AAMI
Advancing Safety in Medical Technology

Basic Concepts in Sterilization Processes Verification, Validation, And Qualification



Donna Swenson

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This publication is intended to be a helpful information resource,
and reflects the expert advice and views of the author.
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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 post-surgical infections did occur, they could be easily treated using 20th century antibiotics.

This almost 150 years of unbroken success in fighting and preventing infections, however, is being challenged. The appearance of antibiotic-resistant bacteria, like methicillin-resistant *Staphylococcus aureus* and carbapenem-resistant *Enterobacteriaceae*, means that hospital-acquired infections can be more dangerous and harder to treat. The increased complexity of new medical instruments—such as endoscopes and those used in robot-assisted surgery—and the incorporation of delicate materials and sensitive electronics into devices, are making the work of reprocessing personnel similarly more complicated and demanding.

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 need to 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.

In this textbook, Donna Swenson distills what she has learned though her education and long career in both industrial and health care sterilization, as well as through her work developing sterilization standards in the U.S. and internationally. It introduces the reader to the basic principles of disinfection and sterilization science and then shows how this science is applied to develop and validate cleaning, disinfection, and sterilization processes. By providing the reader with a good understanding of the esoteric domain of sterilization science and engineering, it is hoped that the quality and efficacy of medical devices can be improved and that patient safety may be advanced.

Joe Lewelling, vice president of standards and emerging technology,
AAMI secretary of ISO/TC 198, Sterilization of health care products

February 2014

Preface

Several years ago, I was speaking with some of my colleagues at an AAMI Sterilization Standards Committee meeting. One of the things that we discussed was how confusing the principles of sterilization verification, validation, and qualification are to many of the people who work in the sterile processing and medical device manufacturing fields. This knowledge seems to be the private domain of sterilization engineers, who appear to possess an almost esoteric knowledge of verification, validation, and qualification of sterilization processes. However, many other people are involved in sterilization, and they need to understand these principles as well. During the course of this conversation, one of my colleagues mentioned that someone needs to write a book that would explain in plain English what sterilization verification, validation, and qualification mean and how they are performed. After the conversation, everyone moved on to other things.

But, this conversation got me thinking. Over the next several months, I kept thinking about that comment that someone needs to write a book. The more I thought about it, the more I agreed that someone *did* need to write a book. I approached Joe Lewelling, AAMI's vice president of standards, and asked him whether AAMI would publish such a book. That conversation led, in turn, to a conversation with Steve Campbell, chief operating officer for AAMI. Steve and I agreed that this was a worthwhile project. In May 2011, Steve and I signed a publishing agreement and thus I began a journey that led to the publication of this book.

This book is about the principles on which sterilization verification, validation, and qualification are based. 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 steam sterilization processes, and product quality assurance testing of steam sterilization processes. Verification of cleaning and steam sterilization processes is also addressed.

This book is written as a textbook. It is meant to provide an explanation of the basic concepts of verification, validation, and qualification of sterilization processes for both healthcare facilities and medical device manufacturers. 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 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.

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.

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 has worked with me for more than two years to make this book a reality. Steve listened when I said that I needed more reviewers, and he made it happen. I want to thank Judy Veale as well, who formerly participated in AAMI standards-development activities and who continues to work on various AAMI projects. This book has been one of those projects. 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.

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 sterilization verification, validation, and qualification. I don't know their names, but I am thankful for their contributions and for the time they all committed to reviewing the original and subsequent drafts of the book. Their comments helped to strengthen the book and to ensure that I actually did achieve the goals that I sent out to accomplish in its writing.

Finally, I want to thank the Publications team and everyone at AAMI who had a hand in making this happen. I know that it was a group decision to agree to publish the book and to continue to support the project over the more than two years that it has taken to write the book. The team would like to thank numerous contributors to the project, including Jonathan Wilder, for their assistance at various stages of the publication process.

Donna Swenson

CHAPTER 1

Introduction

Healthcare sterile processing and medical device manufacturing professionals of today need a comprehensive understanding of sterilization processes 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 and 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 health care is required. Sterile processing professionals must ensure that

a) their sterilization processes meet quality assurance standards;

b) they are adhering to these processes;

c) the methods used for the products that they process are verified; and

d) 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, focusing on steam sterilization as a model process for hospital application and on product quality assurance testing methods used in U.S. hospitals.

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.

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

Bacilli Bacteria that are rod- or stick-shaped. Bacilli are usually spore-forming and aerobic (require oxygen to live and multiply).

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.

Calibration[3] Set of operations that, under specified conditions, in a first step, establishes a relation between the quantity values with measurement uncertainties provided by measurement standards and corresponding indications with associated measurement uncertainties and, in a second step, uses this information to establish a relation for obtaining a measurement result from an indication. 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.

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)[4] Compilation of records which 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)[5] Verification that the proposed specification for the facility, equipment, or system is suitable for the intended use.

Device master record (DMR)[4] 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.

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.

Eucaryotic microorganisms Organisms consisting of cells that each contain 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_0 value[6] 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 that was performed by the manufacturer of the equipment 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 of the process parameters lie outside its/their specified tolerance.

Fungi Single- or multi-celled 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)[5] 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,[4] "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.

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.

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)[5] 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)[5] 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[7] 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.

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

Process challenge device[5] Item designed to constitute a defined resistance to a sterilization process and used to assess performance of the process.

Process parameter[5] Specified value for a process variable.

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

Product family[2] (Sterilization) group or subgroup of product that is characterized by similar attributes, such as mass, material, construction, set weight, shapes, lumens, and packaging 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 particular facility on a particular product family is working as specified.

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[4] 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. Retrospective validation is usually performed to identify the root cause of an identified problem or customer complaint.

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.

Sterility assurance level (SAL)[5] Probability of a single viable microorganism occurring on an item after sterilization.

NOTE: 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}.

Sterilization[5] 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[5] Process whereby product is sterilized within its sterile barrier system. Product with its packaging is subjected to a sterilization process that provides the pre-selected SAL.

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

Validation[5] Documented procedure for obtaining, recording and interpreting the results required to establish that a process

will consistently yield product complying with predetermined specification.

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[4] 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[8] Change in exposure temperature of a thermal sterilization process, which corresponds to a tenfold change in D value.

Abbreviations

AER Automated endoscope reprocessor

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

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 basic 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 health care. For more information, a good book on healthcare microbiology, such as *Microbiology for the Health Sciences*,[9] should be consulted.

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 procaryotes, eucaryotes, and acellular organisms. Procaryotes are simple cells that do not include a nucleus, complex membrane systems, or organelles (specialized cellular subunits with specific functions). Eucaryotes are more complex cells that have a true membrane and membranous organelles. Acellular organisms do not have any cellular structure at all.

Bacteria

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