Designation: ~~F3127 – 16~~ F3127 – 22

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

This standard is issued under the fixed designation F3127; the number immediately following the designation indicates the year of original adoption or, in the case of revision, the year of last revision. A number in parentheses indicates the year of last reapproval. A superscript epsilon (ε) indicates an editorial change since the last revision or reapproval.

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~~,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:*~~ *Exclusions*—The following items / medical devices / processes are excluded from the scope of this document:

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 be a replacement for biological safety testing.

1.5 *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~~ safety, health, and ~~health~~environmental practices and determine the applicability of regulatory limitations prior to use.*

1.6 *This international standard was developed in accordance with internationally recognized principles on standardization established in the Decision on Principles for the Development of International Standards, Guides and Recommendations issued by the World Trade Organization Technical Barriers to Trade (TBT) Committee.*

[1] This guide is under the jurisdiction of ASTM Committee F04 on Medical and Surgical Materials and Devices and is the direct responsibility of Subcommittee F04.15 on Material Test Methods.

Current edition approved ~~April 1, 2016~~Oct. 1, 2022. Published ~~May 2016~~October 2022. Originally approved in 2016. Last previous edition approved in 2016 as F3127 – 16. DOI: ~~10.1520/F3127-16~~10.1520/F3127-22.

2. Referenced Documents

2.1 *ASTM Standards:*[2]

D543 Practices for Evaluating the Resistance of Plastics to Chemical Reagents
E1766 Test Method for Determination of Effectiveness of Sterilization Processes for Reusable Medical Devices
E2857 Guide for Validating Analytical Methods
E3106 Guide for Science-Based and Risk-Based Cleaning Process Development and Validation
E3219 Guide for Derivation of Health-Based Exposure Limits (HBELs)
E3263 Practice for Qualification of Visual Inspection of Pharmaceutical Manufacturing Equipment and Medical Devices for Residues
F619 Practice for Extraction of Materials Used in Medical Devices
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 and Single-Use Sterile Instruments
G121 Practice for Preparation of Contaminated Test Coupons for the Evaluation of Cleaning Agents
G122 Test Method for Evaluating the Effectiveness of Cleaning Agents and Processes
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~~11737-1:2018 Sterilization of ~~Medical Devices—Microbiological~~ Health Care Products—Microbiological Methods—Part 1: Determination of a Population of Microorganisms on Products
ISO 14971 Medical Devices—Application of Risk Management to Medical Devices
ISO 17025 General Requirements for the Competence of Testing and Calibration Laboratories
ISO 19227 Implants for Surgery—Cleanliness of Orthopedic Implants—General Requirements
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:*[4]

USP <61> Microbiological Examination of Nonsterile Products: Microbial Enumeration Test
USP <62> Microbiological Examination of Nonsterile Products: Test for Specified Microorganisms
USP <85> Bacterial Endotoxins Test
USP ~~<87>~~<161> ~~Biological Reactivity Tests, In Vitro~~Transfusion and Infusion Assemblies and Similar Medical Devices
~~USP <88> Biological Reactivity Tests, In Vivo~~
USP <1225> Validation of Compendial Procedures

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

2.5 *FDA Guidance Documents:*[5]

FDA Guidance Pyrogen and Endotoxins Testing: Questions and Answers, issued June 2012

2.6 *European Standards and Pharmacopoeia:*

EN 13018 Non-Destructive Testing—Visual Testing—General Principles
European Pharmacopoeia

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.

[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.
[4] Available from U.S. Pharmacopeial Convention (USP), 12601 Twinbrook Pkwy., Rockville, MD 20852-1790, http://www.usp.org.
[5] Available from U.S. Food and Drug Administration (FDA), 10903 New Hampshire Ave., Silver Spring, MD 20993, http://www.fda.gov.

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~~a level of residues and environmental contaminants which ~~do~~does 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~~ medical devices 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)*~~*1*) biological or non-biological in nature; (~~*(2)*~~*2*) living or dead; (~~*(3)*~~*3*) particles or thin films; (~~*(4)*~~*4*) solid, liquid, or vapor; and (~~*(5)*~~*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 ~~manufacuter~~'s manufacturer'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.~~

3.1.11 *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.~~

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

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

3.1.14 *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.

3.1.15 *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, and semiconductors). Any of these reference documents could provide guidance for a ~~well defined~~ 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~~three 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.~~ (for example, 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~~ presented in Fig. 1~~:~~.

7.3 *Definition of the Cleaning Process:*

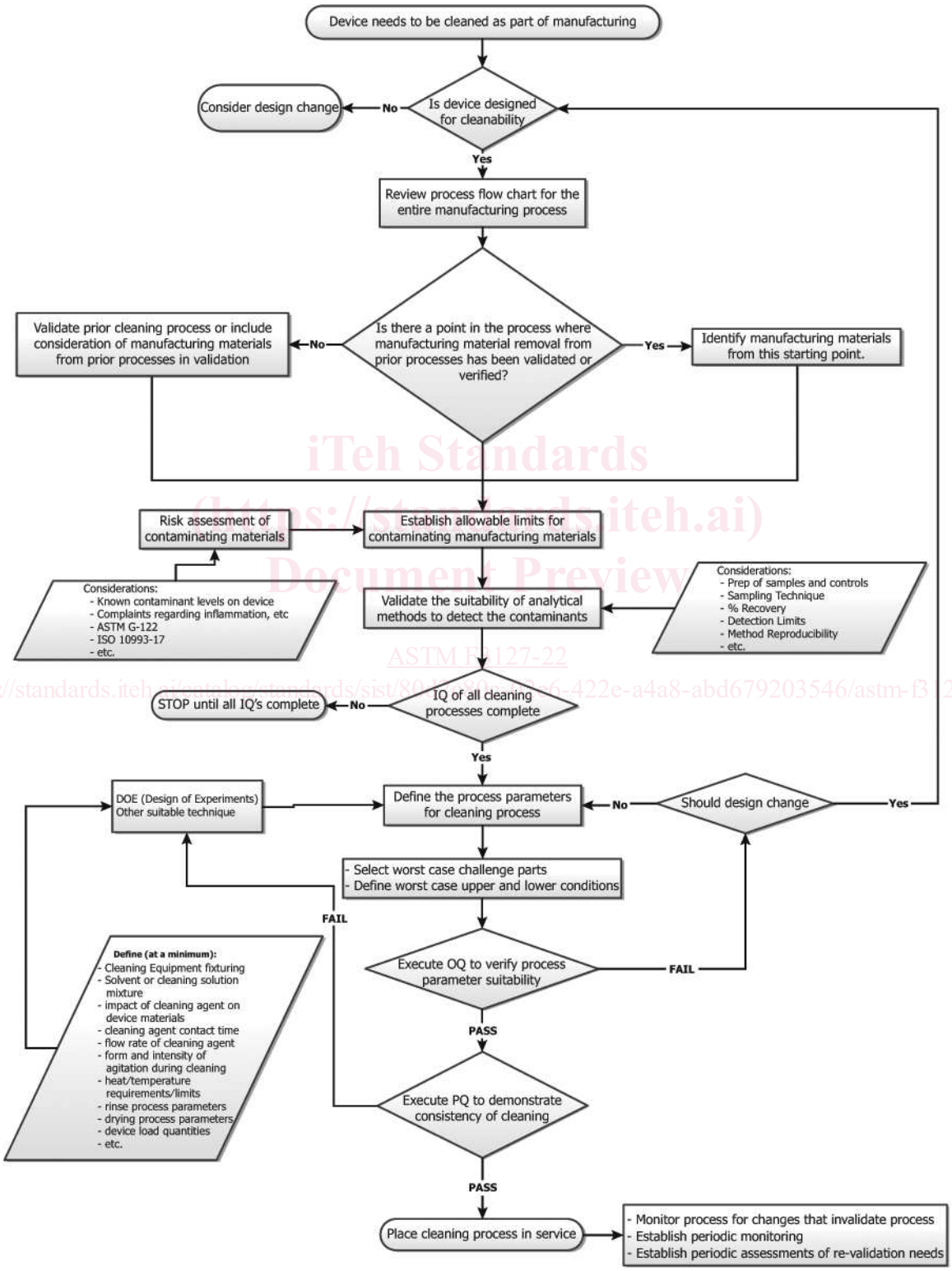

FIG. 1 Process Flow for a Cleaning Validation

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~~is 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~~Practice 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 of approaches to evaluating the risks associated with a cleaning process, including those described in ISO ~~14971~~ 14971, ISO 19227, Guide E3106, 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;~~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.

NOTE 1—In-process cleaning validations may also apply if cleaning is critical to a subsequent process step, such as bonding or inspection steps requiring a clean part.

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.

7.3.5.3 The process flow chart and an appropriate list of materials should be detailed enough to identify all of the materials (including metalworking fluids, polishing compounds, glove contaminants, cleaning agents, etc.) that come in contact with the in-process component or medical device. Without knowing the contact materials, the definition of an adequate cleaning process is incomplete.

(1) The device manufacturer should work with the suppliers of process materials to ~~assure~~ensure that a consistent composition is obtained. Identifying the composition of process materials includes, at a minimum, obtaining a Material Safety Data Sheet (MSDS). However, the focus of an MSDS is worker safety issues and therefore may not reveal ingredients that may have an undesirable interaction with the process, with the device, or with the patient. Further, many process materials, notably metalworking fluids and cleaning agents, may be complex blends where individual components are present at levels that do not have to be listed on the MSDS.

7.3.5.4 The device manufacturer should work with the suppliers of process materials to develop a plan for managing product changes. ~~This is in recognition that products may be reformulated in response to environmental mandates or worker safety issues. These new formulations~~ Any changes to product design or manufacturing process or processing materials have the potential to ~~have an adverse impact on the product.~~adversely impact final product efficacy, and thus, must be assessed.

7.3.5.5 Based on the process flow and the risk analysis, a validation plan that identifies all validation activities required to demonstrate the suitability and effectiveness of the cleaning process should be developed. The validation plan should provide rationale for product type groupings, process definition, sample size selection, numbers of runs, types of analyses, and acceptance criteria. Validation bracketing or grouping approaches may be utilized. Possible criteria for defining cleaning groups should be but are not limited to: cleaning equipment, cleaning program, process flow, device characteristics (such as such as geometry, base material, surface finish, mated components, functionality, critical features), and contact materials.

7.3.6 *Process Qualification:*

7.3.6.1 The plan should consider the requirements of use and can incorporate risk management to prioritize certain activities and to identify a level of effort in both the performance and documentation of qualification activities. The plan should identify the following items:

(1) The studies or tests to use,

(2) ~~The criteria appropriate to assess outcomes.~~Acceptance criteria,

(3) The timing of qualification activities,

(4) The responsibilities of relevant departments and the quality unit, and

(5) The procedures for documenting and approving the qualification.

7.3.6.2 The ~~project~~qualification plan should also include the requirements for the evaluation of changes. Qualification activities should be documented and summarized in a report with conclusions that address criteria in the plan.

7.3.6.3 Installation ~~Qualifications~~qualifications (IQ) should be performed on all equipment used in the cleaning process prior to any ~~validation activities.~~ OQ or PQ execution. At a minimum the IQ should include verifications that utility systems and equipment are built and installed in compliance with the design specifications ~~(e.g.,~~ (for example, built as designed with proper materials, capacity, and functions, and properly connected and calibrated).

NOTE 2—Tests for equipment safety, functional features, training of personnel, software validation, and other necessary tests to ensure quality and traceability have been performed prior to OQ execution, and the results remain at pre-defined requirements until the conclusion of the OQ.

7.3.6.4 The operational qualification (OQ) establishes the ability of the processing equipment to execute the cleaning operation within the allowable process parameters. At a minimum, the OQ should include verification that utility systems and equipment operate in accordance with the process requirements in all anticipated operating ranges. This should include challenging the equipment or system functions while under load comparable to that expected during routine production. It should also include the performance of interventions, stoppage, and start-up as is expected during routine production. Operating ranges should be shown capable of being held as long as would be necessary during routine production. Worst-case product should be tested at the process challenge conditions.

7.3.6.5 Cleaning processes are generally comprised of multiple steps. Each critical step of the process ~~should~~shall have a function and a set of parameters that are controlled within defined ranges to ensure effective residue or contaminant removal. The process parameters for each critical step of the process ~~should~~shall be identified and specified in detail and should be based on empirical evidence.

7.3.6.6 Factors to identify and specify in detail may include the use and type of detergents, solvent grade and lot information, the presence of an acid cleaning step, the concentration of cleaning agents, the contact time of cleaning agents, feed pressure or flow rate, cleaning temperature, sonication energy, ultrasonic frequency, spray pressures, required length or volume of rinse steps, required conditions for drying and/or ~~bakeout,~~bake-out, length of time or number of parts between tank ~~clean out cycles~~ clean-out cycles, and the wait time between cleaning steps in addition to other process specific parameters.

7.3.6.7 Each cleaning process line should be considered independently. The burden of validation for multiple cleaning lines might be reduced based on identical cleaning equipment and processes ~~(i.e.,~~ (that is, process equivalency). Each firm is responsible for determining and justifying the specific criteria for cleaning equivalency between cleaning processes.

7.3.6.8 The process qualification (PQ) combines the actual facility, utilities, equipment (each now qualified), and the trained personnel (including required training programs) with the commercial manufacturing process, control procedures, and components to produce commercial batches. A successful PQ should confirm the process design and demonstrate that the cleaning process performs as expected. The decision to begin manufacturing should be supported by data from commercial-scale batches.

7.3.6.9 ~~Data from laboratory and pilot studies can provide additional~~ Laboratory data from pilot studies performed prior to the qualification can provide assurance that the ~~commercial cleaning process performs as expected.~~process qualification will demonstrate adequate performance.

7.3.6.10 The approach to PQ should be based on sound science, the overall level of product and process understanding, and demonstrable control. The cumulative data from all relevant studies ~~(e.g.,~~ (for example, designed experiments; laboratory, pilot, and commercial batches) should be used to establish the process conditions for the PQ. To understand the production cleaning process sufficiently, the manufacturer will need to consider the effects of scale. However, it is not typically necessary to explore the entire operating range at production scale if assurance can be provided by process design data. Previous credible experience with sufficiently similar ~~products~~devices and processes can also be helpful. In addition, objective measures ~~(e.g.,~~ (for example, statistical metrics) are strongly recommended wherever feasible and meaningful to achieve adequate assurance.

7.3.6.11 In most cases, PQ will have a higher level of sampling, additional testing, and greater scrutiny of process performance than would be typical of routine production. The level of monitoring and testing should be sufficient to confirm uniform product quality throughout the batch. The sample size should be statistically justified for each objective acceptance criterion. A minimum of three production lots should be evaluated to capture production variation prior to cleaning.

7.3.7 *Routine Monitoring:*

7.3.7.1 An output of the cleaning validation should include establishment of ongoing routine process monitoring at predetermined intervals.

7.3.7.2 The collection and evaluation of information and data about the performance of the cleaning ~~process,~~process should allow detection of undesired process variability. Evaluating the performance of the cleaning process can identify problems and determines whether action should be taken to correct, anticipate, and prevent problems so that the cleaning process remains in control.

7.3.7.3 An ongoing program to collect and analyze product and process data that relate to product quality should be established. The data collected should include relevant cleaning process parameter monitoring, trends and quality of incoming materials or components, in-process material, and cleanliness of finished ~~products.~~devices.

7.3.7.4 The data should be statistically trended and reviewed. The information collected should verify that the device cleanliness is being appropriately controlled throughout the process.

7.3.7.5 The methods used for monitoring the cleaning process should be included in the cleaning validation process.

7.3.8 *Re-Validation:*

7.3.8.1 Another output of the validation activities should be a schedule for periodic consideration of re-validation of the cleaning processes.

7.3.8.2 Any changes in the process flow (addition of new equipment, changes to the process parameters, changes to upstream

processes or processing materials, changes to the cleaning agents, etc.) should be ~~assessed to determine whether re-validation should be performed~~ assessed. The necessity of re-validation or verification and the extent of ~~the re-validation.~~it should be risk-based.

~~7.3.8.3 A periodic review of deviations from the original validated cleaning process should be conducted to evaluate if a re-validation is required. The review should be thorough enough to determine if the deviations are enough to warrant re-validation.~~

7.3.8.3 Routine monitoring data used with periodic reviews could provide data to justify continued processing without revalidation.

7.3.9 *Documentation:*

7.3.9.1 The process inputs for the cleaning process should be defined and documented.

7.3.9.2 The documentation of the cleaning process should include, but not be limited to, ~~the following, as defined and pertinent to the user's process:~~documenting all critical, validated parameters. Following is a list of examples:

(1) Water quality (and conditioning/treatment),
(2) Solvent quality,
(3) Makes, models, and serial numbers of the equipment,
(4) Verification of preventative maintenance of tanks to prevent contamination ~~build up,~~buildup,
(5) The concentration of cleaning agents,
(6) Cleaning agent type ~~(Brand~~(brand and manufacturer),
(7) The contact time of cleaning agents,
(8) Feed pressure or flow rate of cleaning agents,
(9) Cleaning temperature,
(10) Cleaning agitation requirements,
(11) Verified delivered ultrasonic power (when used),
(12) Bubbling parameters,
(13) Spray parameters (when used),
(14) Current density in electrolytic descaling systems,
(15) Required length or volume of rinse steps, and change-out cycle (max number of parts cleaned or cleaning cycles performed prior to a change),
(16) Required drying conditions,
(17) Rack configurations,
(18) Rack quantities (min and max quantities in the racks, and min and max quantities of racks should be considered for validations. Standard loading conditions will be defined, along with worst-case loading conditions. Note that there should be evidence to justify worst case conditions), and
(19) Wait times between process steps.

7.3.9.3 The documentation of the cleaning validation should include:

(1) Process flow diagrams,
(2) Process risk assessments,
(3) Validation plans (including, but not limited ~~to,~~to: categorization of ~~products,~~devices, sample size selection and rationale, numbers of runs, types of analyses, positive and negative controls used in analytical methods, analytical method validation, and acceptance criteria),
(4) IQ, OQ, and PQ protocols and reports,
(5) A written statement providing a conclusion about the suitability of the process to clean effectively,
(6) Criteria for routine monitoring, and
(7) Criteria for re-validation.

7.4 *Acceptance Limits:*

7.4.1 The process cleanliness requirement should be defined and documented. The process output requirement as well as expected end use and risk analysis factor into the definition of cleanliness.

7.4.2 The output requirements (measurements of residue levels) of the cleaning process should be determined, established, and justified by the manufacturer. These criteria for ~~"clean,"~~"clean" or acceptance ~~limits,~~limits should be stated with scientific justification (see Appendix X1).

7.4.3 There are many ways to establish acceptance limits for a cleaning process.

7.4.3.1 For existing processes, analysis of current components or product, analysis of product taken from the field, and/or analysis of product returned due to expiration can be helpful in establishing a baseline result that reflects the current state. The current state may provide an acceptable rationale of suitability, assuming no associated complaints or adverse events that can be tied to manufacturing material residues or contaminants.

7.4.3.2 For new processes, or processes with limited product clinical history, several techniques can be used to determine the suitability of cleaning including quantifiable specific and non-specific methods and qualitative methods.

7.4.3.3 ~~ISO 10993-17~~ Limits should be established using a risk-based approach. Guide E3219 provides a ~~method for calculating the tolerable intake (TI) limits of leachable substances based on a substance's "No Observed Adverse Effect Level" (NOAEL) and "Lowest Observed Adverse Effect Level" (LOAEL). These calculated TI's can be converted into a cleaning requirement. The method for establishing limits of leachables requires a detailed knowledge of all leachable contaminants that come into contact with the component or device. It is based on a review of toxicological data that establishes a "no adverse effect level" for a material or agent. The calculations determine a tolerable intake value for specific materials or agents.~~scientifically justified, data-driven approach to deriving health-based exposure limits for unintended exposures to individual substances. These limits may then be further used to calculate cleaning limits used in quality risk assessment for medical devices.

7.4.3.4 For manufacturing materials that do not have ~~well studied~~ well-studied toxic responses, appropriate data may need to be developed to justify the suitability of residue limits. ANSI/AAMI/ISO ~~10993-5, ANSI/AAMI/ISO 10993-11, USP <87> and USP <88>~~10993-5 and Guide E3219 provide guidance on either limits or methods to establish suitable limits for manufacturing materials that are not well studied.

7.4.4 Visual inspection techniques, which should be the first cleanliness inspection step, are often used to evaluate the aesthetics like "visually clean" (at some defined level of magnification and under defined lighting conditions), visible debris or residue, consistent color, discoloration, or presence of surface imperfections. See Practice E3263 or EN 13018 for guidance on visual methods and validation.

7.4.5 ~~There is often a requirement to be microbiologically clean. Most of the time the biologically clean requirement is associated with the finished product. It can also apply~~ Microbiological control is not required for cleaning validation unless it is a final cleaning process before packaging in a clean room. The microbiologically clean requirements are associated with bioburden limits of the finished device. However, it may also be applied to in-process cleaning operations to minimize the carryover of microbial contamination to subsequent operations. ~~See~~ In that respect, the differentiation between viable populations of microorganisms (bioburden) and residue of microorganisms (endotoxins) should be considered. Endotoxin evaluation could be considered part of a validated cleaning process depending on the intended use of the device and for devices with specific patient contact. See for example ISO 11737-1, Test Method E1766, USP <61> for bioburden; ANSI/AAMI ST72, USP ~~<87> and USP <88> for~~ <85>, USP <161>, Section 2.6.14 of the European Pharmacopoeia, and FDA Guidance on Pyrogen and Endotoxins Testing: Questions and Answers for endotoxins and for guidance on methods to evaluate biological contamination.

7.4.6 Note that there are conditions and cleaning parameters in which the cleaning ~~agent,~~agent itself can leave or create unacceptable residues/contaminants or alter the surface of the component. The cleaning agent should be treated exactly like any other process residue or contaminant. Acceptance criteria for residual cleaning agents should be established just as they are for any process material, and analytical techniques shall be established for measuring the residual cleaning compounds. Manufacturers of cleaning agents can sometimes contribute appropriate certification and testing or testing methods. The composition of some complex cleaning agent blends may have to be changed in response to safety and/or environmental regulatory considerations, and such changes may result in undesirable cleaning and/or unacceptable surface residue. Therefore, part of the quality program should include provisions for notification of such changes by suppliers.

8. Analytical Methods

8.1 Use of appropriate analytical methods is essential to any cleaning validation program. Analytical methods ~~should~~shall be demonstrated to adequately detect the residues of concern at or preferably below the acceptable limits. Additionally, adequate recovery ~~should~~shall be defined and demonstrated to justify the appropriateness of the method (see Practice F2847). Selection of an analytical method depends on the nature and level of the expected residue after the cleaning process.

8.2 If a method results in a ~~"Non-Detectable"~~"non-detectable" or ~~"Non-Quantifiable"~~"non-quantifiable" response at a level that is higher than the acceptable limits, then it is not an appropriate method.

8.2.1 The limit of detection (LOD) is generally defined as ~~3~~three times the standard deviation of the blank.

8.2.1.1 For instrumental methods, this limit is often considered to be ~~3~~three times the average value of the noise.

8.2.1.2 An alternative method for determining the LOD is based on detectability through analysis of serial dilutions of the residues in questions. Using this method the LOD can be calculated from the regression curve:

$$\text{LOD} = \text{y-intercept} + 3*\text{SE}\left(\text{standard error of the regression line}\right) \quad (1)$$

8.2.1.3 Samples that are at a level at or below the limit of detection are referred to as ~~"Non-Detectable".~~"non-detectable."

8.2.2 The limit of quantitation (LOQ) is generally defined as ~~10~~ten times the standard deviation of the blank.

8.2.3 For instrumental methods, this is often considered to be ~~10~~ten times the average value of the noise.

8.2.4 An alternative method for determining LOQ is based on detectability through analysis of serial dilutions of the residues in ~~questions.~~question. Using this method the LOQ can be calculated from the regression curve:

$$\text{LOQ} = \text{y-intercept} + 10*\text{SE}\left(\text{standard error of the regression line}\right) \quad (2)$$

8.2.5 Samples that are at a level at or above the limit of detection, but below the limit of quantitation, are referred to as ~~"Non-Quantifiable".~~"non-quantifiable."

8.3 The specificity and limit of detection (sensitivity) of the analytical method used to detect ~~residuals~~residues or ~~contaminated~~contaminants should be determined.

8.4 If levels of contamination or ~~residual~~residue are not detected, it does not mean that there is no residual contaminant present after cleaning. It only means that the levels of contaminant greater than the sensitivity or detection limit of the analytical method are not present in the sample.

8.5 All methods of evaluation of process output (whether quantitative or qualitative, or specific or non-specific) should be evaluated to establish method suitability (adequate limits of detection and ~~quantification),~~quantitation), accuracy, precision, linearity, range, reliability, and robustness. For example, visual examination may not be adequate to identify the presence of microgram quantities of aqueous cleaning agent residue. Test suitability should be demonstrated and justified based on data. ~~ASTM~~Guide E2857, USP <1225>, ~~and ICH Q2~~ICH Q2, and ISO 17025 are standards that describe analytical method validations.

8.6 The analytical method should be challenged in combination with the sampling method used to show that contaminants can be recovered from the device and at what ~~level, (e.g., 50% recovery; 90%~~level (for example, 50 % recovery; 90 % recovery) they can be recovered.

NOTE 3—~~ASTM~~ Test Method F2459 requires ~~75%~~75 % recovery on the gravimetric analysis.

8.7 Inspection processes that only yield a pass/fail result cannot be qualified using standard ~~Repeatability~~repeatability and ~~Reproducibility Testing~~reproducibility testing (R&R) techniques, so in these cases fault seed testing (or other options for qualifying pass/fail testing) can be used. Fault seed testing can be conducted by randomly testing both acceptable and unacceptable product, and verifying that the inspection process yields the desired disposition. The inspector should not know which product is acceptable, and ideally should be unaware that the process is being tested. Acceptance criteria are then based on the criticality of the attribute being inspected. For automated processes, generally all ~~fault seeded~~ fault-seeded product should be rejected.

8.8 It is important to establish analytical method suitability before any conclusions can be made about a cleaning validation based on the sample results. It is up to the user to determine and justify method suitability to screen for unspecified analytes as well as test for specified analytes.