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# Standard Guide for Validating Cleaning Processes Used During the Manufacture of Medical Devices[1]

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## 1. Scope

1.1 This guide provides considerations for validating cleaning processes for medical devices during initial fabrication and assembly prior to initial use. Validated cleaning processes are important for achieving consistency in function and consistency in biocompatibility. The considerations include but are not limited to, validation approach, equipment design, procedures and documentation, analytical methods, sampling, development of limits, and other issues.

1.2 *Inclusions:*

1.2.1 This guide describes the validation of critical cleaning processes for medical devices to reduce contaminants to acceptable levels prior to packaging.

1.3 *Exclusions:*

1.3.1 Reusable medical devices.

1.3.1.1 Validation of cleaning operations for reusable medical devices is not within the scope of this standard guide. Although cleaning of reusable medical devices is beyond the scope of this guide, many of the principles outlined in this guide may be applicable to the validation of cleaning operations for reusable devices.

1.3.2 Cleaning of medical devices in health care facilities.

1.3.2.1 Validation of cleaning processes in patient/health care facilities is not within the scope of this standard guide.

1.4 *This standard does not purport to address all of the safety concerns, if any, associated with its use. It is the responsibility of the user of this standard to establish appropriate safety and health practices and determine the applicability of regulatory limitations prior to use.*

## 2. Referenced Documents

2.1 *ASTM Standards:*[2]

D543 Practices for Evaluating the Resistance of Plastics to Chemical Reagents

E2857 Guide for Validating Analytical Methods

F619 Practice for Extraction of Medical Plastics

F2459 Test Method for Extracting Residue from Metallic Medical Components and Quantifying via Gravimetric Analysis

F2847 Practice for Reporting and Assessment of Residues on Single Use Implants

G121 Practice for Preparation of Contaminated Test Coupons for the Evaluation of Cleaning Agents

G122 Test Method for Evaluating the Effectiveness of Cleaning Agents

G131 Practice for Cleaning of Materials and Components by Ultrasonic Techniques

2.2 *ANSI/AAMI/ISO Standards:*[3]

ISO 10993-5 Biological Evaluation of Medical Devices—Part 5: Tests for Cytotoxicity, In Vitro Methods

ISO 10993-11 Biological Evaluation of Medical Devices—Art 11: Tests for Systemic Toxicity

ISO 10993-17 Biological Evaluation of Medical Devices—Part 17: Establishment of Allowable Limits for Leachable Substances

ISO 11737-1 Sterilization of Medical Devices—Microbiological Methods—Part 1: Determination of a Population of Microorganisms on Products

ISO 14971 Medical Devices—Application of Risk Management to Medical Devices

AAMI ST72 Bacterial Endotoxins—Test Methodologies, Routine Monitoring, and Alternatives to Batch Testing

AAMI TIR30 A Compendium of Processes, Materials, Test Methods, and Acceptance Criteria for Cleaning Reusable Medical Devices

2.3 *United States Pharmacopoeia (USP) – General Chapters:*

USP <85> Bacterial Endotoxins Test

USP <87> Biological Reactivity Tests, In Vitro

USP <88> Biological Reactivity Tests, In Vivo

USP <1225> Validation of Compendial Procedures

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[2] For referenced ASTM standards, visit the ASTM website, www.astm.org, or contact ASTM Customer Service at service@astm.org. For *Annual Book of ASTM Standards* volume information, refer to the standard's Document Summary page on the ASTM website.

[3] Available from American National Standards Institute (ANSI), 25 W. 43rd St., 4th Floor, New York, NY 10036, http://www.ansi.org.

2.4 *International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH):*

ICH Q2 Validation of Analytical Procedures: Text and Methodology

ICH Q9 Quality Risk Management

## 3. Terminology

3.1 *Definitions:*

3.1.1 *analyte, n*—a substance (usually a residue) for which an analysis is being performed. The residue determination may be qualitative, quantitative, specific, non-specific, and/or it may involve compositional identification. The analyte may be determined as an extract or directly on the surface of the device or portion (subassembly) of the device.

3.1.2 *blank, n*—an analytical sample taken to establish the background value for an analytical measurement which may be subtracted from an experimental value to determine the "true" value.

3.1.3 *clean, n*—having an level of residues and environmental contaminants which do not exceed a maximum permissible level for the intended application.

3.1.4 *cleaning, v*—removal of potential contaminants from an item to the extent necessary for further processing or for intended use.

3.1.5 *cleaning process, n*—a process that is used to remove any product, process-related material and environmental contaminant introduced as part of the manufacturing process.

3.1.6 *cleaning validation, n*—the documented evidence providing a high degree of assurance that a cleaning process will result in products consistently meeting their predetermined cleanliness requirements.

3.1.7 *cleaning verification, n*—a one-time sampling and testing to ensure that a medical device has been properly cleaned following a specific cleaning event.

3.1.8 *contaminant, n*—any material that potentially adversely impacts the assembly, the functioning of the device, and/or shows undesirable interaction with the host. A contaminant may be a single component or any combination of components. Examples of possible types of contaminants include: *(1)* biological or non-biological in nature; *(2)* living or dead; *(3)* particles or thin films; *(4)* solid, liquid, or vapor; *(5)* organic or inorganic.

3.1.9 *first use, n*—the initial contact with biological materials or fluids.

3.1.10 *installation qualification (IQ), n*—establishing by objective evidence that all key aspects of the process equipment and ancillary system installation adhere to the manufacutter's approved specification and the recommendations of the supplier of the equipment are suitably considered.

3.1.11 *lowest observed adverse effect level (LOAEL), n*—lowest concentration or amount of a substance found by experiment or observation which causes detectable adverse alteration of morphology, functional capacity, growth, development, or life span of the target organism under defined conditions of exposure.

3.1.12 *monitoring, v*—verification testing at predefined intervals.

3.1.13 *no observed adverse effect level (NOAEL), n*—greatest concentration or amount of a substance found by experiment or observation which causes no detectable adverse alteration of morphology, functional capacity, growth, development, or life span of the target organism under defined conditions of exposure.

3.1.14 *operational qualification (OQ), n*—establishing by objective evidence process control limits and action levels which result in product that meets all predetermined requirements.

3.1.15 *process qualification (PQ), n*—establishing by objective evidence that the process, under anticipated conditions, consistently produces a product which meets all predetermined requirements.

3.1.16 *recovery study, n*—a laboratory study combining the sampling method and analytical method to determine the quantitative recovery of a specific residue for a defined surface.

3.1.17 *residue, n*—a substance present at the surface of an implant or embedded therein that is not explicitly recognized and defined as part of the implant specification. It includes processing-based residues as well as contamination by environmental factors (adsorbates).

3.1.18 *tolerable intake (TI), n*—estimate of the average daily intake of a substance over a specified time period, on the basis of body mass, that is considered to be without appreciable harm to health.

## 4. Summary of Practice

4.1 This guide provides an approach for validating the removal of contaminants and residues introduced during the intermediate process steps so that the terminal cleaning process can result in a consistently clean medical device.

## 5. Significance and Use

5.1 This guide describes an approach to validate a cleaning system for a medical device. It is based on the manufacturer's accurate and comprehensive understanding of their internal manufacturing and cleaning processes.

5.2 This guide is not intended to provide a detailed plan or road map, but will provide considerations that can be used by the device manufacturer to develop a detailed plan for performing cleaning validation.

5.3 In cleaning validation, as with other types of validations, there are multiple ways to achieve a compliant, scientifically sound and practical cleaning validation program.

5.4 There are several reference documents identified in Appendix X3 that describe cleaning validation approaches for non-medical devices (including cleaning for oxygen-enriched environments, pharmaceuticals, semiconductors). Any of these reference documents could provide guidance for a well defined process for establishing a manufacturer's minimum expectation of a specific cleaning validation program.

5.5 This guidance specifically targets cleaning validation for medical devices, in-process and at terminal cleaning so that the

result is a consistently clean medical device that meets the performance expectations for that device.

## 6. General Requirements

6.1 This guidance for the validation of cleaning processes is divided into 3 sets of activities: understanding the upstream manufacturing process, documenting the cleaning process, and establishing the measurement tools used to evaluate cleanliness and to establish the cleaning performance criteria.

6.2 Preliminary process characterization, whether in the laboratory or on the manufacturing floor, provides the data necessary to establish cleaning parameter control ranges.

## 7. Cleaning Validation Approach

7.1 A typical approach to a cleaning validation includes:

7.1.1 An assessment of the risks and benefits of the cleaning process and the impact of the cleaning processes on the medical device and on downstream processes.

7.1.2 Identification of contaminants from raw materials and manufacturing and processing operations (e.g. machine oils) that could be residuals on the medical device.

7.1.3 Establishment of allowable limits for contaminants (determining "How clean is clean?") based on the product and process needs. Acceptance criteria for "clean" should be stated with scientific justification for the criteria.

7.1.4 A validation of the analytical methods used to measure the residues or contaminants.

7.1.5 A qualification or determination of the sampling techniques used for evaluating the cleanliness of a medical device.

7.1.6 A determination that statistical requirements and documentation are adequate to conclude that the result of testing meets the output specification of the process.

7.2 A general process flow for a cleaning validation program is represented by the Fig. 1:

7.3 *Definition of the Cleaning Process:*

7.3.1 The definition of the process should include an evaluation of the device, the equipment to be used for the cleaning process, the process parameters, the process chemicals, and the manufacturing materials that should be removed by the process.

7.3.2 *Device Design:*

7.3.2.1 The design, material composition, and intended end use of the device have a significant impact on the suitability of a cleaning process. A non-exhaustive list of examples are provided:

*(1)* A cleaning process that will not reach a blind hole in a medical device will not get the blind hole clean.

*(2)* Densely populated electronics assemblies may not be readily accessed by cleaning chemistries. As a result, conductive and non-conductive residue may remain.

*(3)* The cleaning process should not have an adverse effect on the materials of construction of the medical device, the cleaning equipment, or the functionality of the medical device. For example, for plastic devices, ASTM D543 may be used for guidance on how to determine the suitability of specific cleaning agents to medical devices. Chemical compatibility of the cleaning process should be determined prior to cleaning process validation.

*(4)* In some instances, the structure of the device or the surface of the device may cause liquid or vapor-phase residue to be entrapped. Such occurrences are generally not considered to constitute a materials compatibility problem, if the residue is readily removed with extensive rinsing and/or drying (bake-out). However, given the potential negative impact on performance and/or interaction with the host, the design and materials of construction may qualitatively and quantitatively impact the rinsing and/or drying portions of the cleaning process.

7.3.2.2 While the discussion of device design (design for cleanability) is critical to a cleaning validation, a full discussion is not within the scope of this guide.

7.3.3 *Risk Analysis:*

7.3.3.1 The risks and benefits associated with a specific cleaning process should be addressed. There are a number approaches to evaluating the risks associated with a cleaning process, including those described in ISO 14971 and ICH Q9.

7.3.3.2 The process risks evaluated should include the risk to the patient.

7.3.3.3 All cleaning operations should be considered, including processes conducted by contract manufacturers.

*(1)* Some cleaning operations may not be termed cleaning; and the terminology may be specific to a given technical field. Passivation, surface preparation, and surface modification may or may not have a cleaning function. The manufacturer should determine the function and efficacy of each process.

*(2)* If an in-process cleaning operation is considered to be critical and therefore should be validated, acceptance limits for this in-process operation may be established by considering the effect of residue levels after this operation on the final residue levels of the device following the final cleaning step. For example, a manufacturer may perform an OQ on this in-process step to see what in-process residue levels start to impact the final residue levels beyond their acceptable levels. By reducing the in-process residue levels below this limit, the manufacturer can establish the process conditions for validating this in-process operation.

7.3.3.4 Risks that should be considered include the impact on the subsequent process yields or the potential for carryover of residue to the next process or the final product.

7.3.4 In-process cleaning operations that are not critical to subsequent processes or the final product could be included in other process validation activities or, if appropriately justified, may not need to be validated.

7.3.5 *Cleaning Process Development:*

7.3.5.1 The process development should include the development of a process flow chart.

7.3.5.2 The process flow chart should begin with the process steps immediately after the previous validated cleaning step (all steps subsequent to the previous validated cleaning step are residue inputs to the current cleaning step). The process flow chart should end after the cleaning operation and should include an evaluation of the impact of the cleaned device on the subsequent operations.