

CONTAMINATION CONTROL IN HEALTHCARE PRODUCT MANUFACTURING

Volume 4



Russell E. Madsen and Jeanne Moldenhauer
Editors

www.pda.org/bookstore

Contamination Control in Healthcare Product Manufacturing Volume 4

Russell E. Madsen and Jeanne Moldenhauer
Editors

PDA
Bethesda, MD, USA
DHI Publishing, LLC
River Grove, IL, USA

www.pda.org/bookstore

10 9 8 7 6 5 4 3 2 1

ISBN: 1-933722-98-3

**Copyright © 2016 Russell E. Madsen and Jeanne Moldenhauer
All rights reserved.**

All rights reserved. This book is protected by copyright. No part of it may be reproduced, stored in a retrieval system or transmitted in any means, electronic, mechanical, photocopying, recording, or otherwise, without written permission from the publisher. Printed in the United States of America.

Where a product trademark, registration mark, or other protected mark is made in the text, ownership of the mark remains with the lawful owner of the mark. No claim, intentional or otherwise, is made by reference to any such marks in the book. Websites cited are current at the time of publication. The author has made every effort to provide accurate citations. If there are any omissions, please contact the publisher.

While every effort has been made by the publisher and the authors to ensure the accuracy of the information expressed in this book, the organization accepts no responsibility for errors or omissions. The views expressed in this book are those of the editors and authors and may not represent those of either Davis Healthcare International or the PDA, its officers, or directors.



Connecting People, Science and Regulation®



This book is printed on sustainable resource paper approved by the Forest Stewardship Council. The printer, Gasch Printing, is a member of the Green Press Initiative and all paper used is from SFI (Sustainable Forest Initiative) certified mills.

PDA Global Headquarters

Bethesda Towers, Suite 150
4350 East-West Highway
Bethesda, MD 20814
United States
www.pda.org/bookstore
001-301-986-0293

Davis Healthcare International Publishing, LLC

2636 West Street
River Grove
IL 60171
United States
www.DHIBooks.com

www.pda.org/bookstore

CONTENTS

REGULATORY CHANGES RELATIVE TO CONTAMINATION CONTROL

| | | |
|----------|---|----------|
| I | ISO 14644 PARTS 1 AND 2 — THE REVISED CLEANROOM STANDARD AND CONTAMINATION CONTROL | 3 |
| | <i>Tim Sandle</i> | |
| | Introduction | 3 |
| | Cleanrooms and Contamination Control | 5 |
| | Brief History of Cleanroom Standards | 7 |
| | ISO 14644 | 9 |
| | ISO 14644 and Cleanroom Classification | 14 |
| | On-Going Compliance with ISO 14644-1 | 16 |
| | Risk Assessment | 21 |
| | Revisions to ISO 14644 (2015) | 21 |
| | Conclusion | 28 |
| | References | 29 |
| | About the Author | 32 |

| | | |
|----------|--|-----------|
| 2 | UPDATES TO THE ISO BIOBURDEN STANDARD | |
| | P.S. WHAT HAPPENED TO THE MICRO-BIOLOGISTS? | 33 |
| | <i>Martell Winters</i> | |
| | Additions to ISO 11737-1 | 33 |
| | P.S. Where are the Microbiologists? | 34 |
| | Developing a Bioburden Test Method | 36 |
| | Rationales and Documentation | 38 |
| | Low Bioburden | 39 |
| | Zero CFU Results | 40 |
| | Increasing Bioburden Test Sensitivity | 41 |
| | Pooling of Product Items for Testing | 43 |
| | Bioburden Test Methods | 46 |
| | Dealing with TNTC Results | 50 |
| | Bioburden Spikes | 51 |
| | Sources of TNTC and Bioburden Spike Results | 53 |
| | This is Microbiology, Not Chemistry or Physics | 54 |
| | References | 55 |
| | About the Author | 55 |

RISK ASSESSMENT

| | | |
|----------|--|-----------|
| 3 | RISK OF MICROBIOLOGICAL SPORES, PREVENTION MEASURES AND DISINFECTION STRATEGIES | 59 |
| | <i>Tim Sandle</i> | |
| | Introduction | 59 |
| | Spores: Types and Differences | 60 |
| | The Problem of Spores | 67 |
| | Cleanroom Microbiology | 69 |
| | Reducing the Risk of Spores | 75 |
| | Sporicidal Disinfection | 76 |
| | Environmental Monitoring | 87 |
| | Summary | 88 |
| | References | 88 |
| | About the Author | 94 |

CLEANING

| | | |
|----------|--|-----------|
| 4 | HOW ISSUES RELATED TO UTILITIES, SURFACES AND PRACTICES IMPACT CLEANROOM ENVIRONMENTS | 97 |
| | <i>Jim Polarine and Beth Kroeger</i> | |
| | Introduction | 97 |
| | HVAC and HEPA Filters | 98 |
| | Pressure Differentials | 108 |
| | Temperature and Humidity | 112 |
| | Damaged Flooring | 113 |
| | Damaged Duct Work | 114 |
| | Coldrooms | 114 |
| | Cleanroom Access | 115 |
| | Cleanroom Apparel and Personnel Practices | 116 |
| | References | 118 |
| | About the Authors | 120 |

GOWNING AND CLEANROOM BEHAVIOR

| | | |
|----------|---|------------|
| 5 | CLEANROOM GOWNING | 123 |
| | <i>Crystal M. Booth</i> | |
| | Introduction | 123 |
| | An Overview of Cleanroom Gowning | 124 |
| | Gowning for Grade D Areas | 128 |
| | Gowning for Grade C Areas | 129 |
| | Gowning for Grades B/A Areas | 129 |
| | Establishing a Compliant Aseptic Personnel Gowning Program | 131 |
| | FDA Warnings Pertaining to Poor Aseptic Technique and Gowning Practices | 143 |
| | Conclusion | 145 |
| | References | 149 |
| | About the Author | 151 |
| 6 | HANDWASHING IN THE PHARMACEUTICAL INDUSTRY | 153 |
| | <i>Jeanne Moldenhauer</i> | |
| | Background | 153 |
| | What is Handwashing? | 155 |
| | Regulatory and Industry Guidance on Handwashing | 155 |

| | |
|-----------------------------------|-----|
| Should Jewelry be Allowed or Not? | 156 |
| Components of Handwashing | 157 |
| Automated Handwashing Systems | 163 |
| Training and Accountability | 164 |
| Conclusion | 166 |
| References | 166 |
| About the Author | 169 |

INVESTIGATIONS

| | | |
|----------|--|------------|
| 7 | INVESTIGATION OF MICROBIOLOGICAL CONTAMINATION IN WATER SYSTEMS: A CASE STUDY | 173 |
| | <i>Walid El Azab</i> | |
| | Introduction | 173 |
| | Water Types | 176 |
| | Microbiological Contamination and Biofilm Generation | 178 |
| | Case Study: Water System Biofilm Contamination | 180 |
| | Key Lessons Learned | 196 |
| | Industry Best Practices on Water Microbial Contamination and Biofilm Eradication | 198 |
| | Conclusion | 200 |
| | Definitions | 201 |
| | References | 202 |
| | About the Author | 206 |
| 8 | THE FIGHT AGAINST CONTAMINATION IS DIFFICULT BUT NOT LOST | 207 |
| | <i>Olivier Chancel</i> | |
| | Perfidious Gaskets | 212 |
| | Perfidious Manual Diaphragm Valves | 215 |
| | Perfidious Drains | 218 |
| | Perfidious Cooling | 220 |
| | Perfidious Rinsing | 223 |
| | Perfidious Skin | 226 |
| | Perfidious Molds | 230 |
| | Perfidious O-ring Seals | 239 |
| | The Fight Against Contamination is Difficult but not Lost | 242 |
| | About the Author | 244 |

ENVIRONMENTAL MONITORING

| | | |
|-----------|---|------------|
| 9 | MICROBIAL MONITORING IN CLEANROOMS: USE OF CONTAMINATION RECOVERY RATES (USP <1116>), REAL TIME MONITORING, AND THE STATE OF CONTAMINATION CONTROL | 247 |
| | <i>Claudio Denoya and Gilberto Dalmaso</i> | |
| | Key Objectives of the Chapter | 247 |
| | Introduction | 248 |
| | Pharmaceutical Industry and the Need for Aseptic Processing | 248 |
| | Aseptic Processing and Environmental Monitoring | 250 |
| | Microbiological Control and Monitoring of Aseptic Processing Environments | 251 |
| | Main Changes in the Revised USP Chapter <1116> When Compared to Previous Version | 252 |
| | Microbial Monitoring: Instrumentation and Real Time Monitoring | 266 |
| | Real Time Monitoring Using Laser-Induced Fluorescence | 267 |
| | Surface Sampling | 270 |
| | Final Words | 271 |
| | References | 272 |
| | About the Authors | 273 |
| 10 | APPROACHES TO CHARTING AND SETTING CONTROL LIMITS FOR ENVIRONMENTAL MONITORING MICROBIAL DATA | 277 |
| | <i>Raphael Bar</i> | |
| | Introduction | 277 |
| | Practical Approaches to EM Microbial Data Evaluation | 279 |
| | Evaluation of Sets of EM Data as “High Counts” | 281 |
| | Examples of EM Data Evaluation as “High Counts” | 287 |
| | Evaluation of Sets of EM Data with “Low Counts” | 295 |
| | Example of EM Data Evaluation as “Low Counts” | 296 |
| | Evaluation of Sets of EM Data as “Rare Events” | 302 |
| | References | 308 |
| | About the Author | 309 |

| | |
|---|------------|
| 11 A PRACTICAL APPROACH TO INVESTIGATING ENVIRONMENTAL MONITORING EXCURSIONS | 311 |
| <i>Robert Westney</i> | |
| Introduction | 311 |
| Fundamentals of an Investigation Plan | 313 |
| Step-by-Step Investigation Points | 313 |
| Root Cause Analysis | 320 |
| Corrective/Preventive Action and Assessing Effectiveness | 321 |
| Assessing Facility and Product Impact | 322 |
| Summary | 323 |
| References | 324 |
| About the Author | 325 |

| | |
|--|------------|
| 12 RISK BASED ENVIRONMENTAL MONITORING IN ASEPTIC PROCESSING, IN THE ERA OF BIG DATA | 327 |
| <i>Parsa Famili, Susan Cleary and Marsha Hardiman</i> | |
| Introduction | 327 |
| What is Environmental Monitoring? | 328 |
| Big Data | 330 |
| Big Data and Environmental Monitoring | 331 |
| Risk Assessment | 333 |
| Risk Management Model | 336 |
| Identifying Areas of Risk | 337 |
| Importance of Automation | 348 |
| Environmental Monitoring Route Cause Analysis and Risk Mitigation Using Computerized System (A Case Study) | 350 |
| References | 355 |
| About the Authors | 356 |

IDENTIFICATION SYSTEMS

| | |
|--|------------|
| 13 PROS AND CONS OF USING MALDI-TOF MS FOR MICROBIOLOGICAL IDENTIFICATION | 361 |
| <i>Elvira Engelmann and Frank Kugler</i> | |
| MALDI-TOF MS Methodology | 363 |
| Pros and Cons of Using MALDI-TOF MS for Microbial Identification | 369 |
| MALDI-TOF Method in GMP Environment | 375 |

Contents

ix

| | |
|-------------------------------------|-----|
| Limitations of the MALDI-TOF Method | 376 |
| Creation of an In-House Database | 378 |
| Continuous Fine-Tuning Necessary | 379 |
| Conclusions | 380 |
| References | 382 |
| About the Authors | 387 |

INDEX

389