



## **Technical Report No. 70**

# **Fundamentals of Cleaning and Disinfection Programs for Aseptic Manufacturing Facilities**

## **PDA Fundamentals of Cleaning and Disinfection Programs for Aseptic Manufacturing Facilities Technical Report Team**

---

### **Authors**

---

**Arthur Vellutato Jr.**, Veltek Associates, Inc. (Chair)

**Cindy Adams**, Northampton Community College

**Barbara M. Andon**, Merck and Company, Inc.

**Michael B. Dolan**, Merck and Company, Inc.

**Pamela D. Deschenes**, Veltek Associates, Inc.

**Roger E. Deschenes**, Cubist Pharmaceuticals

**Jayne Dovin**, Sanofi Pasteur

**Barry A. Friedman**, Ph.D., Consultant

**Jill K. Giulianelli**, West-Ward Pharmaceuticals

**Peter Koger**, Veltek Associates, Inc.

**Alison Livsey**, Contec, Inc.

**Carol Molinaro**, Sanofi Pasteur

**James N. Polarine Jr.**, Steris Corporation

**Dona Reber**, Pfizer, Inc.

**Mike Sarli**, Steris Corporation

**Michael A. Szymanski**, GlaxoSmithKline Biologicals

**Steve Trombetta**, Hospira, Inc.

**Brent Watkins**, Veltek Associates, Inc.

---

PDA would like to recognize **Glenn Wright** of the PDA Science Advisory Board for supporting this technical report as the SAB subject matter advisor.

**DISCLAIMER:** The content and views expressed in this Technical Report are the result of a consensus achieved by the authorizing Task Force and are not necessarily the views of the organizations they represent.

# **Fundamentals of Cleaning and Disinfection Programs for Aseptic Manufacturing Facilities**

**Technical Report No. 70**

ISBN: 978-0-939459-77-3

© 2015 Parenteral Drug Association, Inc.

All rights reserved.



# Table of Contents

<b>1.0 INTRODUCTION</b> .....	<b>1</b>	9.1.1 Cleaning and Disinfecting Grade A (ISO 5) and Grade B (ISO 5 at Rest, 6/7 in operation) Areas .....	27
1.1 Purpose .....	1	9.1.2 Cleaning and Disinfecting Grade C (ISO 7 at rest / ISO 8 in operation) and Grade D (ISO 8 at rest) Areas.....	28
1.2 Scope .....	1	9.2 Application Methods .....	29
<b>2.0 GLOSSARY OF TERMS</b> .....	<b>2</b>	9.3 Cleaning and Disinfecting Materials and Workstations .....	30
<b>3.0 SANITIZER, DISINFECTANT, AND SPORICIDE CLAIMS AND CLASSIFICATIONS</b> .....	<b>5</b>	9.3.1 Cleaning and Disinfecting Curtains ...	30
<b>4.0 REGULATORY EXPECTATIONS</b> .....	<b>6</b>	9.3.2 Cleaning and Disinfecting Unidirectional Airflow Hoods, Benches, and Biosafety Cabinets .....	30
4.1 Regulations and Guidance .....	6	9.4 Cleaning and Disinfecting Equipment Surfaces.....	31
4.2 Regulatory Inspections .....	7	9.4.1 Non-product-contact Equipment Surfaces.....	31
<b>5.0 QUALIFICATION OF NEW SUPPLIERS AND AGENTS</b> .....	<b>8</b>	9.4.2 Work Surfaces.....	31
5.1 Qualification Testing .....	9	9.4.3 Nonstructural Clean Room and Hard-to-Clean Surfaces.....	31
5.2 Efficacy Testing .....	9	9.5 Cleaning and Disinfecting Tools .....	32
5.2.1 In-Suspension Studies.....	10	9.6 Cleaning and Disinfecting Water Points of Use.....	33
5.2.2 Carrier Surface Studies.....	11	9.7 Disinfecting Drains.....	33
<b>6.0 IN-USE EXPIRATION DATING</b> .....	<b>15</b>	9.8 Reducing Corrosion and Deterioration of Surfaces .....	34
<b>7.0 CONTROL OF THE ENVIRONMENT</b> .....	<b>16</b>	9.9 Cleaning and Disinfection of Nonclassified Areas.....	34
7.1 Introduction of Clean Room Manufacturing Supplies.....	17	<b>10.0 FREQUENCY FOR CLEANING AND DISINFECTION</b> .....	<b>35</b>
7.1.1 Types of Clean Room Disinfecting Agents .....	18	<b>11.0 RESISTANCE AND ROTATION</b> .....	<b>38</b>
7.1.2 Introduction of Tanks, Vessels, Carts, and Equipment into the APA .....	18	<b>12.0 RETURN FROM A SHUTDOWN</b> .....	<b>39</b>
7.1.3 Introduction of Cleaning Supplies and Equipment into the APA.....	19	<b>13.0 HOLD TIMES FOR CLEANED AREAS, NON-PRODUCT-CONTACT EQUIPMENT, AND UTENSILS</b> .....	<b>40</b>
7.1.4 Introduction of Components into the APA .....	20	<b>14.0 TRAINING</b> .....	<b>41</b>
7.2 Environmental Monitoring Data Analysis.....	20	14.1 Basic Microbiology .....	41
7.3 Attaining and Selecting Environmental Isolates.....	21	14.2 Contamination Sources and Risks .....	42
<b>8.0 IN-SITU FIELD STUDIES</b> .....	<b>22</b>	14.3 Facility Design and Airflow .....	42
8.1 Environmental Monitoring Before and After the Start-up of a Facility or Area .....	22	14.4 Gowning .....	42
8.2 Environmental Monitoring Before and After Cleaning and Disinfection During Routine Operation .....	23	14.5 Clean Room Behavior and Personal Hygiene .....	42
<b>9.0 CLEANING AND DISINFECTION</b> .....	<b>24</b>	14.6 Basic Environmental Monitoring .....	43
9.1 Area Classifications and Cleaning and Disinfecting Approaches.....	24	14.7 Aspects of a Cleaning Program.....	43

14.8 Aspects of a Disinfection Program.....	43	20.0 APPENDIX IV: OVERVIEW OF THE EU BIOCIDAL REGULATIONS .....	53
14.9 Assessment of Understanding and Qualification .....	44	21.0 APPENDIX V: EPA-RELATED SAFETY LABELING INFORMATION .....	54
<b>15.0 CONDUCTING INVESTIGATIONS RELATED TO CLEANING AND DISINFECTION .....</b>	<b>45</b>	22.0 APPENDIX VI: AOAC PROTOCOL TESTING FOR DISINFECTANT REGISTRATION .....	57
<b>16.0 CONCLUSION .....</b>	<b>47</b>	23.0 APPENDIX VII: EN TESTS FOR DISINFECTION EFFICACY .....	60
<b>17.0 APPENDIX I: HISTORY OF DISINFECTION .....</b>	<b>48</b>	24.0 APPENDIX VIII: LARGE-SCALE GASSING OR FOGGING OF CLEAN ROOMS.....	62
17.1 Disinfecting Technologies of the Past .....	48	25.0 REFERENCES.....	65
17.2 Disinfecting Technologies in the Age of Chemistry .....	48	26.0 SUGGESTED READING.....	66
17.3 Discovering Microorganisms as a Basis of Disease.....	49		
17.4 Microbiological Contamination Control Today.....	49		
<b>18.0 APPENDIX II: REGISTRATION OF SANITIZERS, DISINFECTANTS AND SPORICIDES .....</b>	<b>51</b>		
<b>19.0 APPENDIX III: OVERVIEW OF THE U.S. ENVIRONMENTAL PROTECTION AGENCY .....</b>	<b>52</b>		

## FIGURES AND TABLES INDEX

<b>Table 5.2.1-1</b>	Commonly Used Neutralization Agents .....	11	<b>Figure 10.0-1</b>	Example Risk-Based Approach for Selection of Routine Cleaning and Disinfection Frequencies for Classified Manufacturing Areas .....	37
<b>Table 5.2.2-1</b>	Recommended Acceptance Criteria..	14	<b>Table 21.0-1</b>	Toxicity Categories .....	54
<b>Figure 7.0-1</b>	Considerations to Maintain Low Levels of Contamination.....	17	<b>Table 21.0-2</b>	Precautionary Statements by Route of Entry .....	55
<b>Table 9.1-1</b>	Area Classifications: Cleanroom Standards–Airborne Particulate Limits..	25	<b>Table 23.0-1</b>	Summary of EN Test Criteria for Registration for Established Claims...	60
<b>Table 9.1-2</b>	Environmental Monitoring Requirements/Guidance.....	26			
<b>Table 9.4.3-1</b>	Examples of Surfaces .....	32			

# 1.0 Introduction

While sterile product manufacturing has the most stringent application, these concepts can also be used to design a program for the manufacture of nonsterile products. To ensure a consistently controlled production environment, a comprehensive cleaning and disinfection program together with a contamination control program should be supported by the following:

- Sound facility design and maintenance
- Established documentation systems
- Validated/qualified disinfection procedures
- Reliable process controls
- Good housekeeping practices
- Effective area traffic and access controls
- Effective training, certification/qualification, and evaluation programs
- Quality assurance of materials and equipment
- Risk management mitigation

The purpose of the cleaning and disinfection program is not only to control microbial contamination, but also to serve as a corrective action for the loss of control for viable excursions contamination. While the destruction of viable cells are an integral part of the cleaning and disinfection program, the use of disinfection as a singular focus without efforts to control contamination from entering the area is without technical merit. Environmental monitoring (EM) evaluates the efficacy of controls on the manufacturing environment. It is through control of bioburden levels entering the area, along with cleaning and disinfection, that acceptable viable control of the manufacturing or appropriate testing environment is achieved. This technical report provides comprehensive information and suggested best practices as well as appropriate references to support such guidance.

For individuals wanting a historical perspective of disinfection, a summary can be found in Appendix I (**Section 17.0**).

The technical report team consisted of members who are cleaning and disinfection experts from various global pharmaceutical and biopharmaceutical companies, academia, and companies that manufacture agents used in disinfection.

## 1.1 Purpose

The purpose of this document is to identify systematic elements that are essential to assuring an appropriate and compliant cleaning and disinfection program for aseptic and bioburden controlled manufacturing facilities and classified environments.

## 1.2 Scope

The document covers cleaning and disinfection within controlled and noncontrolled environments using chemical agents that reduce or destroy microorganisms. The document provides guidance for non-product-contact surface cleaning and disinfection. This document is not intended to fully address product-contact surface cleaning from a clean-in-place (CIP) or clean-out-of-place (COP) system which is specifically addressed in PDA's *Technical Report No. 29 (Revised 2012): Points to Consider for Cleaning Validation* and *Technical Report No. 49: Points to Consider for Biotechnology Cleaning Validation (1,2)*.

This document should be considered as technical guidance; it is not intended to establish any mandatory or implied standard.