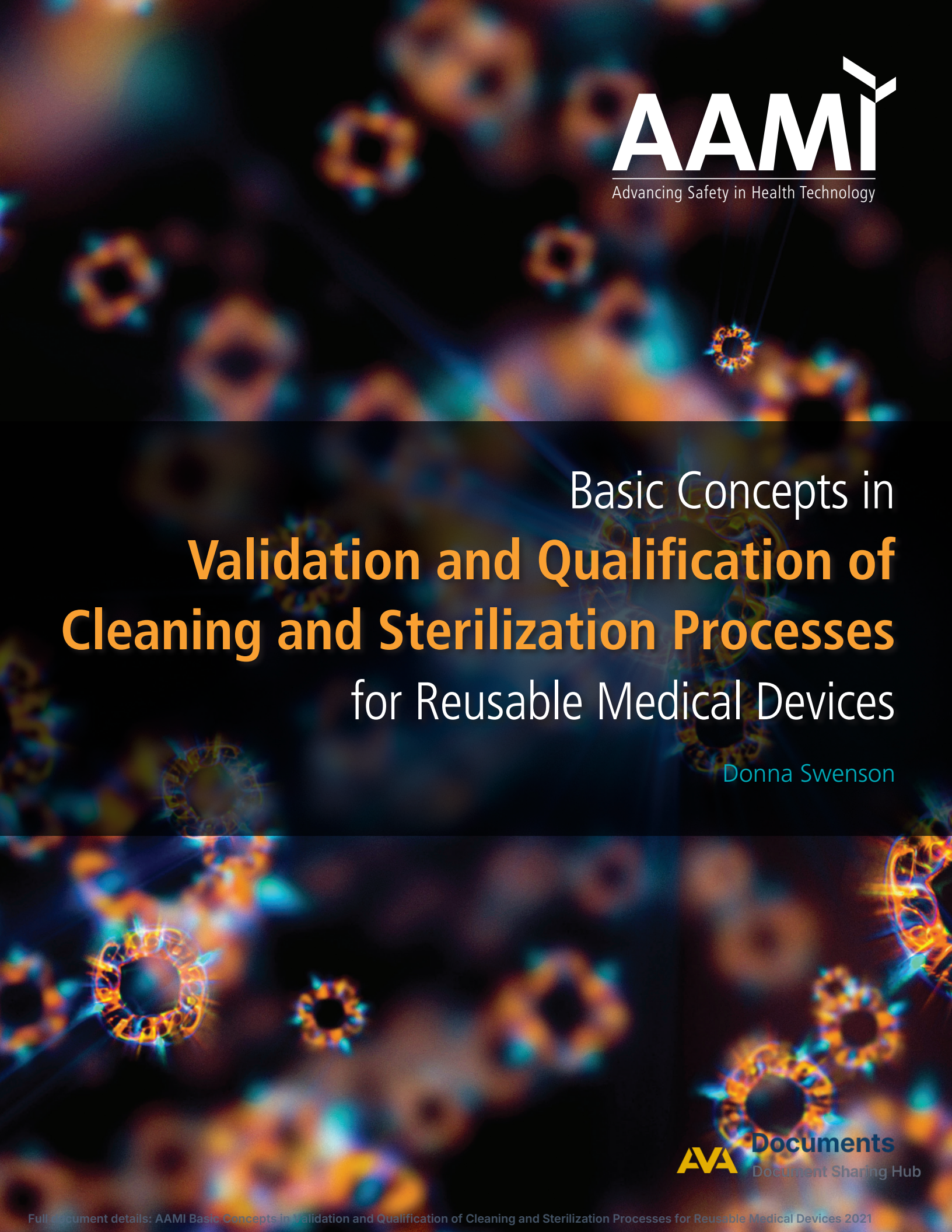



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Published by
AAMI
901 N. Glebe Road, Suite 300
Arlington, Virginia 22203
www.aami.org

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Printed in the United States of America

ISBN 978-1-57020-786-0

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AAMI
Advancing Safety in Health Technology

# Basic Concepts in Validation and Qualification of Cleaning and Sterilization Processes for Reusable Medical Devices

Donna Swenson

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# Table of Contents


*Page*

**Foreword** . . . . . **vii**

**Preface** . . . . . **ix**

**Acknowledgments** . . . . . **xi**

**Chapter 1. Introduction** . . . . . **1**

**Chapter 2. Definitions and Abbreviations** . . . . . **3**

**Chapter 3. The Science of Sterilization** . . . . . **9**
- Introduction . . . . . 9
- Types of Microorganisms . . . . . 9
- Microbial Growth . . . . . 12
- Bioburden . . . . . 13
- Microbial Resistance . . . . . 13
- Microbial Lethality . . . . . 13
- Microbial Control . . . . . 15

**Chapter 4. The Quality Management System** . . . . . **23**
- Introduction . . . . . 23
- General Requirements . . . . . 23
- Documentation Requirements . . . . . 23
- Management Responsibility . . . . . 24
- Resource Management . . . . . 25
- Product Realization . . . . . 26
- Purchasing Requirements . . . . . 26
- Production and Service Provisions . . . . . 27
- Measurement, Analysis, and Improvement . . . . . 27
- New Products . . . . . 30
- Summary . . . . . 30



Documents
Document Sharing Hub





Full document details: AAMI Basic Concepts in Validation and Qualification of Cleaning and Sterilization Processes for Reusable Medical Devices 2021

*Page*

**Chapter 5. Process Validation and Verification Concepts . . . . . 31**
Introduction. . . . . 31
Why and When to Conduct Validation Testing . . . . . 32
Validation Plans. . . . . 33
Types of Validation . . . . . 36
Statistical Process Control . . . . . 39
Product Design . . . . . 39
Process Design . . . . . 42
Installation Qualification . . . . . 45
Operational Qualification . . . . . 48
Performance Qualification . . . . . 49
Process Control . . . . . 51

**Chapter 6. Cleaning Validation and Verification . . . . . 53**
Introduction. . . . . 53
Selection of Cleaning Method . . . . . 53
Cleaning Process Validation. . . . . 56
Cleaning Process Verification . . . . . 59

**Chapter 7. Sterilization Validation. . . . . 69**
Introduction. . . . . 69
Product Design . . . . . 70
Process Design . . . . . 75
Qualification Studies. . . . . 78
Installation Qualification . . . . . 78
Operational Qualification . . . . . 80
Performance Qualification . . . . . 80
Specific Considerations for Steam Sterilization . . . . . 86
Specific Considerations for Ethylene Oxide Sterilization. . . . . 95
Specific Considerations for Chemical Sterilization: Hydrogen Peroxide, Ozone, LTSF . . . . 99

**Chapter 8. Product Quality Assurance Testing in Healthcare Facilities. . . . . 105**
Introduction. . . . . 105
Use of Normal Production Cycles . . . . . 106
Identification of Product Families and Master Products . . . . . 106
Use of Chemical and Biological Indicators for Sterilization Processes . . . . . 107
Placement of Master Products . . . . . 108
Load Configuration . . . . . 108
Drying Time and Cooling for Steam Sterilization . . . . . 109
Aeration for EO Sterilization . . . . . 109
Aeration for LTSF, $H_2O_2$, and $H_2O_2$/Ozone Combination Sterilization . . . . . 109
Test Results for Sterilization Processes. . . . . 109
Test Results for Cleaning Processes . . . . . 109
Frequency of Testing. . . . . 110

Documents
Document Sharing Hub



Full document details: AAMI Basic Concepts in Validation and Qualification of Cleaning and Sterilization Processes for Reusable Medical Devices 2021

*Page*

**Chapter 9. Human Factors Testing for Processing of Reusable Medical Devices . . . . . 111**
Introduction. . . . . .111
Human Factors Engineering and Design Control . . . . . 112
Design of Devices . . . . . 112
Design Principles . . . . . 113
Material Characteristics . . . . . 114
Design of Processing Procedures . . . . . 114
Processing Personnel . . . . . 116
Design of Processing Instructions. . . . . 116
Education, Training, and Competency . . . . . .117
Validation. . . . . .117

**Bibliography . . . . . 119**
Cited References . . . . . 119
Other Resources . . . . . 121

**Annexes**
A Sample Protocol for Operational Qualification of a Sterilizer . . . . . 125
B Sample Outline of a Cleaning Process Validation Protocol . . . . . 127
C Sample Outline of a Cleaning Process Validation Report . . . . . 129
D Sample Outline for a Formative Human Factors Usability Study. . . . . 131

**Figures**
1 Microbial Lethality Measures . . . . . 15
2 Example of an Audit Form . . . . . 29
3 Sample Outline of a Validation Master Plan . . . . . 35
4 Sample Outline of a Validation Protocol . . . . . 36
5 Sample Installation Drawing Showing Minimum Service Clearance. . . . . 46
6 Control Chart for Cannula Inner Diameter . . . . . 52
7 Manual Cleaning. . . . . 55
8 Visual Inspection of an Instrument. . . . . 63
9 Visual Inspection of an Instrument with Magnification Shown on a Computer Screen . . . 63
10 Various Types of Sterilization Packaging . . . . . 74
11 Sample Checklist for Installation of a Steam Sterilizer . . . . . 89
12 Sample Checklist of Service and Utility Requirements for a Medium-Size Healthcare Steam Sterilizer. . . . . 90
13 Diagram of Data Logger Placement for Empty-Chamber Heat Distribution Study. . . . . 94
14 Sample Checklist for Installation of an EO Sterilizer. . . . . 98
15 Sample Checklist for Installation of an $H_2O_2$ Sterilizer . . . . . 101

**Tables**
1 Exponential Growth of Unicellular Organisms . . . . . 12
2 Sterility Assurance Level/Spore Log Reduction . . . . . 14
3 Additional Reprocessing Criteria and Issues . . . . . 41
4 Sample Service/Utility Requirements for an Installation Qualification . . . . . 47

Documents
Document Sharing Hub



Full document details: AAMI Basic Concepts in Validation and Qualification of Cleaning and Sterilization Processes for Reusable Medical Devices 2021

*Page*

**Tables (continued)**


5 Laboratory Residue Detection Methods . . . 57
6 Acceptance Criteria . . . 58
7 In-Use Tests Available to Assess Efficacy of Cleaning of Medical Devices . . . 60
8 In-Use Tests Available to Assess Efficacy of Wash Processes/Automated Wash Equipment Used for Medical Device Reprocessing . . . 61
9 IES-Recommended Illuminance Levels for Work Environments . . . 64
10 Soils Removed by Detergents of Various pH Levels . . . 67
11 Terminal Sterilization Process Development . . . 82
12 Considerations for Placement of BIs and CIs in Master Products . . . 85
13 Sample Product Density Calculations . . . 87
14 Time and Temperature Parameters for Gravity-Displacement Steam Sterilization Cycles in Healthcare Facilities . . . 88
15 Time and Temperature Parameters for Dynamic-Air-Removal Steam Sterilization Cycles in Healthcare Facilities . . . 88
16 Steam Quality Requirements for Sterilization . . . 91
17 Contaminants in Condensate Measured at the Steam Inlet to the Sterilizer to Be Considered in Relationship to the Corrosion of Materials (for Clean Steam) . . . 92
18 Contaminants in Condensate from Steam Used by the Sterilizer to Be Considered in Relation to Contamination of the Load . . . 93
19 Operational Qualification Performance Tests . . . 95
20 Examples of User Demographics . . . 114
21 A Simple Task Analysis for Automated Washer Cleaning of a Needle Holder . . . 115



Documents
Document Sharing Hub





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# Foreword

Modern medicine as we know it would never have existed without the advent of disinfection and sterilization. Through the early 19th century, the inside of the living human body was the doctor's equivalent to those areas on old maps marked "Here there be dragons"—it was dangerous territory to be avoided whenever possible. Voluntary surgery was largely limited to minimally invasive procedures such as blood-letting, tooth extraction, and removing kidney stones by dilating the urethra. Invasive surgery's high rate of mortality, which resulted from both infections and the rudimentary nature of surgical technique, made such procedures a tool of last resort.

Medical pioneers like Louis Pasteur and Edward Jenner changed this. Not only did they establish the causal connection between microbes and infections, they created methods and technologies to control the former and thereby prevent the latter. With the introduction of these practices, the interior body cavity was no longer terra incognita for doctors. Physicians were able to surgically treat conditions previously considered death sentences; surgery became safer, medical knowledge flourished, and surgical technique advanced. Since the first successful appendectomy in 1884, surgery has progressed to the point where robots are now used to repair the heart, and what were formerly major surgeries have become outpatient procedures.

Key to this battle against surgical infections has been the role played by those who reprocess the medical instruments used in surgery. Since the invention of the autoclave in 1879, steam sterilization has been the primary choice for treating heat-resistant surgical instruments, like those made of metal or glass. Instruments that could not withstand the high temperatures or humidity of steam sterilization were treated using dry heat or by a variety of chemical sterilants or disinfectants. When devices were properly cleaned and disinfected or sterilized, post-surgical infections arising from device contamination were extraordinarily rare—and where they did occur, they could be easily treated using 20th century antibiotics.

Despite two centuries of progress in fighting and preventing infections, the battle continues. Illnesses resulting from newly evolved bacteria, like methicillin-resistant Staphylococcus aureus, or from more-recently discovered infectious agents, like prions, are harder or impossible to treat. Complex new medical instruments—such as endoscopes and those used in robot-assisted surgery—incorporate delicate materials and sensitive electronics that make the work of reprocessing personnel similarly more complicated. Finally, modern-day epidemics, such as the Ebola outbreaks and COVID-19 pandemic, create new challenges in preventing infections as well as in making sure urgently needed healthcare products like masks and ventilators are available.

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Dealing with these challenges will require that those involved in reprocessing—both device manufacturers and sterile processing personnel—have deeper knowledge of the science and practices that underlie reprocessing. For sterile processing personnel, it is not enough to know how to load and run a sterilizer or how to follow manufacturer's instructions. Today, they must understand how cleaning, disinfection, and sterilization processes are developed and validated, and they should possess at least a basic understanding of the microbiology, chemistry, and physics behind those processes. Similarly, medical device designers and manufacturers can no longer wait until a device is ready to go to market to figure out how it will be reprocessed. They need this knowledge in advance so that sterilization requirements can be appropriately addressed as part of device design, ensuring that reprocessing the devices they create in the future will be simpler, safer, and more effective.

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# Preface

This book is about the principles on which cleaning and sterilization validation and qualification are based. The first edition of this book, *Basic Concepts in Sterilization Processes: Verification, Validation, and Qualification,* used steam sterilization as an example to explain the various principles discussed. This edition has been expanded to include all sterilization modalities that are commonly used by healthcare facilities to process reusable medical devices, and it uses the same approach to facilitate understanding of those principles. I begin with basic information about the science behind sterilization and quality management. Next, the book covers the principles of validation and then how those principles apply to cleaning processes, the validation of various sterilization processes, and product quality assurance testing of cleaning and sterilization processes.

This book is written as a textbook. It is meant to provide an explanation of the basic concepts of validation and qualification of cleaning and sterilization processes for reusable medical devices in both healthcare facilities and medical device manufacturing facilities. The intent of the book is to help sterile processing and medical device manufacturing personnel be on the "same page" and to be able to use the same language and concepts in discussing and understanding cleaning and sterilization processes. I also expect that this book will help different groups understand each other's needs. I believe that with the help of the many reviewers and the editor, I have accomplished these goals. I am hopeful that with improved understanding of each group's requirements, we will be able to obtain medical devices that meet the needs of all involved parties: the patient, the user of the device, and the reprocessor of the device.

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# Acknowledgments

Many people have helped bring this book to publication. I would first like to thank my husband, Charles (Chuck) Swenson. Without Chuck, I would never have become the person capable of writing this book. I remember that he used to introduce me to people as "Donna, my A student, my wife." In his eyes, I was and still am, first and foremost, Donna, the person he helped to become an expert on the sterilization of medical devices. Thanks for all the years of support. Since the writing of the first edition of this book, Chuck passed. Even though he is no longer physically part of my world, I still feel his support and believe that without his support I would not have been capable of writing either the first edition or this revsion. I am still "his A student."

Next, I would like to thank several people at AAMI. Joe Lewelling believed in me and in the importance of this book. Without his support, this book would never have been begun. I also want to thank Steve Campbell, who worked with me to make the first edition of this book a reality. Steve listened when I said that I needed more reviewers, and he made it happen. Judy Veale, who formerly participated in AAMI standards-development activities and who continues to work on various AAMI projects, has worked with me closely on both the first and second editions. Judy's skills as an editor have been invaluable. She has been insightful, has offered many suggestions, and has helped to clarify many points by asking questions. For this second edition of the book, Melissa Coates has been my AAMI contact; she has been every bit as helpful as the people who originally supported this work. The comments she obtained from several people helped me decide how to expand the book. Much has changed in the processing of reusable medical devices since the first edition was published in 2014. In general, the reviewers agreed that it was time to expand the material in the book to make it more useful to today's sterile processing and manufacturing personnel.

Many people reviewed this book and helped make it into a better product that answers the questions that sterile processing and medical device manufacturing personnel have about cleaning and sterilization validation and qualification. I am thankful for their contributions and for the time they all committed to reviewing the original and subsequent drafts of both the first and second editions of the book. Their comments helped to strengthen the book and to ensure that I actually did achieve the goals that I set out to accomplish in its writing.

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CHAPTER 1

# Introduction

Healthcare sterile processing and medical device manufacturing professionals of today need a comprehensive understanding of cleaning and sterilization processes for medical devices and how to produce sterile product. Device manufacturers are required to provide information to the Food and Drug Administration (FDA) on how they will address the manufacturing of all products and how reusable products are to be cleaned, disinfected, and/or sterilized by the end user or sterile processing professional. For device manufacturers to fulfill this obligation, an understanding of the cleaning and sterilization processes used in healthcare is required. Sterile processing professionals must ensure that

- Their cleaning and sterilization processes meet quality assurance standards.
- They are adhering to these processes.
- The methods used for the products that they process are verified.
- The processes used for the sterile products they create are validated.

This book is intended to be used as a textbook by medical device manufacturers, healthcare sterile processing professionals, and students of sterilization. It explains concepts and provides examples and definitions for sterilization science, quality management, validation theory, and cleaning and sterilization practices used in healthcare applications.

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CHAPTER 2

# Definitions and Abbreviations

## Definitions

**Acceptable quality level (AQL)**[1] For a continued series of lots, the quality level that for the purpose of sampling inspection is the limit of a satisfactory process average.

NOTE: AQL defines a producer's protection level in the sense that a lot at the stated AQL has a high probability of acceptance and, therefore, a low probability of rejection.

**Acellular infectious agent** Acellular microorganism capable of causing disease.

**Acellular microorganism** Microscopic organism that does not have any cells and must partner with a living cell in order to live and grow. Examples include viruses, viroids, prions, and plasmids.

**Antiseptic** Substance that stops or reduces the growth of microorganisms.

**Attribute data** Data representing an individual characteristic that either exists or does not exist.

**Bacilli** Bacteria that are rod- or stick-shaped. Bacilli often are spore forming.

**Bacteria** Prokaryotic round, spiral, or rod-shaped single-celled microorganisms.

**Bioburden**[2] Population of viable microorganisms on a product and/or a sterile barrier system.

NOTE: When measured, bioburden is expressed as the total count of bacterial and fungal colony-forming units (CFUs) per single item.

**Biological indicator**[3] Test system containing viable microorganisms providing a defined resistance to a specified sterilization process.

**Calibration**[4] A set of operations that establish, under specified conditions, the relationship between values of quantities indicated by a measuring instrument or measuring system, or values represented by a material measure or a reference material, and the corresponding values obtained using working standards.

Calibration should not be mistaken with adjustment of a measuring system nor with verification of calibration. Often the first step alone in the above definition is perceived as being calibration.

**Change control** Systematic approach to ensuring that a process change is implemented in a controlled manner.

**Cocci** Bacteria having a spherical or near-spherical shape.

**Colony-forming unit (CFU)** An individual colony of bacteria or fungi. In microbiology, the number of colony-forming units is an estimate of the number of viable bacteria or fungi.

**Concurrent validation** Validation study conducted as part of routine production of a product.

**Data logger** Electronic device that records information (data), usually at specified time intervals.

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**Decimal reduction value (D value)**[2] Time or dose required to achieve inactivation of 90% of a population of the test microorganism under stated conditions.

NOTE: The larger the D value, the more resistant the microorganism is to destruction. The value can be derived by plotting the logarithm of the number of microbial survivors against sterilization exposure time; the time corresponding to a 1-logarithm reduction in numbers can then be directly measured.

**Design history file (DHF)**[5] Compilation of records that describes the design history of a finished device.

NOTE: Each time that a device design is changed, the change needs to be documented in the design history file.

**Design qualification (DQ)**[6] Verification that the proposed specification for the facility, equipment, or system is suitable for the intended use.

**Device master record (DMR)**[5] Compilation of records containing the procedures and specifications for a finished device.

NOTE: The DMR contains all the information needed to manufacture a specific device to company specifications.

**Disinfectant** Physical or chemical method that destroys microorganisms on inert surfaces.

**Disinfection**[2] Process that kills pathogenic and other microorganisms by physical or chemical means.

NOTE: Disinfection destroys most recognized pathogenic microorganisms but not necessarily all microbial forms, such as bacterial spores. Disinfection processes do not ensure the margin of safety associated with sterilization processes.

**Eukaryotic microorganisms** Organisms consisting of cells with a distinct nucleus within which the genetic material is contained.

**Exponential** Increase or decrease in number or exponent at a constantly growing rate; raising or lowering a number by a specified power. The increase or decrease will become steeper or shallower the higher the power to which the exponent is raised.

**$F_{bio}$** Microbiological lethality of a sterilization process expressed in terms of the equivalent time, in minutes, at a given sterilization temperature. The most common $F_{bio}$ is $F_0$, which uses a sterilization temperature of 121.1°C.

**$F_0$ value**[7] Microbiological lethality of a sterilization process expressed in terms of the equivalent time, in minutes, at a temperature of 121.1°C with reference to microorganisms with a z value of 10°C.

**Factory acceptance test (FAT)** Testing of new equipment performed by the equipment manufacturer before shipping the equipment to the customer. This testing is intended to ensure that the machine is performing as designed before release to a customer.

**Fault condition** Situation in which one or more process parameters is outside its/their specified tolerance.

**Fungi** Single- or multicelled plants that do not contain chlorophyll and that live by decomposing and digesting the organic material on which they grow. Examples include yeast and mold.

**Installation qualification (IQ)**[2] Process of obtaining and documenting evidence that equipment has been provided and installed in accordance with its specification.

**LD50** Dose of a specific chemical administered by a specific route that is lethal to 50% of an animal population.

**Limit of detection (LOD)** Lowest amount of a substance that can be detected by a specific test method.

**Limit of quantitation (LOQ)** Lowest amount of a substance that can be quantified by a specific test method.

**Lowest therapeutic dose (LTD)** Lowest amount of a therapeutic agent that causes the desired therapeutic effect to occur.

**Management representative** Member of management who is responsible for ensuring that a company's quality system is implemented and adhered to. This person is usually the liaison between the company and regulatory agencies.

**Management review** Periodic review of a quality system to ensure that the system is suitable and effective.

NOTE 1: According to the FDA,[5] "Management with executive responsibility shall review the suitability and effectiveness of the quality system at defined intervals and with sufficient frequency according to established procedures to ensure that the quality system satisfies the requirements of this part and the manufacturer's established quality policy and objectives. The dates and results of quality system reviews shall be documented."

NOTE 2: It is generally recommended that management reviews be conducted at least annually.

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**Master product**[2] (Sterilization) product designated as representative of all members of a product family. This product has the most difficult-to-sterilize attributes of any member of the family.

NOTE: The concept of product families and master products can be applied to all types of processes (i.e., manufacturing, cleaning, and sterilization).

**Maximum allowable carry over (MACO)** Maximum amount of a specific chemical residual that is acceptable to still be present on a device after completion of a process.

**Operational qualification (OQ)**[2] Process of obtaining and documenting evidence that installed equipment operates within predetermined limits when used in accordance with its operational procedures.

**Organelle** Specialized subunit within a cell that performs a specific function within the cell. Examples include mitochondria, vacuoles, and chloroplasts.

**Pathogen** Disease-producing agent capable of producing illness or disease in a host organism.

**Performance qualification (PQ)**[2] Process of obtaining and documenting evidence that the equipment, as installed and operated in accordance with operational procedures, consistently performs in accordance with predetermined criteria and thereby yields product meeting its specification.

**Prions**[8] Transmissible pathogenic agents that cause a variety of neurodegenerative diseases of humans and animals, including scrapie in sheep and goats, bovine spongiform encephalopathy (BSE) in cattle, and Creutzfeldt-Jakob disease (CJD) in humans. They are unlike any other infectious pathogens, including viruses, because they are composed of an abnormal conformational isoform of a normal cellular protein, the prion protein (PrP). Prion diseases are disorders of protein configuration involving template-assisted replication and resulting in abnormal protein accumulation in the brain, which causes neuronal dysfunction, degeneration, and death. Prions are extremely resistant to inactivation by heat and disinfecting agents.

**Process challenge device**[2] Item designed to constitute a defined resistance to a sterilization process and used to assess performance of the process.

**Process parameter**[6] Specified value for a process variable.

NOTE: The specification for a sterilization process includes the process parameters and their tolerances.

**Product family**[2] Group or subgroup of product that is characterized by similar attributes, such as mass, material, construction, set weight, shapes, presence of lumens, and type of sterile barrier system, and that presents a similar challenge to the sterilization process.

NOTE: In grouping products by construction, it is necessary to consider size and/or surface area, surface finish or texture, and the presence of any cannulations, lumens, or mated surfaces.

**Product quality assurance (PQA) testing** Quality assurance testing of routinely processed items representing a product family intended to verify that the process being used by a facility on a particular product family is working as specified.

**Prokaryotic microorganisms** Group of organisms that lacks a true nucleus with a membrane and other membrane-bound organelles. Examples include bacteria and archaea.

**Prospective validation** Validation study conducted before the product is entered into routine production.

**Protozoa** Single-celled, usually microscopic, eukaryotic organisms. Examples include amoebae, ciliates, flagellates, and paramecia.

**Quality audit**[5] Systematic, independent examination of a manufacturer's quality system that is performed at defined intervals and at sufficient frequency to determine whether both quality system activities and the results of such activities comply with quality system procedures, that these procedures are implemented effectively, and that these procedures are suitable to achieve quality system objectives.

**Retrospection validation** Validation study conducted on processes or products that are already in use or distribution.

**Spirilla** Bacteria having a spiral, twisted, or coiled shape. Spirilla can consist of long chains or be short and comma-like.

**Spore log reduction (SLR)** Log of the initial number of spores minus the log of the spores surviving the treatment.

**Statistical process control (SPC)** Monitoring of a process by using statistical methods to determine if a process is in or out of control.

**Sterilant** Physical or chemical agent that is applied to inanimate objects to kill all microorganisms, including bacterial endospores.

**Sterility assurance level (SAL)**[2] Probability of a single viable microorganism occurring on an item after sterilization. SAL is normally expressed as $10^{-n}$. An SAL of $10^{-6}$ means that there is less than or equal to one chance in a million that a single viable microorganism is present on a sterilized item.

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**Sterilization**[2] Validated process used to render a product free from viable microorganisms.

NOTE: In a sterilization process, the nature of microbiological inactivation is exponential and thus the survival of a microorganism on any individual item can be expressed in terms of probability. While this probability can be reduced to a very low number, it can never be reduced to zero. See also **sterility assurance level**.

**Terminal sterilization**[2] Process whereby the product is sterilized within a sterile barrier system that permits storage for use at a later time.

**Thermocouple** Device used as a temperature sensor for measurement and, possibly, control of a process.

**Validation**[9] Documented procedure for obtaining, recording and interpreting the results required to establish that a process will consistently yield product complying with predetermined specifications.

**Validation master plan (VMP)** Overall document that defines the approach to be used for validation, which specific processes and equipment need to be validated, the tests that need to be performed for each validation process, and the type of validation to be performed for each process or piece of equipment.

**Validation protocol (VP)** Documentation of the specific processes and criteria that need to be met for a product validation. The validation protocol provides the specific criteria that define each step of the validation process for a specific process, product, or type of equipment.

**Variable data** Data that are quantified and usually expressed as a range of acceptable limits.

**Verification**[5] Confirmation by examination and provision of objective evidence that specified requirements have been fulfilled.

**Viroid** Infectious particle smaller than a virus. Viroids usually infect plants.

**Virulence** Capacity to cause a disease; quality of being extremely infectious.

**Virus** Submicroscopic parasite that often causes disease in the cell that it invades. Viruses cannot replicate without a host cell.

**Z value**[3] Change in exposure temperature of a thermal sterilization process, which corresponds to a tenfold change in D value.

## Abbreviations

**AQL** Acceptable quality level

**ATP** Adenosine triphosphate

**BI** Biological indicator

**CDC** Centers for Disease Control and Prevention

**CFU** Colony-forming unit

**CI** Chemical indicator

**DHF** Design history file

**DMR** Device master record

**DOE** Design of experiment

**DQ** Design qualification

**EO** Ethylene oxide

**FAT** Factory acceptance test

**FDA** U.S. Food and Drug Administration

**HAI** Healthcare-associated infection

**IFU** Instructions for use

**IQ** Installation qualification

**LD** Lethal dose

**LOD** Limit of detection

**LOQ** Limit of quantitation

**LTD** Lowest therapeutic dose

**MACO** Maximum allowable carry over

**NCG** Noncondensable gas

**NPT** National pipe thread

**OOC** Out of control

**OOS** Out of specification

**OQ** Operational qualification

**OSHA** Occupational Safety and Health Administration

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**PCD** Process challenge device

**PNSU** Probability of a nonsterile unit

**PQ** Performance qualification

**PQA** Product quality assurance

**RLU** Relative light unit

**RTD** Resistance temperature detector

**SAL** Sterility assurance level

**SDS** Safety data sheet

**SLR** Spore log reduction

**SOP** Standard operating procedure

**SPC** Statistical process control

**SV** Stated value

**TSE** Transmissible spongiform encephalopathy

**URS** User requirements specification

**VMP** Validation master plan

**VP** Validation protocol

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CHAPTER 3

# The Science of Sterilization

## Introduction

This chapter is intended to provide a thorough understanding of the science behind the sterilization of medical devices. A basic review of microbiology is provided to ensure that the reader understands the concepts upon which the science of sterilization is based. This chapter describes the microorganisms of concern, microbial lethality, and the mode of action of the sterilization methods commonly used in industry and healthcare. For more information, consult a good book on healthcare microbiology, such as *Microbiology for the Healthcare Professional*[10] or *Medical Microbiology for Health Professionals*.[11]

## Types of Microorganisms

Microorganisms are too small to be seen without a microscope. Not all microorganisms are harmful. However, *all* microorganisms that are present on a medical device that is to be used inside the body are "THE ENEMY." It is useful for those working in the medical device sterilization field to picture the microorganisms that they are trying to kill so that they can better understand that the principles upon which microbial control is based cannot be compromised and must be rigorously adhered to. Microorganisms can be divided into prokaryotes, eukaryotes, and acellular organisms. Prokaryotes are simple cells that do not include a nucleus, complex membrane systems, or organelles (specialized cellular subunits with specific functions). Eukaryotes are more complex cells that have a true membrane and membranous organelles. Acellular organisms do not have any cellular structure at all.

### Archaea

Originally, prokaryotic microorganisms were classified on the basis of biochemistry, morphology, and metabolism. Today a phylogenetic approach is used. This approach uses the sequences of the genes to determine how the prokaryotes relate to each other. The archaea were first classified separately from bacteria in 1977.

Archaea are single-celled prokaryotic organisms similar to bacteria. Unlike bacteria, however, archaea do not contain peptidoglycan in the cell wall. Originally, archaea were found in very harsh conditions (e.g., highly salty environments or volcanic stents). Improved detection tools have led to discovery of archaea that live in almost every environment, including the gastrointestinal tract and on the skin of humans. At present, there are no known pathogenic or parasitic archaea.

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## Bacteria

Bacteria are the most well-known of the prokaryotes. These microorganisms are responsible for many of the infectious diseases that we know. Bacteria come in two forms: vegetative cells and spores (or endospores). Vegetative cells are capable of actively growing and reproducing; they are easily killed by most disinfection methods and by sterilization. Some bacteria can enter a spore state that provides extra protection, making these bacteria much more difficult to kill.

Bacteria can be classified in many ways, including cell shape, nutritional requirements, biochemical and physiologic characteristics, staining reactions, atmospheric requirements, pathogenicity, and genetic composition.

### *Cell Shape*

Bacteria come in three basic shapes: cocci (sphere-shaped), bacilli (rod-like), and spirilla (spiral-shaped). The name of a bacterium sometimes indicates its shape. If *bacillus* appears in the name, then it is known that the shape is rod-like. For example, *Geobacillus stearothermophilus*, the reference microorganism used for testing many sterilization processes, are rod-like bacteria that in the spore state are very difficult to kill. Methicillin-resistant *Staphylococcus aureus* (MRSA) is a sphere-shaped microorganism responsible for severe skin infections, among other conditions.

### *Nutritional Requirements*

Bacteria differ in their nutritional requirements. All organisms require essential nutrients for survival. These essential nutrients are provided in the form of food that the organisms take in. Nutrients serve as a source of energy and of the basic elements needed for life: carbon, nitrogen, hydrogen, and oxygen.

Differences in nutritional requirements can help in the identification of microorganisms. For example, *S. aureus*, the most prevalent pathogen that affects humans, can be grown in a medium that has a high concentration of salt, mannitol, and a pH indicator dye. Most bacteria will not tolerate high-salt growth media. *Staphylococcus epidermis* tolerates a high concentration of salt but cannot ferment mannitol, whereas *S. aureus* can; when *S. aureus* ferments mannitol, it produces an acid that reacts with the pH indicator. Thus, bacterial growth in a high-salt growth medium indicates that *Staphylococcus* is present, but the response to the mannitol and the pH indicator differentiates between *Staphylococcus* species.

### *Biochemical and Physiological Characteristics*

Bacteria can be identified by the temperature at which they will grow and thrive. Psychrophiles, the cold-loving bacteria, like temperatures in the range of –10°C to 20°C (14°F to 68°F). Mesophiles prefer a temperate climate, with temperatures between 20°C (68°F) and 45°C (113°F). Thermophiles thrive in a hot climate, with temperatures between 45°C (113°F) and 75°C (167°F). Some hyperthermophiles are known to grow at temperatures of up to 122°C (252°F).[12] Bacteria are known to survive at higher and lower extremes of temperature, especially when in the spore state.

Most bacteria will not grow in an acid environment. They usually prefer a near-neutral pH of 7.1 to 7.4. Moisture and relative humidity can affect growth. If an environment is too dry, many bacteria will die; others can survive dry conditions for extended periods. Sunlight can be lethal to vegetative forms of pathogenic organisms. As bacteria grow, they excrete many products, some of which are enzymes that break down various potential food sources. Other excretions might be microbial toxins, which can cause disease in a host if the toxins are ingested or injected. Bacteria can be either motile or nonmotile. Cocci are generally nonmotile, whereas most spirilla are motile and many bacilli are motile with the use of flagellae.

### *Staining Reactions*

Several different stains are used in the microbiology laboratory to identify or differentiate bacteria. The most common is the Gram stain. At the end of the procedure, the cells will either be blue-to-purple or pink-to-red. Blue-to-purple cells are said to be "Gram-positive," whereas pink-to-red cells are said to be "Gram-negative." Some cells can be Gram-variable (not consistently one color or the other). Members of the *Mycobacterium* family are Gram-variable. *M. tuberculosis*, the bacterium responsible for tuberculosis, is included in this group.

### *Atmospheric Requirements*

Bacteria can be classified on the basis of their need for and how they utilize oxygen. Bacteria can be either aerobic (requiring oxygen to live) or anaerobic (not requiring oxygen to live). Aerobic bacteria are further classified as either obligate aerobes or microaerophilic aerobes. *Obligate aerobes* need free oxygen at 20% to 21% in the atmosphere to live (about the same as that found in normal room oxygen). *Microaerophilic aerobes* also require free oxygen but in lower quantities than the obligate aerobes; some organisms prefer an atmosphere of only about 5% oxygen to thrive.

Anaerobes do not require free oxygen, and growth will be inhibited by free oxygen in the atmosphere. The various terms

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for anaerobic bacteria describe the degree of tolerance that the organism has to the presence of oxygen. *Facultative anaerobes* can live and thrive with or without free oxygen; many disease-causing organisms are facultative anaerobes (e.g., *E. coli*). *Aerotolerant anaerobes* can survive in the presence of oxygen, but they will only thrive in the absence of oxygen. Obligate anaerobes can only grow in the absence of free oxygen; they will die in the presence of oxygen in the atmosphere (e.g., *Clostridium difficile*).

### *Pathogenicity*

Pathogenic organisms can cause disease in other organisms. Under the right circumstances, almost any bacteria can become pathogenic. Some bacteria can be both beneficial and pathogenic, depending on the circumstances. For example, *E. coli* is a common bacterium found in the colon. In this location, it performs a valuable function and aids in the breakdown and digestion of food. Outside of the colon, however, it can become an opportunistic pathogen and is responsible for many cases of food poisoning. It is also a common cause of septicemia and urinary tract infections.

### *Genetic Composition*

In the modern microbiology laboratory, bacteria are frequently identified by their genetic composition. Specific strains of bacteria can be identified, which aids in determining whether a disease is caused by the same strain as a previous disease or is a new or different strain. Determining the cause of a disease enables healthcare professionals to decide on the steps that can be taken to fight it.

## Eukaryotic Microorganisms

More complex organisms that contain a true nucleus and organelles are known as eukaryotes. In the microscopic world, eukaryotes include protozoa, fungi, and algae. Protozoa and algae are not discussed here because they are not historically found on medical devices and, therefore, are not a concern in the device sterilization field.

Fungi are plant-like organisms that have no chlorophyll. There are single- and multicelled varieties. Not all fungi are microscopic; mushrooms, for example, are a type of fungi. Some fungi are saprophytes; that is, they obtain their nutrients by decomposing dead and decaying organic matter. Many fungi are useful. They are involved in the production of most kinds of antibiotics. Yeast is used to make bread dough rise, and molds are used to flavor many types of cheese. Other types of fungi are troublesome. Superficial fungi attach to skin, hair, nails, and mucosal surfaces and can cause a variety of surface mycoses (e.g., athlete's foot). Other fungi cause subcutaneous and systemic mycoses, which can be more severe infections.

## Acellular Infectious Agents

Acellular infectious agents include viruses, viroids, and prions, which are not considered living cells. They need components of a living cell in order to multiply. These agents lack most of the characteristics of cells.

### *Viruses*

Viruses are 1,000 times smaller than bacteria. Because they are incomplete cells, viruses cannot be grown on artificial media; they can only be grown in cell cultures. They have no mechanisms for movement and must rely on outside forces to move them. Viruses can only multiply within living cells, but they can survive away from a host cell for many hours, or even days, if in organic material.

Viruses usually attack a specific part of the host's body. Infection by a virus might produce a lasting immunity against re-infection. This characteristic is the basis for vaccinations, which involve inoculating a person with antibodies or a mild form of the virus. Common viral diseases include colds, mumps, polio, shingles, cold sores, warts, acquired immunodeficiency syndrome (AIDS), and hepatitis. Antibiotics are not effective against viruses, but there are some antiviral agents available, which work by interfering with virus production within the host cell.

### *Viroids*

Viroids are infectious ribonucleic acid (RNA) particles that resemble a virus but are smaller. These agents cause diseases in plants, but at this time none are known to produce disease in any animal.

### *Prions*

Prions are mutant forms of normal proteins that, unlike viruses, contain no nucleic acid and do not trigger an immune response. Prion proteins accumulate in the brain and, over time, kill brain cells, leaving spaces where nerve cells used to be. Prions are extremely resistant to the usual disinfection and sterilization methods employed in healthcare. Prion diseases known as transmissible spongiform encephalopathies (TSEs) are fatal. There is no proven treatment available. Patients at risk of acquiring a prion disease include recipients of dura mater transplants, pituitary hormones derived from human cadavers, and corneal transplants. Persons who have neurosurgery and members of families with a history of inherited TSE are also at risk.

Prion diseases can be spread by iatrogenic transmission, by treatment for something else, or by ingestion of infectious material; and some individuals have a hereditary predisposition to acquire the disease. Sporadic transmission is very rare.

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Isolation of patients suspected of having a prion disease is not necessary. No special precautions are required for noninvasive items used on a patient. Invasive items used in areas of high infectivity require special decontamination procedures. Single-use invasive devices are recommended; they should be incinerated after use. For the processing of reusable devices exposed to prions, the World Health Organization recommends the following[13]: "If material has been contaminated with prions or contamination is suspected the preferred method is steam sterilization for at least 30 minutes at a temperature of 132°C [270°F] in a gravity displacement sterilizer. If a prevacuum sterilizer is used, 18 minutes at 134°C [273°F] has been found to be effective. Semicritical and noncritical items may be immersed in 1N sodium hydroxide, a caustic solution, for 1 hour at room temperature and then steam sterilized for 30 minutes at a temperature of 121°C [250°F]." At this time, no sterilization method has been FDA cleared for use in processing devices contaminated by prions.

## Microbial Growth

Various factors influence the rate at which microorganisms will grow. In the presence of certain adverse conditions, bacteria might not be able to grow at all. To inhibit or encourage the growth of microorganisms, it is necessary to understand microbial needs.

Nutrients and water are necessary for all life to grow. Different types of microorganisms require different nutrients to survive and without moisture microorganisms will either die or enter a protective state (e.g., by forming bacterial spores). The temperature must be within a range that the microorganism finds suitable. The pH of the environment is also important. Most microorganisms prefer a neutral to slightly alkaline environment, but some do prefer acid or alkaline environments. Osmotic pressure can cause a cell to take on or to lose fluid. In situations with extreme differences in solution inside and outside the cell, the cell can become desiccated or can lyse, which kills the cell.

Microorganisms can reproduce by sexual or asexual means. Bacteria reproduce asexually by a process called binary fission, in which one cell splits into two cells that are identical to each other. Eukaryotes reproduce by either sexual or asexual methods. Fungi reproduce in a variety of ways: spores, fruiting bodies, and binary fission.

Under ideal conditions, microbial cells can grow at very rapid rates. The time that it takes for a cell to reproduce (generation time) varies among species, from as little as 10 minutes to 24 hours or more. Bacteria that can reproduce once every 20 minutes will produce over 2 million cells in just 7 hours (see Table 1).

TABLE 1 **Exponential Growth of Unicellular Organisms**

| Time (min) | Number of divisions | Total number of microorganisms |
|---|---|---|
| 0 | 0 | 1 |
| 20 | 1 | 2 |
| 40 | 2 | 4 |
| 60 | 3 | 8 |
| 80 | 4 | 16 |
| 100 | 5 | 32 |
| 120 | 6 | 64 |
| 140 | 7 | 128 |
| 160 | 8 | 256 |
| 180 | 9 | 512 |
| 200 | 10 | 1024 |
| 220 | 11 | 2048 |
| 240 | 12 | 4096 |
| 260 | 13 | 8192 |
| 280 | 14 | 16384 |
| 300 | 15 | 32768 |
| 320 | 16 | 65536 |
| 340 | 17 | 131072 |
| 360 | 18 | 262144 |
| 380 | 19 | 524288 |
| 400 | 20 | 1048576 |
| 420 | 21 | 2097152 |

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## Bioburden

Bioburden is the total number of viable microorganisms present on a device. The effectiveness of disinfection and sterilization procedures depends on the removal of bioburden. If the bioburden present on a device is too high, then the effectiveness of the disinfection or sterilization process could be affected. Cleaning processes are designed to remove visible soil and organic markers to defined criteria. During cleaning, however, there is the additional benefit that some bioburden will be removed. Disinfection and sterilization processes are designed to inhibit growth or kill the microorganisms remaining on a device. If enough soil remains after cleaning, it could have an impact on the disinfection or sterilization process by protecting the microorganisms, resulting in a failure of the process. In some situations, it might not be possible to sterilize devices with gross soil or debris remaining on them after cleaning, because the gross soil or debris might prevent the sterilant from reaching all the surfaces of the item being sterilized. Only validated cleaning processes should be used prior to disinfection or sterilization processes.

## Microbial Resistance

Microorganisms vary in their ability to resist destruction by physical or chemical means. Enveloped viruses are generally considered the least resistant to destruction and bacterial spores the most resistant to destruction. Cellular structures such as the slime layer in mycobacteria provide some protection to the cell. Bacterial spores are resistant to extremely high or low temperatures, extremely low humidity, and most chemicals; only sterilization processes are effective in destroying spores. Vegetative bacteria, viruses, fungi, and mycobacteria can usually be destroyed by chemical or physical disinfection methods. Depending on the resistance characteristics of the organism, certain chemicals will be more or less effective. For example, enterococci are less sensitive than staphylococci to many disinfectants. Built-in resistance is found in bacterial spores, mycobacteria, and some Gram-negative bacteria.

## Microbial Lethality

### General Considerations

Microbial death can be accomplished through several physical or chemical means. The most common physical sterilization methods are moist heat, dry heat, and radiation. The most common chemical agents are ethylene oxide, hydrogen peroxide, ozone, formaldehyde, and peracetic acid. Irrespective of the sterilization method, microbial death follows a logarithmic function of time of exposure to or dose of the sterilant.

A logarithm is the factor by which a fixed number, the base, must be raised to produce that number. For example, the logarithm of 10,000 to base 10 is 4, i.e., $10 \times 10 \times 10 \times 10$ (in other words, the number of times that the base needs to be multiplied by itself to produce the number). A logarithmic function follows a straight line. Microbial death or sterility assurance uses a logarithmic base of 10. This means that application of a process for x number of minutes will produce a one-log reduction in the number of microorganisms present. A one-log reduction of a microbial population in base 10 amounts to a 90% reduction of the population.

### Sterility Assurance Level

Sterility assurance level (SAL) is a microbiological term used to describe the "probability of a single viable microorganism occurring on an item after sterilization. The term SAL takes a quantitative value, generally $10^{-6}$ or $10^{-3}$. When applying this quantitative value to assurance of sterility, an SAL of $10^{-6}$ has a lower value but provides a greater assurance of sterility than an SAL of $10^{-3}$."[6] The probability of a nonsterile unit (PNSU) is the probability that viable microorganisms are present on a product after sterilization; this could be one or many microorganisms. A sterilization process with an SAL of $10^{-6}$ (the most common SAL used for the sterilization of invasive medical devices) means that there is a probability that one in a million of the products subjected to that process will have one microorganism on it after completion of the sterilization process.

An SAL of $10^{-6}$ cannot be directly measured because multiples of 1 million products would be required for testing, which is not practical. Instead, calculations of SAL are based on validated sterilization processes. It is impossible to prove that all microorganisms have been destroyed by a given sterilization process. As described earlier, different types of microorganisms require different conditions for optimal reproduction. It could be that the microorganisms present simply have not been given the conditions needed for them to thrive and reproduce. Some organisms will remain in a spore state to protect them from a hostile environment, such as the environment established by a sterilization process. Also, sterility testing of a device results in a device that cannot be used for its intended purpose. Moreover, it is possible that the product tested was indeed sterile but that the product next to it, which was not tested, was not sterile. It is impossible to test all sterilized devices to ensure that they are sterile. If the bioburden present on the devices was higher than the sterilization process is intended to kill, then the devices might still be contaminated at the end of the sterilization process. For these reasons, sterilization processes must be validated. Validation provides a very high probability that the sterilization process will be effective.

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Whether a device is intended for single use or is reusable, the bioburden present on the device prior to the sterilization process must be reduced to a level that the sterilization process is capable of killing within the parameters specified for that sterilization process.

### Spore Log Reduction

A spore log reduction (SLR) of 12 is needed to reduce a population of 1 million organisms to an SAL of $10^{-6}$. A microbial population of 1 million bacteria reduced to 100,000 bacteria would be reduced by 1 log or 90%. A 6 SLR is needed to reduce 1 million bacteria to one. To then reduce the microbial population to a $10^{-6}$ SAL requires an additional 6-log reduction or a 12 SLR. See Table 2.

### Lethality Values

In microbiology, the time needed for a processing condition to reduce a microbial population by 90% or 1 log is known as the decimal reduction value (D value). Biological indicators (BIs) containing spores resistant to a sterilization process are used to test that process. For example, *Geobacillus stearothermophilus* spores are used to test the steam sterilization process because this organism is a thermophile and the spore form has an even greater resistance to high temperatures. (As noted previously, thermophiles prefer hot temperatures.) The D value can be used to measure a sterilant's efficacy at reducing the population of the specific microorganisms present on a biological indicator. Typically, the sterilization condition being measured is given as a subscript when noting the D value for an organism; for example, a $D_{270°F\ (132°C)}$ of 20 seconds means that an exposure time of 20 seconds at this temperature yields one spore log reduction (SLR). Each BI lot usually has a distinctive D value. The D value of *Geobacillus stearothermophilus* is about 2 minutes at 121°C (250°F) and about 20 seconds at 132°C (270°F). Therefore, after exposure to moist heat at 132°C (270°F) for 2 minutes, it is possible that one organism of *Geobacillus stearothermophilus* out of one million organisms on a biological indicator could still be alive. These recommendations are minimum acceptable parameters. Depending on factors outside the manufacturer's control (e.g., packaging, loading configuration, adequacy of cleaning), these parameters might not be adequate to achieve sterilization. See Figure 1.

TABLE 2 **Sterility Assurance Level/Spore Log Reduction**

| Number of microorganisms | Log of microbial population | Spore log reduction from original population |
|---|---|---|
| 1,000,000 | $10^{6}$ | 0 |
| 100,000 | $10^{5}$ | 1 |
| 10,000 | $10^{4}$ | 2 |
| 1,000 | $10^{3}$ | 3 |
| 100 | $10^{2}$ | 4 |
| 10 | $10^{1}$ | 5 |
| 1 | $10^{0}$ | 6 |
| 0.1 | $10^{-1}$ | 7 |
| 0.01 | $10^{-2}$ | 8 |
| 0.001 | $10^{-3}$ | 9 |
| 0.0001 | $10^{-4}$ | 10 |
| 0.00001 | $10^{-5}$ | 11 |
| 0.000001 | $10^{-6}$ | 12 |

The z value relates to the resistance of a microorganism to heat at a particular temperature amd "is defined as the number of degrees temperature change to change the D value by a factor of ten (10) or one log unit."[14] A typical z value for *Geobacillus stearothermophilus* is about 10°C (18°F). At a temperature of 121°C (250°F), for *Geobacillus stearothermophilus* with a z value of 10°C (18°F) and a D value of 1.25 minutes, it will take 15 minutes to achieve a 12 SLR (an SAL of $10^{-6}$). For the same organism with the same z value at a temperature of 132°C (270°F), the D value is 20 seconds and a 4-minute exposure time will be needed to achieve a 12 SLR (an SAL of $10^{-6}$).

### Terminal Sterilization

In terminal sterilization, the medical device in its sterilization package is exposed to a sterilization process that will result in the predetermined SAL. Terminally sterilized devices can be placed in storage for later distribution and use. Manufacturers of reusable medical devices need to be familiar with the specific sterilization cycles that their customers' sterilizers have been cleared to use. Although it is possible to develop and validate sterilization cycles specific to individual reusable medical devices, it is preferable to design devices that can be sterilized in the standard cycles in use by a manufacturer's customers. These standard cycles vary in different parts of the world. In the United States, the FDA has cleared sterilizers for use in healthcare with specific cycles that have been validated. To the extent possible, manufacturers of reusable products to be sold in the United States should design devices that can be sterilized in these cleared cycles.

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Manufacturers of single-use medical devices can develop sterilization cycles that are specific to their products, volumes, and loading configurations.

## Microbial Control

### Fundamentals of Microbial Control

As previously discussed, microbial growth is influenced by many factors. With an understanding of the conditions necessary for microbial growth, the conditions detrimental to microbial growth, and the conditions needed to destroy microorganisms, it is possible to control microorganisms and disinfect or sterilize contaminated items.

There are three categories of infection risk for medical devices. Critical devices are introduced directly into the blood stream or other sterile areas of the body; sterility at the time of use is required. Semicritical items contact intact mucous membranes but do not penetrate body surfaces; sterilization is desirable and high-level disinfection is required. Noncritical items have no patient contact or direct contact only with intact skin; low-level or intermediate-level disinfection is recommended for these items.[15]

Mitigating the infection risk is achieved by cleaning and disinfection or sterilization of medical devices prior to product use.

### Cleaning

The first step in controlling microorganisms and preventing the spread of infection is to clean the contaminated device prior to disinfection or sterilization. Cleaning is the removal of all visible dust, soil, and any other foreign material. It is the most important step in the decontamination, disinfection, and sterilization process.

Prompt cleaning will minimize damage to devices (e.g., prolonged contact with blood will corrode many metals). In addition, if gross debris remains on a device for an extended period, the device will become much more difficult to clean—in some cases, even impossible to clean.

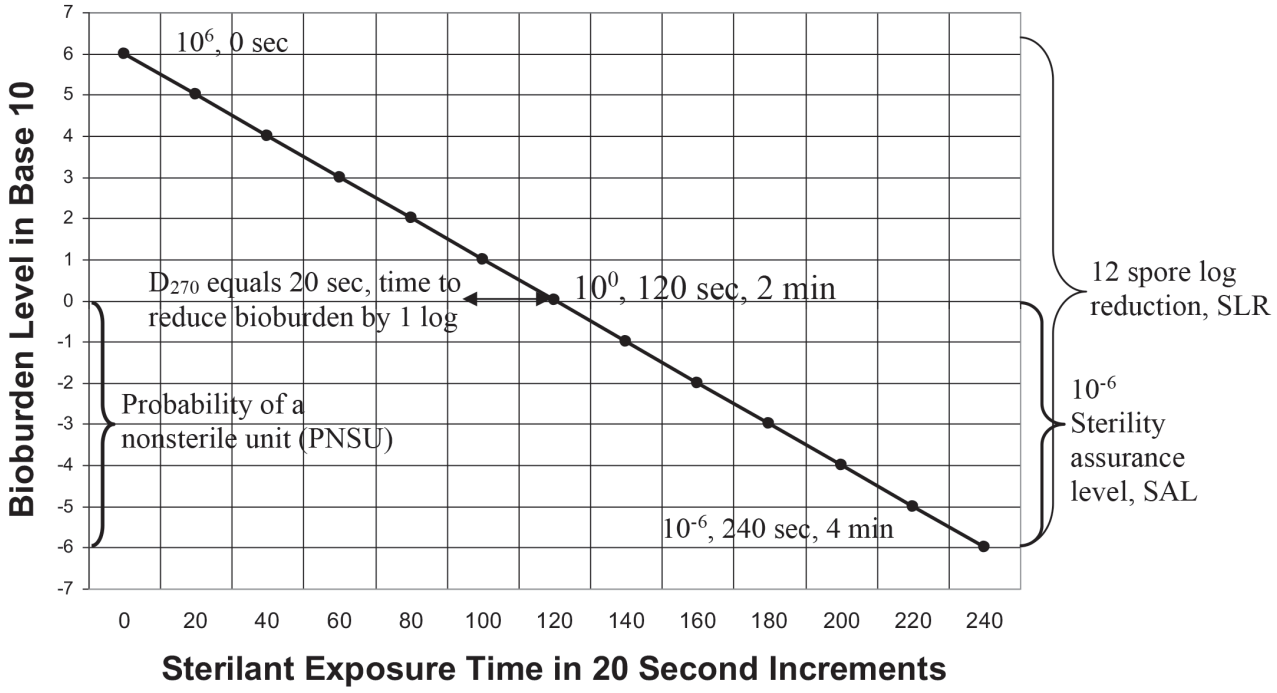



FIGURE 1 **Microbial Lethality Measures**

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Before cleaning a device, it is first necessary to determine the type of cleaning agent that will be used. The appropriate cleaning agent depends on the type of soil that is expected to be encountered and on the material that the device is made of. An ideal cleaning agent would have the following characteristics:

- Nonabrasiveness
- Low-foaming and free-rinsing properties
- No toxicity
- Biodegradability
- Cost-effectiveness
- Rapid soil dispersion
- Effectiveness on all types of soil
- Long shelf life and use life
- A mechanism for monitoring effective concentration and use life (a detergent with such a mechanism is not currently available)

Cleaning can be performed by manual or mechanical methods; which method is used will be determined by the manufacturer of the device based on its design. For example, some devices cannot be immersed in fluids and so might need to be manually cleaned. When possible, device manufacturers should design devices that can be immersed and cleaned by mechanical methods because of the greater cleaning efficacy. If mechanical cleaning methods are used, it is necessary to determine which type of mechanical process or machine is appropriate for the device being cleaned.

Special machines or mechanical processes might be needed to clean specific features (e.g., lumens, cannulas). In general, mechanical methods are preferred to manual methods because the more precise control associated with mechanical methods enables them to be validated.

## Disinfection

### *General Considerations*

Disinfection is the destruction of nearly all microorganisms on an inanimate surface. Three levels of disinfection can be employed: low, intermediate, and high. The level of disinfection used depends on the type of microorganism to be destroyed and the level of contact that the device will have with the patient. Low- to intermediate-level disinfection is used to disinfect work surfaces, patient care equipment, and items that will contact intact skin only. High-level disinfection is used for medical devices that contact intact mucous membranes but will not contact any sterile areas of the body or contact blood through nonintact skin or mucous membranes. Devices that contact the sterile areas of the body or with nonintact skin or mucous membranes should be sterile because even high-level disinfection will not destroy bacterial spores.

Disinfection can be accomplished by either physical or chemical means. The primary physical disinfection method used for medical devices is moist heat. Chemical disinfection can be accomplished by a variety of chemicals, which can provide low- to high-level disinfection depending on the concentration of the chemical and the exposure time.

### *Physical Disinfection*

Vegetative forms of bacteria are easily killed by boiling in water for 30 minutes; however, spores, thermophiles, and some viruses will survive this process. Pasteurization is the process of heating a substance, typically food, for a specified period of time and then cooling it immediately. This process is also used for the disinfection of some medical devices, primarily devices used in anesthesia or respiratory therapy. Today many of these devices are single-use devices. Pasteurization is intended to reduce the number of viable pathogens present on a device, so this process (when used for terminal reprocessing) is only acceptable for devices that will come into contact with intact skin or mucous membranes but will not contact normally sterile areas of the body.

Thermal disinfection is also used in many automated washer cleaning processes. Depending on the time and temperature used, the thermal disinfection process can result in intermediate-level to high-level disinfection. An $A_0$ of 600 will protect employees who handle devices between cleaning and sterilization and is acceptable for patient use when the device will only contact intact skin, not mucous membranes, sterile tissue, or the vascular system. An $A_0$ of 3000 is appropriate for disinfection of semicritical instruments that undergo thermal disinfection but not sterilization. Typical thermal disinfection cycle parameters to achieve an $A_0$ of 600 include the following:

- 10 minutes at 80°C
- 1 minute at 90°C
- 30 seconds at 93°C

Thermal disinfection cycle parameters to achieve an $A_0$ of 3000 include the following.

- 5 minutes at 90°C
- 2 minutes 30 seconds at 93°C

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### *Chemical Disinfection*

Chemical disinfectants include quaternary ammonium compounds, phenols, alcohols, halogens, glutaraldehyde, ortho-phthalaldehyde, hydrogen peroxide, and peracetic acid. Many medical devices are disinfected after cleaning, either as a terminal processing step or to make the devices safe for handling before sterilization. Care needs to be taken in the selection of chemical disinfectants. Some chemicals will damage certain materials (e.g., alcohol can dry out some plastic materials and cause the plastic to crack or craze, especially with repeated exposure).

**Quaternary ammonium compounds** are low-level disinfectants used primarily for environmental sanitation of walls and floors. **Phenols** are also primarily used for environmental sanitation; they should not be used in food preparation areas, nurseries, or the operating room. **Alcohols** are intermediate-level disinfectants that, because of their strong drying effect, can damage some materials, especially if used repeatedly. Alcohols are most effective at a 70% dilution; stronger dilutions evaporate too rapidly to be effective.

**Halogens** are primarily used as antiseptics because they are corrosive to metal and might damage rubber and some plastics. Chlorine-based halogen compounds can be used for cleaning up blood spills, although large amounts are needed because organic material inactivates the chlorine. These compounds can also be used to clean environmental surfaces and in hospital laundry. They are usually considered disinfectants, but in some combinations and strengths they can be effective sterilants.

**Glutaraldehyde** can be used as either a disinfectant or sterilant. However, its use as a sterilant is limited because there is no way to effectively maintain the sterility of a device after it has been soaked in glutaraldehyde. A relatively short exposure time (10 to 45 minutes) is needed for disinfection, whereas sterilization takes several hours.

**Ortho-phthalaldehyde** is a high-level disinfectant used to disinfect endoscopes and other heat-sensitive devices. Unlike glutaraldehyde, ortho-phthalaldehyde is not classified as a sterilant; it can only be used for high-level disinfection.

**Hydrogen peroxide** can be used as a disinfectant and is used as a sterilant for heat-sensitive medical devices. It can also be used as a room disinfectant.

**Peracetic acid** can be used either as a disinfectant or a sterilant. A relatively short exposure time (5 to 7 minutes) is needed for disinfection.

Chemical disinfectants should not be mixed with other chemicals unless specified by the disinfectant manufacturer. When dilution is required, chemical disinfectants should be mixed with purified water (e.g., reverse osmosis, distilled, or deionized water). The manufacturer's instructions for use (IFU) and safety data sheet (SDS) should be consulted for specific information. Water impurities can have an impact on the effectiveness of many chemicals; water hardness is the most problematic. Hard water contains large amounts of calcium and magnesium, whereas soft water has few or no extra elements. The minerals in hard water prevent the water from interacting with chemical disinfectants, resulting in the need for higher concentrations of most chemicals for the chemical to be effective.

Other impurities can also have an impact on the effectiveness of water in acting as a solvent. Bicarbonates (sodium, calcium, or magnesium), chlorides, sulfates, and silica can cause formation of scale. Oxygen, carbon dioxide, chlorides, and sulfates can cause corrosion. An unusually high water pH (above 8.5) or an unusually low water pH (below 5) can alter chemical efficiency by allowing corrosion and soil deposition to occur. Directions for mixing need to be closely followed because small changes in dilution can cause big changes in the effectiveness of some chemical disinfectants. Chemical disinfectants should only be used in well-ventilated areas. Organic residue left after cleaning can minimize the effectiveness of a disinfectant by diluting or inactivating the disinfectant and by preventing contact with all surfaces to be disinfected. Devices should be dry prior to disinfection because excessive moisture can dilute disinfectants.

## Sterilization

### *General Considerations*

Sterilization is a process that, when applied correctly, kills all forms of microbial life on or within the device, material, or liquid to which it is applied. It is achieved by applying the proper combination of parameters for the sterilization process being used. Parameters include temperature, time, chemical concentration, humidity, and irradiation dose, depending on the sterilization process being used.

Proving sterility is very difficult. For this reason, sterilization processes are designed to provide a very high probability that all microorganisms were killed (i.e., an SAL of $10^{-6}$). Three factors are essential to the effectiveness of a sterilization process:

- Conditions lethal to microorganisms must be present.
- The bioburden should not exceed the level defined for the specific sterilization process.
- Adequate contact of the sterilant with all surfaces of the devices being sterilized must occur for sufficient time.

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If any of these conditions is not satisfied, sterilization to the desired SAL will not occur.

The presence of lethal conditions involves ensuring that the sterilization parameters occur as programmed for a given sterilization process. If all parameters are not met, then the devices processed in that load cannot be considered sterile. Sterilizers provide documentation of the output of the cycle, which should be checked to ensure that all sterilization parameters were met. If not, the items in the load should not be released for distribution and use.

Several factors can influence whether a sterilant will be able to contact all surfaces of the item being sterilized. The design of the device might necessitate careful positioning of the device in the sterilizer. For example, if a device with a concave surface is placed in a downward position, an air pocket could form, which could prevent the sterilant from contacting the surface. If the opening of the device faces upward, steam condensate could fill the concavity; the condensate will be difficult to drain, and a wet pack might be the result. Factors affecting the ability of a sterilant to contact device surfaces are discussed in more detail later in this chapter.

The density of an item affects the amount of time needed for a sterilant to penetrate the item. If an item is extremely dense, it might not be possible for the sterilant to penetrate to all surfaces in the time that is allotted for sterilant penetration and exposure to occur. This situation could necessitate an extended sterilization exposure time or adjustments to other sterilization parameters.

Sterilization processes used in healthcare facilities include moist heat sterilization and low-temperature sterilization processes (ethylene oxide, ozone, hydrogen peroxide, chemical vapor, and liquid chemicals).

### *Moist Heat Sterilization*

Moist heat sterilization is frequently thought of as steam sterilization, but moist heat sterilization can also be achieved with liquid water. Moist heat sterilization is defined as "thermal energy in the presence of moisture provided as steam or liquid water for the purpose of achieving microbial lethality."[7]

The parameters used in moist heat sterilization are time, temperature, and moisture. Manufacturer-recommended cycles are usually based upon half-cycle development. These recommendations are minimum acceptable parameters. Depending on factors outside the manufacturer's control (e.g., packaging, loading configuration), these parameters might not be adequate to achieve sterilization. The company or healthcare facility that processes reusable devices needs to verify that the manufacturer's recommendations work in that facility. Medical device manufacturers that process reusable devices need to validate their sterilization processes, and it might be necessary for the healthcare facility to do so as well. Sterilization process validation is discussed in detail in Chapter 7.

Saturated steam transmits thermal energy to a device being sterilized until the device reaches the temperature of the steam, a process that normally takes only a few minutes. Moist heat sterilizers are fitted with one or more temperature gauges, depending on the size of the sterilization chamber, to measure the temperature of the steam at the potential "cold spots" in the chamber. Typically, if only one temperature gauge is used, it will be placed in the drain of the sterilizer because the drain is usually the last place that will heat to the sterilizing temperature. In automated sterilization processes, the sterilizer will automatically start timing the exposure phase when the sterilization temperature is reached in the "cold spot."

For saturated steam sterilization to work there must be adequate moisture in the steam. Steam quality is measured by a dryness fraction commonly referred to as steam quality. High-quality steam contains very little moisture in the form of water droplets, whereas low-quality steam has a high percentage of water droplets. High-quality steam having a dryness fraction of at least 95% (5% moisture) is recommended for sterilization of loads containing metals.[16] Dry steam, steam with lots of air or noncondensable gases, and wet steam do not transfer energy well, with the result that the devices being processed might not reach sterilization temperature or that sufficient energy to kill the bioburden might not be delivered to the load.

Relative humidity is the amount of water vapor present in air and is commonly expressed as the percentage of water vapor present compared to the amount of water vapor that the air could hold at a specific temperature. The higher the temperature, the more water vapor the air will hold. If the air then cools, the water vapor will condense. This is similar to what happens in saturated steam sterilization. The saturated steam contacts the cooler surface of the device being sterilized. The steam condenses and releases thermal energy, which results in sterilization. Steam will continue to condense until the temperature of the device reaches the temperature of the steam. Saturated steam exerts a constant pressure at a given temperature.

Provided that air, noncondensable gas, or superheated steam is not present, temperature and pressure will vary in direct proportion to each other. If pressure increases, temperature also increases; if pressure decreases, temperature decreases. If the pressure is higher than the corresponding temperature, the steam contains air. If the pressure is lower than the corresponding temperature, the steam could be superheated. Either condition can cause problems with sterilization. Steam containing air can

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prevent the steam from reaching all surfaces of the devices being processed, which will result in sterilization failure. Superheated steam is too dry, necessitating higher temperatures and longer exposure times for sterilization to occur.

As noted earlier, there must be adequate contact of the saturated steam with all surfaces of the item being processed for sterilization to occur. Several factors can affect the ability of the steam to contact all device surfaces:

- Inadequate cleaning will prevent contact of the steam with the surface of the device. Soil can also provide a protective cover to the microorganisms present.
- Wrapping devices made of flexible materials (e.g., surgical textiles) too tightly can cause air pockets, which might interfere with sterilant contact, or prevent the sterilant from penetrating to the interior of packages in the prescribed sterilization time.
- Crowding packages on a sterilizer cart can cause similar problems to wrapping a package too lightly because the density of the packages could be altered.
- Incorrect positioning of items on the sterilizer cart can create air pockets in devices that have concave or convex surfaces.
- Air leaks from the sterilizer or inadequate air removal from the sterilizer, which can be caused by a malfunctioning vacuum pump or a clogged strainer or drain, can also cause air pockets.

### *Low-Temperature Sterilization*

Many reusable medical devices cannot withstand the moisture and high temperatures associated with saturated steam sterilization processes. A variety of low-temperature chemical sterilization processes have been developed for the sterilization of these products. Two types of chemical sterilization processes are available: those that use gaseous chemicals, such as ethylene oxide (EO), ozone, formaldehyde, and hydrogen peroxide; and those that use liquid chemicals, such as glutaraldehyde and peracetic acid.

**Ethylene Oxide.** Ethylene oxide is one of the most widely used industrial chemicals. It is vital to the production of many products, including detergents, solvents, many plastics, and various chemicals, such as antifreeze (ethylene glycol). As a component/ingredient in these products, EO is not usually considered dangerous, but by itself as a precursor, it has potentially severe acute and chronic exposure effects. Chronic effects of exposure to EO include carcinogenicity, birth defects, fertility problems, and neuropathy. Acute effects of exposure include nausea, dizziness, difficulty breathing, skin and mucous membrane irritation, and headache. Ethylene oxide use must be closely controlled through implementation of engineering controls and employee protection measures. Monitoring ambient gas concentration levels is needed to ensure that exposure levels remain below acceptable limits. Facilities that use EO must comply with OSHA regulations on exposure to ethylene oxide.[17]

The parameters of EO sterilization are gas concentration, moisture (humidity), temperature, and exposure time. Ethylene oxide gas concentration is measured as milligrams per liter (mg/L) in the sterilization chamber space. Increasing concentration decreases the exposure time needed. The specified concentration must be maintained throughout the exposure phase of the sterilization cycle. Moisture is essential to EO sterilization. If moisture levels are too low (below about 30%), it might not be possible for EO to penetrate microbial cell walls, which will prevent the chemical from reacting with cellular DNA and will ultimately make it impossible for the EO to achieve sterilization within the time allowed, if sterilization can be achieved at all. If moisture becomes too high and there is an excess of water present in the sterilization atmosphere, ethylene glycol might be produced as a byproduct, reducing the EO concentration.

Higher temperatures can result in a faster, more effective process. However, if the device can withstand higher-temperature sterilization, saturated steam sterilization should be considered. Exposure time must be long enough to allow the sterilant to penetrate through all items being sterilized. The necessary exposure time varies with the gas concentration and temperature used. The density, thickness, configuration, and permeability of the devices in the load also affect the time needed for penetration of the sterilant. The standard cycles used in healthcare are set to accommodate the most difficult processing conditions expected to be encountered. These conditions can be affected by the configuration of devices created by the healthcare facility and by the loading configuration.

Because EO penetrates at a molecular level, it is necessary to remove the EO after the sterilization process. Residuals remain after sterilization and must be reduced to safe levels before patient use. Ethylene oxide can be removed through a process known as aeration, which causes the EO to be desorbed and displaced by air, thus allowing the gas to dissipate from the device. Aeration can take several hours to several days to accomplish, depending on the device materials, the composition of the load, the temperature used for aeration, and the amount of air flow. The higher the temperature, the shorter the aeration time required. Devices made of metal or glass do not require aeration because they do not absorb EO. Typically, devices made of metal or glass can be sterilized with moist heat.

**Hydrogen Peroxide Gas Plasma.** Gas plasma sterilization involves creating plasma by subjecting a gaseous chemical to an electrical field. Currently, hydrogen peroxide and ozone are used in gas plasma sterilization processes. Hydrogen peroxide has

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strong oxidizing properties that make it useful as a sterilizing agent. Hydrogen peroxide sterilization cycles can be shorter than ethylene oxide cycles.

Material compatibility issues are created by the strong oxidizing characteristics of hydrogen peroxide. According to the Centers for Disease Control and Prevention (CDC), there are concerns about material compatibility between hydrogen peroxide and brass, zinc, copper, and nickel/silver plating.[18] When exposed to hydrogen peroxide, brass and copper will exhibit some surface discoloration, and zinc will oxidize and corrode. When neoprene is exposed to hydrogen peroxide, a small amount of surface powdering might occur. Natural rubbers decompose when exposed to hydrogen peroxide. The device manufacturer should be consulted to determine if there any material compatibility issues with hydrogen peroxide; the sterilizer manufacturer can be consulted for general information. General information can also be found in AAMI TIR17.[19]

Products or packages containing cellulose cannot be sterilized by this method because the cellulose will bind the hydrogen peroxide, causing the concentration of hydrogen peroxide to drop below what is needed to achieve sterilization. Because the penetration capability of hydrogen peroxide is not as good as that of ethylene oxide, there are limitations on the length and diameter of lumens that can be sterilized with hydrogen peroxide. The IFU of both the device manufacturer and the sterilizer manufacturer should be consulted for guidance.

As with any sterilant, care must be taken in handling the sterilant and sterilized devices. Hydrogen peroxide can cause bleaching or ulceration of skin if direct contact occurs at a high enough concentration and for a sufficient period of time. The sterilizers in use today have been engineered to minimize the possibility of any exposure to the hydrogen peroxide, but it is recommended that personnel wear chemical-resistant gloves when handling the sterilant container and when handling devices being removed from the sterilizer. Routine employee monitoring is not recommended at present, but users might choose to monitor for the presence of hydrogen peroxide.

**Combined Ozone and Hydrogen Peroxide.** The FDA has cleared a hydrogen peroxide–ozone sterilizer for sterilization of metal and plastic instruments, hinged instruments, and instrument with lumens having a specified inside diameter and a specified maximum length. Free radicals formed by the two sterilizing agents act to sterilize devices. Hydrogen peroxide reacts to ozone similarly to how it reacts to plasma in other sterilization processes. The hydrogen peroxide–ozone sterilization process begins with the formation of radicals produced by the hydrogen peroxide. The ozone then reacts with the hydrogen peroxide, water, and radicals already present in the chamber. The combination of the two chemicals creates a very powerful oxidizing agent capable of penetrating lumens and other hard-to-reach device designs.

**Low-Temperature Steam/Formaldehyde.** Low-temperature steam/formaldehyde (LTSF) is not a typical gas sterilization process but rather a modified steam sterilization process. Steam fractionation with multiple formaldehyde injections is used to ensure penetration of the sterilant. The process consists of the following consecutive steps:

- Air removal
- Steam/formaldehyde penetration
- Condensation of steam/formaldehyde on all surfaces being sterilized
- Long convection and/or diffusion to achieve equilibrium
- Sterilant exposure time
- Elution of formaldehyde with steam/water
- Aeration and deaeration

**Liquid Chemicals.** Liquid chemical sterilization can only be used for items that can be immersed in the liquid. Because it is difficult to maintain the sterility of an item after removal of the device from the liquid sterilant, these processes are often used for immediate-use sterilization or for high-level disinfection in healthcare settings. A long exposure time is needed for glutaraldehyde to achieve sterilization.

### Healthcare-Associated Infections

#### *Background*

Healthcare-associated infections (HAIs) affect patients or staff in a healthcare facility who did not have an infection upon arrival at the facility but who become infected as a result of being in the facility. For patients, these include infections that do not manifest until after discharge. An infection in healthcare workers due to occupational exposure is considered an HAI.

HAIs are the most common adverse healthcare event in the world, accounting for 7% to 8% of patients experiencing adverse healthcare events in developed countries. Approximately 23,000 people who get an HAI in the U.S. each year will die from the infection. Additional people suffer from complications associated with the HAI.[20] HAIs are a global problem and affect all areas of the healthcare facility. Invasive medical devices are implicated in many HAIs (e.g., a duodenoscope infection caused by cleaning challenges). No institution or country has solved the HAI problem.

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### *Risk Factors*

Invasive medical devices can be a major factor in HAIs. Any time that there is a breach in the skin barrier, an HAI can result. The longer that the device is in place or in use, the greater the likelihood for an infection to occur because of contamination. If the device is reusable, then there are additional issues related to cleaning, disinfection, and/or sterilization of the device. Many reusable medical devices require multiple steps to clean the device and prepare it for disinfection and/or sterilization. The FDA requires device manufacturers to provide comprehensive, validated instructions for cleaning, disinfection, and sterilization of reusable medical devices. It is important that these instructions be followed exactly as written.

Some patients have health conditions that increase the likelihood that the patient will get an HAI. Comorbidities such as diabetes, autoimmune diseases, and immunosuppression can increase the likelihood of an HAI occurring.

The area around the patient also needs to be considered when trying to prevent HAIs. Proper cleaning of the environment and use of aseptic practices are needed to minimize the transference of pathogenic organisms to the patient.

### *Impact of HAIs*

HAIs can have a significant impact on the patient, the patient's family, society, the healthcare facility, and healthcare workers. In addition to the patient's pain and suffering, an HAI can have a significant impact on the cost of providing healthcare and on lost productivity. Direct costs for a single HAI in a U.S. hospital can be in the thousands of dollars.[21]

### *Causes of HAIs*

Many factors have a direct effect on whether an HAI will occur. One of the most important factors in preventing HAIs is leadership. Senior leadership in the healthcare facility must promote a culture of safety to ensure that employees can and will report issues that can have an impact on the occurrence of HAIs. The 2016 Hospital Survey on Patient Safety Culture by the Agency for Healthcare Research and Quality (AHRQ) indicates that there are several areas where hospitals need to improve in patient safety culture. Some of the areas where improvement is needed include the following:[22]

- Teamwork
- Leadership expectations
- Staffing
- Handoffs and transitions
- Nonpunitive response to error

Patient-related factors that have an impact on HAIs include the following:

- Patients can be a source of microorganisms.
- The patient could be a susceptible host.

There are several ways in which each of these factors can be prevented from being involved in transmitting an infection. Through diet and exercise, patients can minimize the potential for becoming a susceptible host. Personal protective equipment can minimize the chance that a patient might be exposed to pathogenic microorganisms. Appropriate surgical site preparation can minimize the potential for the patient's own body flora causing an infection.

Microorganisms can move from one place to another by several means. These include direct and indirect contact, airborne, and common vehicle spread. Surgical devices can act as a common vehicle for infection transmission if the device was not properly cleaned, disinfected, or sterilized. Healthcare workers must strictly follow the validated reprocessing procedures for reusable devices.

### *Preventing HAIs*

Many steps can be taken to prevent an HAI from occurring. Of critical importance is a surveillance system that can be used to monitor improvement and to perform trend analysis of infections that do occur. Surveillance systems can help to pinpoint causes of HAIs. Core components of preventing infections include the following:

- Use of standard precautions, including hand hygiene
- Staff education in infection control and prevention practices
- Involvement of patients, families, and visitors in the use of standard precautions and other infection control practices
- Use of aseptic practices in clean and sterile procedures
- Adequate cleaning, disinfection, and/or sterilization of reusable medical devices

One of the most serious surgical complications is a surgical site infection. Both the World Health Organization and the CDC have developed programs for use in prevention of surgical site infections. Improperly processed reusable medical devices have been implicated in many infection incidents.[23,24,25,26]

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CHAPTER 4

# The Quality Management System

## Introduction

Companies and healthcare facilities must have a system in place to ensure that product quality is maintained. A comprehensive quality management system (QMS) addresses all specified requirements for a product and consists of several components, including designation of overall quality management system requirements, management responsibility requirements, resource requirements, product realization requirements, and measurement, analysis and improvement requirements. This chapter of the book discusses quality management in general terms and its application to all companies and healthcare facilities engaged in producing sterile product. The specifics of how medical device manufacturers and healthcare facilities can apply these principles are covered later in the book.

If an organization, healthcare facility, or medical device manufacturer, decides to implement a quality management system, it should adhere to the appropriate requirements. ANSI/AAMI/ISO 13485, *Medical device—Quality management system—Requirements for regulatory purposes*,[27] and ANSI/AAMI ST90, *Processing of health care product—Quality management systems for processing in health care facilities*,[28] are two examples of applicable standards.

## General Requirements

The organization must document and maintain the effectiveness of the QMS. For every process that is part of the QMS, the organization must determine the sequence of these processes and ensure that the resources are available to implement these processes. Processes must be managed and evaluated for their effect on the QMS. A risk-based approach is used to control these processes. Any outsourced processes must conform to the quality requirements and must be controlled to ensure compliance. Computer software used in the quality system must be validated.

## Documentation Requirements

The QMS includes requirements for documentation, including the following:[29,30]

- A documented quality policy and quality objective
- A quality manual

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- Documented procedures required by the standard
- Documents needed for effective planning, operation, and control of processes
- Records required by the standard

A comprehensive quality system begins with development of a quality manual, which can consist of several tiers that become progressively more detailed. One approach is for the quality manual to specify the overall policies that govern the facility's approach to quality, with supporting procedure manuals. The procedure manuals provide specific information on how to perform a function and might, in turn, be supported by instructions for specific procedures. Instructions are step-by-step information on how to perform a specific procedure and are used when it is likely that the person performing the procedure might perform the procedure in such a way that the quality of the product will be compromised. For example, the quality manual might state that the facility complies with all requirements for ensuring that the product contains all specified components, is packaged in accordance with packaging requirements, and meets all functionality tests before being provided to customers. The following procedures might then be written to support this policy:

- Identification of product components
- Product assembly and packaging
- Functionality tests and acceptance criteria
- Product release

For a specific product, instructions might be needed to support the product assembly and packaging procedure. For example: *Assemble all components and ensure that product is functioning properly before placing it in sterilization packaging and submitting it for sterilization*.

In addition to the policies, procedures, and instructions, the following types of documentation in a medical device file or files might be needed to support the quality system:

- General description, intended use/purpose, and labeling, including any IFUs
- IFU for processing of reusable medical devices, including cleaning, assembly, and sterilization details and acceptance criteria
- Product specifications, including inspection requirements and acceptance criteria
- Manufacturing procedures for packaging, storage, handling, and distribution
- Procedures for measuring and monitoring
- Requirements for installation, if needed
- Requirements for servicing, if needed
- Design verification records
- Process verification records
- Process validation records
- Product quality assurance (PQA) testing records (full-cycle process validation for healthcare facilities)
- Routine monitoring records
- Product release records

NOTE: In healthcare facilities, the medical device file for reusable devices/sets could include a tray list with pictures and specific notes on the manufacturer's IFU for cleaning, disinfection, and sterilization. This could be part of an instrument tracking/sterile processing management software program.

Quality system records must be maintained for the life of the medical device that the record refers to. Device life is defined by the manufacturer or healthcare facility or might be set by regulation for some devices. It is important that this documentation is available to support that the product has been produced in accordance with its product specifications and that it meets its performance requirements. These records might be needed should there be a report of a product quality problem. Investigation of product problems begins with a review of the records, followed by an analysis of any breakdowns that might have occurred and how such breakdowns can be minimized or prevented in the future.

NOTE: In healthcare facilities, the quality system documentation includes the records maintained each time a tray or device is processed.

## Management Responsibility

Top management responsibilities include the following:

- Defining and documenting the company's or healthcare facility's quality policy, including quality objectives and the commitment to quality
- Conducting management reviews of the quality system
- Ensuring the availability of resources needed for the proper functioning of the quality system

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- Communicating to the organization the importance of the QMS and its impact on meeting customer requirements

The management representative must have the authority to establish and make changes to the quality policy. Depending on the size of the company or healthcare facility, this person might also be responsible for the development of all policies, procedures, and instructions. In larger facilities, additional people will be responsible for various aspects of the quality program. It is acceptable to delegate some aspects of the quality program, including (a) the establishment of quality objectives, (b) designation of the actual methods and procedures to be used, and (c) implementation of the various steps in the quality program. Larger facilities might have a separate quality department responsible for ensuring that all employees (administrative, production, distribution, and support personnel) comply with the quality policies and procedures.

Individual department management is responsible for ensuring that employees adhere to the facility's quality requirements. If any employee is not adhering to the quality system requirements, management is responsible for taking appropriate action to ensure compliance. Actions to ensure compliance with the quality system include initial orientation, ongoing retraining, and discipline when needed. All such actions should be documented.

The suitability and effectiveness of the quality system must be reviewed at designated intervals. Participants in this review should include representatives of all facility departments that can have an impact on the quality system (e.g. quality, production, purchasing, distribution, sterilization, marketing, sales, and administration). The purpose of this review is to determine if the facility's quality policies and objectives are being achieved. The review could include the following:

- A review of the organizational structure, including staffing and other resources
- A comparison of finished device quality to the specified quality objectives
- A review of audit results
- A review of complaint files
- A review of corrective and preventive actions taken in response to audits, complaints, or other reports
- A review of quality reports on raw materials, product performance, and process performance
- A review of potential updates of the quality system, including frequency of reviews
- A review of follow-up actions from previous management reviews
- Recommendations for improvements
- A review of new or revised regulatory requirements

Management review is a broad review meant to ensure that the facility's quality policy has been implemented and the objectives are being met. Additional quality meetings should be carried out by the quality management representative and/or department management personnel to review supporting activities and ensure that each area or department is complying with the established quality policy.

## Resource Management

Resources needed to implement the QMS must be provided. These resources include human resources, infrastructure, work environment, and contamination control. Human resources must be competent to perform their jobs. Proving competence might require training, testing, or other actions to show that an employee can perform the required processes. Employees must also be aware of the importance of their jobs and how it relates to the requirements of the QMS. Records of competence must be maintained.

Infrastructure includes buildings, workspaces, utilities, process equipment, and supporting services (e.g., transport and communications). The need for infrastructure, including maintenance, must be determined and made part of the QMS.

Any special requirements for the work environment must be determined. Such requirements could include the need for clean-room environments or for separate rooms for specific purposes (e.g., a separate room for decontamination and/or a separate room for EO sterilization). Procedures for monitoring and controlling the environment, hygiene, and clothing requirements need to be addressed.

Contamination control also needs to be addressed. Contamination control is particularly important if product being manufactured will be sterilized before sale or release to the customer. In the healthcare facility, it is also necessary to determine the need for separation of clean, soiled, and sterile areas of the department. Medical device manufacturers might require a clean-room environment. The ISO standards on clean rooms should be consulted for detailed information on these requirements.

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## Product Realization

Planning and development of processes needed for product realization, including development of risk management processes, are required. Procedures that specify the steps needed to ensure that finished product meets its quality requirements must be developed and implemented. These procedures include the following:

- Planning for product realization
- Identification of customer-related processes
- Design and development requirements
- Product identification and traceability specifications
- Measurement system calibration

Planning for product realization involves developing product quality objectives and requirements, including customer-related requirements. Resources specific to the product need to be provided and procedures need to be developed that will ensure that required verification, validation, monitoring, measurement inspection and test, handling, storage, distribution, and traceability activities specific to the product are developed and implemented.

Product design and development needs to be planned and controlled. Reviews are needed at each stage of development. Design inputs include functional, performance, usability, safety, and regulatory requirements for the product. These inputs are used to create the design outputs. Design outputs provide the information needed for purchasing, production, and servicing. Each step of the design and development process needs to be verified. The final design will need to be validated; validation might also be required at different points during the design and development process. Changes that occur during design and development need to be controlled.

Change control, an integral part of design and development, is a systematic approach to managing all changes that might occur when producing a product. It is very important that any changes in the production process are controlled so that all personnel who need to be aware of the change are informed. When a procedure is put into place, it is sometimes discovered that there might be a better way to perform it. Or, the component list for a product is updated (e.g., instruments might be added to or subtracted from an instrument tray as techniques or surgeons at a healthcare facility change). Employees need to understand that it is not acceptable to just begin performing a procedure in a new way, and that if a customer requests a change in a product, the person who receives the request cannot just go ahead and change the product or process. There must be a formal procedure in place for handling requests for changes in products or processes. Change requests can be made verbally, in writing, or on a change request form. (Verbal change requests should be documented, and there should be a follow-up signature from the requesting person verifying that the requested change was understood.) Whichever method is used, it is very important that the request is categorized and recorded. An assessment of the change, its importance, and the difficulty of implementing the change should be part of the documentation.

Each change request should be formally reviewed, and a decision made on whether the change will be accepted. The decision and the reasons for the decision should be documented and reported to the party who made the change request. Some requests don't require an in-depth analysis, and it will only take a few minutes to decide whether to accept the change, to implement the change if accepted, and then to inform the requesting party of the decision and its implementation. (For example, a request for the removal of a surgical instrument from an instrument tray because the instrument is no longer used can be handled quickly.) Other change requests must be analyzed in some detail to determine whether the current method or the proposed method is the best way to perform the procedure. This type of change might require use of various quality management tools, such as a Pareto chart, a fishbone diagram, or a failure mode and effects analysis (FMEA).

Once a change is accepted, a person or team is assigned responsibility for the change. This person or team will create a plan for designing and implementing the change. Each step of the implementation is monitored and, if needed, the change is rolled back should it be deemed that the plan does not work. At the end of the implementation, a final assessment is performed to ensure that the change is having the desired effect. If necessary, the steps for evaluating and analyzing the change are repeated with additional implementation steps until the change is satisfactory.

## Purchasing Requirements

Purchasing procedures are needed to ensure that purchased product meets the specified requirements. Criteria should be developed specifying the product requirements, and then the vendor's product should be compared to the specification to ensure that the product meets the requirements. Receipt of product should be verified against the purchase order. Any product that does not meet purchase specifications should be reviewed and the disposition determined. It might be necessary to return the product for the correct or specified product. Before beginning to purchase product from a supplier, it is necessary to qualify that vendor. Vendor qualification might include site visits to ensure that manufacturing processes are acceptable for purchased subassemblies. All departments that will use the products should be part of the vendor review process. In healthcare facilities

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the clinical, sterile processing, distribution, and purchasing departments should participate in vendor qualification.

## Production and Service Provisions

Production and service requirements must be monitored and controlled to ensure that finished product meets its specifications and to facilitate any recalls necessitated by problems later found with the production process. Product cleanliness needs to be addressed. Some devices are provided nonsterile but must be cleaned and sterilized by the customer prior to use. In this case, procedures for processing must be developed and validated by the manufacturer. Other products are provided sterile to the customer. In this situation, the manufacturer must determine the procedures that will be needed to maintain product cleanliness prior to sterilization and sterilization processes will need to be developed.

Some products need to be installed at the customer's location. In this situation, the manufacturer must provide procedures for qualifying the installation. Usually an operator's manual and a maintenance manual also need to be provided for this type of product. Some devices also require periodic servicing. If so, the manufacturer must provide procedures for servicing of the product. These procedures might require that the servicing be performed by a qualified person.

Cleaning and sterilization processes must be defined. In the case of reusable devices, the manufacturer must develop cleaning and sterilization procedures that the user facility must follow. These procedures need to be validated. Validation might include human factors testing to ensure that the customer will be able to follow the manufacturer's instructions for cleaning and sterilization.

Procedures must be developed that allow for identification and traceability of the product and its components throughout the production process. Identification and traceability can be accomplished by using a unique identifier such as a bar code or simply by ensuring that all components are kept together during the production process. The simplicity or complexity of identifying and tracing product will depend on the specific product and the steps in the production process. The FDA unique device identifier (UDI) regulation requires direct marking of the UDI information on all classes of reusable medical devices intended to be processed between uses. In the United States, UDI compliance is in the final stages of implementation, with UDI labeling, data submission to the GUDID (Global Unique Device Identifier Database), and Standard Date Formatting (YYYY-MM-DD) for class I medical devices and accessories due 24 September 2022 and direct marking due 24 September 2021. Direct marking of implantable devices is not required.

Any equipment or tools needed to measure specific parts of the production process should be calibrated to a national standard. Such equipment includes measurement devices on washers and sterilizers. Although washers and sterilizers are not used to create a device, they do produce the final sterile product, so the measurement devices on these machines must be accurate. A review of key measurements during the production processes allows for early recognition of possible nonconforming product. A final review of the production measurements ensures that the product meets its specifications and is acceptable for distribution. For these inspections to be meaningful, any measurement systems used must be accurate. Accuracy of the measurement system is ensured through calibration of the equipment.

## Measurement, Analysis, and Improvement

Monitoring, measurement, analysis, and improvement processes are needed to ensure product conformity, conformity of the QMS and to maintain the effectiveness of the QMS.

### Monitoring and Measurement

Several different processes are included in a monitoring and measurement system. These include feedback, complaint handling, reports to regulatory authorities, internal audits, and monitoring and measurement of processes and products.

#### *Feedback*

Feedback is integral to monitoring and management of the QMS. Information gathered during feedback is used as input into product improvement and to risk management. One type of feedback is postmarket surveillance. Regulatory authorities require postmarket surveillance for certain products. There are four types of medical devices for which the FDA usually requires postmarket surveillance:

- Class II or class III devices that could cause serious adverse health consequences if they fail
- Class II or class III devices with widespread use in pediatrics
- Class II or class III devices that are intended to be implanted in humans for longer than one year
- Class II or class III devices that are intended for life-sustaining or life-saving use outside of medical facilities

Postmarket surveillance is not usually required for Class I devices. In the European Union, postmarket surveillance is required for all devices or a justification needs to be provided for not doing so.

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### *Complaint Handling*

Organizations are responsible for creating complaint-handling procedures. Complaint-handling procedures should include processes for receiving and recording the complaint information, investigating complaints, evaluating information, determining the need to report the complaint to regulatory authorities, handling complaint-related product, and determining the need to initiate corrections or corrective actions. Any follow-up steps needed to address the complaint must be documented. If an outside organization or agency contributed to a complaint, any information generated must be shared with that organization/agency.

### *Internal Audits*

Internal audits should be conducted at planned intervals to ensure that the quality policies and procedures are being adhered to. The purpose of a quality audit is to ensure that the quality system complies with the specified requirements and to determine the effectiveness of the quality system. The frequency of the audits depends on the complexity of the process being audited, the difficulty of performing the steps of the process, the importance of the activity being audited, the severity of a problem that might occur because of noncompliance, and the number of issues that are found during previous audits. As a quality system matures, it might be possible to reduce the number of quality audits performed. At minimum, a quality audit of the entire quality system should be conducted annually. Additional audits of specific areas may be conducted based on the criteria described above.

Personnel conducting a quality audit should not have direct responsibility for the process or product being audited. If possible, personnel who have no production responsibility should conduct all audits. In any case, the person performing the audit cannot audit his or her own work.

The results of a quality audit must be documented, and these results should be provided to the person responsible for the area where any problems were identified. A formal report should become part of the quality documentation and should be reviewed as part of management review meetings. Any issues identified during a quality audit must be reviewed and appropriate corrective action developed and implemented. Audits should be followed up to ensure that the corrective actions taken were effective in preventing recurrence of the same problem.

Figure 2 is an example of an audit form.

### *Monitoring and Measurement of Processes and Products*

Monitoring and measurement of processes are intended to demonstrate the ability of a process to achieve expected results. If these results are not achieved, then it is necessary to either make corrections or to take corrective actions as appropriate. These actions must be documented.

Product characteristics must be measured to ensure that the product meets its specifications. Evidence of conformity to the specifications must be maintained. Personnel performing product release and inspection of implantable medical devices must be identified in the documentation.

## Control of Nonconforming Product

Product that does not meet its specifications must be identified and controlled by segregating the nonconforming product from conforming product.

Product that does not meet its designated specifications should not be distributed for use. If the product is in process when the nonconformity occurs, the product should not proceed to the next step of the process. (For example, an instrument that fails inspection after cleaning because debris is still present in a lumen or in the ratchets should be returned to the decontamination area for further cleaning.) There need to be procedures to ensure that nonconforming product is not accidentally distributed or moved to the next step.

When nonconforming product is identified, it must be quarantined or segregated from other products and an investigation conducted to determine what caused the nonconformity and whether it is okay to use the product. Depending on the results of the investigation, corrective and/or preventive actions might need to be implemented.

Corrective action involves deciding what steps can be taken to address and prevent the recurrence of a problem. Before deciding what corrective action steps to take, it is necessary to identify the root cause of the problem; actions to prevent recurrence of the problem can then be taken. A decision needs to be made as to the disposition of the affected product:

- Destruction of the product
- Rework or reprocessing of the product
- Use of the product under concession

Product can be accepted by concession only if justification is provided, approval is obtained, and regulatory requirements are met. The final decision will depend on what the investigation reveals.

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Sometimes it is possible to predict that a problem might occur. Preventive action involves analyzing processes to determine if there is potential for a problem to occur. When a potential problem is identified, steps can be developed that will prevent the problem from occurring. The difference between corrective and preventive action is the difference between being reactive versus being proactive. It is best to prevent problems when possible. Unfortunately, not all problem occurrences can be predicted.

NOTE: In healthcare facilities, a nonconforming product could be a tray that is missing required components or instruments or that has additional, nonspecified components or instruments in it.

Sometimes nonconforming product is not identified until after delivery to the customer or use of the product has started. Depending on the results of the investigation into this type of nonconformity, it might be necessary to recall all products in a lot or batch and to notify regulatory authorities of the nonconformity.

### Analysis of Data

Data is generated from a variety of sources. These data need to be analyzed to determine if the QMS is suitable, adequate, and effective. The result of this analysis is used as input for QMS improvements. Records of any data analysis must be maintained.

### Improvement

Based on the data analysis, it might be necessary to implement changes that will improve the QMS. These improvements are intended to maintain the suitability, adequacy, and effectiveness of the QMS as well as the safety and performance of the medical devices. The data analysis might reveal a need for corrective or preventive action. Corrective action is intended to eliminate the cause of nonconformities that have been identified. The effectiveness of corrective action must be verified.

Sometimes data analysis reveals the need for preventive action. Preventive action involves identifying potential nonconformities that could occur but have not yet happened. Steps should be taken to prevent these potential nonconformities from occurring. Records of any investigations performed and of the actions taken as a result must be maintained.

**Management Review Audit Form**

DATE_____ AUDITOR_____

| Parameter | Yes | No | Comments |
|---|---|---|---|
| Management review meetings are conducted at least annually | | | |
| Each department is represented at the management review meetings | | | |
| A quality policy and objectives have been established | | | |
| Corrective and preventive action reports are included in the management review meeting | | | |
| Customer complaints are analyzed for root cause | | | |
| Implementation plans for customer complaints are reviewed for adequacy | | | |
| Customer complaints and corrective/preventive actions are reviewed for potential trends | | | |
| Resources needed to accomplish the quality objectives are reviewed at the management review meetings | | | |

COMMENTS _____

FIGURE 2 **Example of an Audit Form**

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## New Products

New products are developed periodically for several reasons:

- A specific customer request is identified
- An improvement in production technology becomes available
- Improvements in construction materials become available
- Manufacturing production designs are improved
- Business is being lost because a better product is available from a competitor

Medical device manufacturers and healthcare facility sterile processing departments should review their production processes and products to ensure that they continue to meet their customers' needs.

It is necessary to review the new product and meet with potential customers to determine if the new product will meet a customer's needs. If customers do not perceive a need for the product, it might not make sense to develop it. Sometimes it might be necessary to point out how the customer's needs will be met by the new product or possibly explain how the product change will enable the facility or department to provide the product at reduced cost, faster, or with some other intangible benefit (to the customer). The facility or department will also need to work with the customer to evaluate the product and help the customer determine if the product will meet the customer's needs.

Sometimes a focus group can be used to determine how much interest there is in the proposed new product. If it is determined that there is a need for the product, the facility or department needs to look to the change control process to formulate a plan to develop and begin production of the new product.

Depending on the extent of the change to a product or the features of a new product, the customer might want to conduct a formal evaluation of the product before the change is made.

The manufacturer or department will want to work with the customer to conduct a product evaluation and formal review of the product. The review of new products will usually include the following steps:

- Establishment of a multidisciplinary committee
- Review of how the product will contribute to safety
- Review of how the product will improve process flow, costs, ease of product use, environmental impact, and/or product standardization
- Review of the opinions of experts or peers who currently use the product or a similar product
- Determination of the compatibility of the product with existing product and processes
- Determination of the employee training that will be needed

The new-product review and decision must be documented.

## Summary

A comprehensive QMS is needed to ensure that reusable medical devices are processed after each patient use with effective cleaning, disinfection, and sterilization methods. These methods need to be validated by the device manufacturer. The facility that uses the device needs to ensure that the validated processing methods are followed. The next chapter discusses process validation and verification concepts in a general sense. Later chapters discuss how the validation and verification concepts can be applied to specific processing methods.

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CHAPTER 5

# Process Validation and Verification Concepts

## Introduction

All processes used in producing medical devices need to be validated, and each time that the process is used it needs to be verified that the process works as intended. Medical device manufacturers must validate both their products and the processes used to produce the product. Healthcare facilities must validate the processes used to produce their products. Product quality assurance testing, as defined in ANSI/AAMI ST79,[2] is a type of process validation used by healthcare facilities. Product quality assurance testing of routinely processed items representing a product family is intended to validate that the process being used by a facility on a particular product family is working as specified in the manufacturer's IFU. Process validation is specific to the machine, utilities, and processes used in a specific location.

The basic concepts of validation and verification as they relate to medical devices are discussed in this chapter. The following topics will be covered:

- The various types of validation and verification that can be conducted
- How each of these validation and verification processes should be performed
- The frequency with which the various types of validation and verification testing should be performed
- How validation and verification should be documented
- Statistical process control (SPC)
- Product design
- Process design
- Process control

There is a tendency for the terms "validation" and "verification" to be used interchangeably. These are actually very different things. Validation is a "documented procedure for obtaining, recording and interpreting the results required to establish that a process will consistently yield product complying with predetermined specification."[9] In essence, validation involves proving that a process performs as it is intended and will do so consistently. Verification is the "confirmation by examination and provision of objective evidence that specified requirements have been fulfilled."[5]

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