

# CONTAMINATION CONTROL IN HEALTHCARE PRODUCT MANUFACTURING

Volume 2



Russell E. Madsen and Jeanne Moldenhauer  
Editors

[www.pda.org/bookstore](http://www.pda.org/bookstore)

---

# CONTENTS

<b>I</b>	<b>INTRODUCTION</b>	<b>I</b>
	<i>Russell E. Madsen and Jeanne Moldenhauer</i>	
<b>2</b>	<b>MICROBIOLOGICAL PRODUCT SAFETY AND CONTAMINATION CONTROL IN A CHANGING TECHNOLOGICAL ENVIRONMENT</b>	<b>9</b>
	<i>Jim Akers</i>	
	Introduction	9
	A Review of Contamination Control Experience in Sterile Product Manufacturing	14
	Aseptic Manufacturing, Safety and Evolving Contamination Control	16
	Contamination Control is not Contamination Monitoring	19
	Summary: Sterile Products and Contamination Control	21
	Contamination Control in Non-sterile Product Manufacturing	24
	Product Safety: The Objective of Contamination Control	26
	Routes of Product Administration and Product Risk	28
	Microbial Risks of Non-sterile Products and the HMP	32
	Environmental Monitoring for Non-sterile Products	42
	The HMP and Production Facilities	42
	Conclusion	44
	References	45
	About the Author	48

iii

<b>3</b>	<b>APPLICATION OF HUMAN FACTORS IN ASEPTIC PROCESSING</b>	<b>51</b>
	<i>Miguel A. Nogueras</i>	
	Cognitive Workload and Human Performance	56
	Ergonomics and Human Performance	60
	Case study 1	68
	Case study 2	69
	Warnings and Labels and Human Performance	69
	Process Design and Human Performance	71
	Environmental Controls and Human Performance	82
	Case study 3	86
	Risk Management and Human Factors	88
	Validation of Aseptic Process Considering Human Performance	92
	Summary	94
	References	96
	About the Author	98
<b>4</b>	<b>CONTAMINATION RISKS AND THE PATIENT</b>	<b>99</b>
	<i>Mark Hunter, Michelle Luebke, and Mark Pasmore</i>	
	Patient 1	100
	Patient 2	100
	Infection	101
	Sepsis	103
	Signs and symptoms of infection/sepsis	104
	Patient risk factors	107
	Infection/sepsis: the perfect storm	111
	Investigation: the causal continuum	113
	Intrinsic continuum	115
	Extrinsic continuum	116
	Manufacturing contamination impacts on patients	122
	Microbial Contamination in the Manufacturing Environment	123
	Non-sterile, terminally sterilized, aseptically filled	125
	Proliferation	127
	Ingress	127
	Biofilms as an elevated risk	128
	Conclusions	129
	References	130
	About the Authors	136

<b>5</b>	<b>PARTICULATE MATTER IN INJECTABLE DRUG PRODUCTS</b>	<b>139</b>
	<i>Stephen E. Langille</i>	
	Introduction	139
	Classification and Sources of Particulate Matter	140
	Clinical Effects of Injected Particulate Matter	143
	Route of administration	144
	Size and shape	145
	Number	148
	Composition	149
	Patient population	153
	Relevant Regulations and Standards	155
	Continuing Efforts	161
	Conclusion	162
	References	163
	About the Author	173
<b>6</b>	<b>THE MICROBIOLOGIST'S CONTAMINATION CONTROL KIT</b>	<b>175</b>
	<i>Hilary Chan, Lynn Johnson and Jill Larivee</i>	
	Introduction	175
	Risks and Consequences of Microbial Contamination in a Non-Sterile Manufacturing Environment	176
	Anatomy of a Contamination Response Team	177
	Root cause analysis	179
	Remediation/control phase	180
	Contamination Support: What a Microbiologist Brings to the Table	181
	Trending of microorganisms	182
	Risk assessment: a microbiologist's retrospective perspective	184
	Rapid microbiological methods	186
	Be Prepared: Build your Knowledge Base for Enhanced Contamination Responsiveness	191
	What is a microbiologist's contamination control kit?	191
	Contents of a microbiologist's contamination control kit	192
	Building a base of knowledge: prospectively gathering data	197
	Practical Applications of the Microbiologist's Contamination Control Toolkit: Experimental Studies	203
	Building the study foundation: basic microbiological preparation techniques	203

Microbial survival studies	220
Summary	228
References	229
About the Authors	234
<b>7 IMPLEMENTING A CONTAMINATION CONTROL STRATEGY IN THE BIOTECH INDUSTRY TO EFFECTIVELY MAINTAIN MICROBIAL CONTAMINATION CONTROL</b>	<b>237</b>
<i>Jane Wyatt</i>	
Introduction	237
Background: Contamination Sources	239
People	240
Equipment	240
Building fabric	241
Environment and incoming materials	241
Contamination Controls	242
Clean room design/HVAC/material flow	243
Cleaning and sanitisation	245
Personnel behaviour/gowning	251
Environmental monitoring	254
Case study: applying a risk-based approach to Grade C/D clean room in support of sterile manufacturing	256
Alert and action levels	259
Trending and reporting of data	261
Communication of data (ICH Q10)	262
Risk Based Contamination Control Plan	263
Risk assessment overview	264
Project prioritisation	265
Conclusion	267
References	267
About the Author	268
<b>8 NEW RISK ASSESSMENT TOOLS FOR STERILE PRODUCTS</b>	<b>271</b>
<i>Gunther Gapp</i>	
Introduction	273
Risk Analysis Methods	278
Description of the initial method from 2006	278

Sterile API plants	283
Sterile FDF plants (without sterile filtration)	287
Sterile FDF plants (with sterile filtration)	288
Examples of the initial risk assessments	289
Improvement and Final Versions	289
Implementation of knock-out questions	289
Impact of knock-out questions to the risk assessment outcome and TRF	299
Interpretation of knock-out questions	301
Setting a variable risk emphasis factor for the aseptic operations unit	302
Important note on background	304
Current status	304
Use of FMEA as Sterile Risk Assessment Tool	311
Discussion	314
References	316
About the Author	317

**9 ASSESSING RESISTANCE AND APPROPRIATE ACCEPTANCE CRITERIA OF BIOCIDAL AGENTS 319**

<i>Art Vellutato</i>	
Introduction	319
Understanding Antimicrobial Effectiveness Studies	321
Case Study: Testing the Resistance Theory (Aseptic Processing, Inc.)	325
Interpreting the Results	338
Assessing Appropriate Acceptance Criteria for Sanitizers, Disinfectants, and Sporicides in Validation Studies	339
Interpreting Realistic Bioburden in Areas	341
Determining Critical Elements of the Protocol	345
Determining Acceptance Criteria	346
Federal/Country Law, Guidelines, and Technical Report Analysis	348
Corrosive/Residual Characteristics	349
Conclusion	350
References	351
About the Author	352

<b>10</b>	<b>STERILIZATION PROCESSES</b>	<b>355</b>
	<i>Jeanne Moldenhauer</i>	
	Microbiological Control Strategies in the Manufacture of Pharmaceutical Products	356
	Defining Sterilization	358
	What is the Difference between Sterilization and Sanitization?	360
	Key Concepts for the Validation of Sterilization Processes	361
	What Regulatory Requirements must be met for Sterilization Validation?	363
	Types of Sterilization Processes	367
	Sterilizing filtration	367
	Chemical sterilization methods — also known as liquid phase sterilization	373
	Gas sterilization	376
	Vapor sterilization	381
	Radiation sterilization	383
	Moist heat sterilization	388
	Sterilizer Configurations	390
	Determining Worst Case Conditions	391
	Load Configurations	393
	Cycle Monitoring	394
	Sterilization and how microorganisms die	394
	Biological indicators	395
	D-values	396
	z-values	397
	F-value	398
	Probability of a non-sterile unit	400
	Commissioning or engineering studies	401
	Validating moist heat sterilization systems	407
	Challenges for porous load cycles	417
	Sterilizer equivalence	417
	Dry heat sterilization	418
	Dry heat depyrogenation (and sterilization) tunnels	420
	Validating dry heat sterilization processes	421
	Systems to Maintain Sterilizer Qualification	423
	Personnel training	423
	Conclusion	424
	References	425
	About the Author	433

<b>II</b>	<b>MICROBIAL DECONTAMINATION USING CHLORINE DIOXIDE GAS</b>	<b>435</b>
	<i>Kevin Lorcheim</i>	
	Introduction	435
	Use	435
	Properties of Chlorine Dioxide Gas	436
	CD Gas Process	437
	Pre-condition	437
	Condition	437
	Injection	438
	Exposure	439
	Aeration	440
	Vacuum Chambers	441
	Residues and Off-gassing	441
	Efficacy	442
	Biological Efficacy	443
	Non-Biological Efficacy	444
	Concentration Monitoring	445
	Target Concentration vs. Exposure Time	446
	Control by time	447
	Control by dosage	447
	Cycle Development	448
	Process flexibility	448
	Process repeatability	449
	Validation	450
	Material compatibility	451
	Incompatibilities	452
	Chemical formulation	453
	Environmental factors	454
	Safety	455
	References	458
	About the Author	461
<b>I2</b>	<b>CONTAMINATION CONTROL IN DRUG SUBSTANCE MANUFACTURE</b>	<b>463</b>
	<i>David Fletcher</i>	
	Introduction	463
	Regulations	464
	The Operating Envelope	465
	Cross-contamination	467
	Batch disposition decision	468



<b>x</b>	<i>Contamination Control in Healthcare Product Manufacturing</i>	
	Managing cross-contamination	469
	Cleaning	473
	Visually clean — how clean is clean?	476
	Stain maps	479
	Direct Contamination	480
	Solid particulates	481
	Mechanical seal fluid	486
	Leachables	486
	Conclusion	488
	References	490
	About the Author	491
	Appendix	493
	Index	497