Designation: F3127 – 16

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, 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

[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. Published May 2016. DOI: 10.1520/F3127-16

[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.

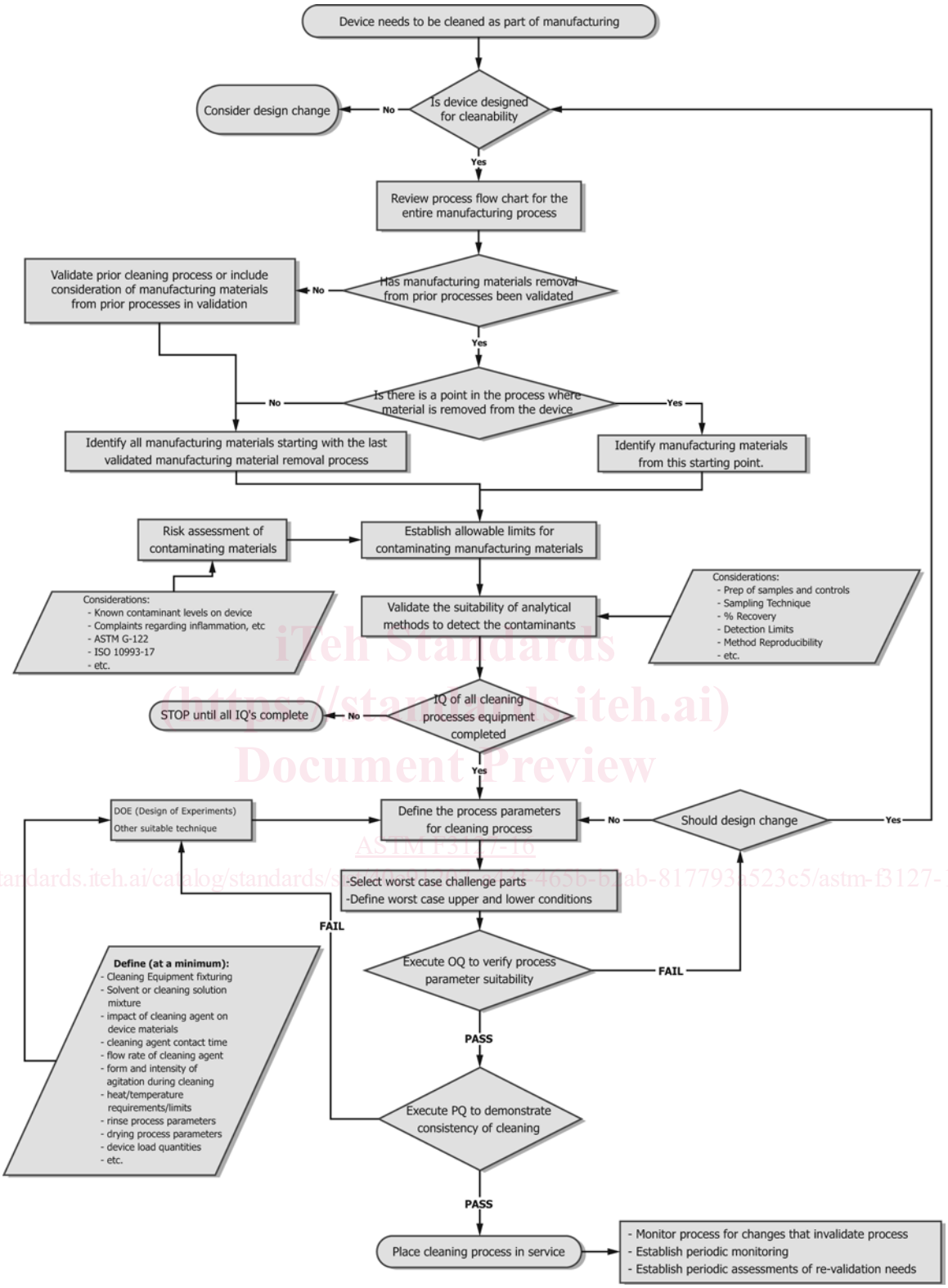

FIG. 1 Process Flow for a Cleaning Validation

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 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 have the potential to have an adverse impact on the product.

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.

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,

(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 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 (IQ) should be performed on all equipment used in the cleaning process prior to any validation activities. 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., built as designed with proper materials, capacity, and functions, and properly connected and calibrated).

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 step of the process should 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 step of the process should 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, length of time or number of parts between tank 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., 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 assurance that the commercial cleaning process performs as expected.

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., 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 and processes can also be helpful. In addition, objective measures (e.g., 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, 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.

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 and the extent of the re-validation.

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.

7.3.8.4 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:

(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,

(5) The concentration of cleaning agents,

(6) Cleaning agent type (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, categorization of products, sample size selection and rationale, numbers of runs, types of analyses, 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," or acceptance 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 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