Flora Grown on the Gelatin Filters

Species Identified

Statistics

Conclusion

Results

References

About the Authors

II RAPID, SIMPLE AND COST-EFFICIENT ENVIRONMENTAL MONITORING OF MICROORGANISMS BY FOURIER-TRANSFORM INFRARED SPECTROSCOPY

Mareike Wenning, Gernot Rieser and Siegfried Scherer

Introduction

FR-IR Spectroscopy — Technological Background

Sampling of Microorganisms

Reproducibility and Sensitivity

Reference Databases

How to Establish a Reference Database

Existing Reference Databases

How to Identify Unknown Spectra

Validation of Databases

Conclusions

References

About the Authors

Index